Review Article

Persistent genital arousal disorder it’s etiology, treatment guideline and management strategy

Preksha T. Singh*, Shreyans D. Singhvi

Department of Obstetrics and Gynaecology, Smt. N. H. I. Municipal Medical College, Ahmedabad, Gujarat, India

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*Correspondence:
Dr. Preksha T. Singh,
E-mail: prekshasingh@icloud.com

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ABSTRACT

Persistent genital arousal disorder is a recently recognized disorder. Its first case was reported in 2001, since then many cases have been diagnosed and treated with various methods, yet no FDA approved treatment guidelines have been proposed. Although it is a cause of not only sexual, but also psychological impairment to the patients of the disorder, Persistent genital arousal disorder is not well recognized currently due to the social stigma attached to it. The study is important for the physicians treating a case of PGAD, as it has all the published data about the disorder. The review of literature was done by using all the research articles and case reports of PGAD using keywords like ‘persistent’, ‘genital’, ‘arousal’, ‘disorder’ on platforms like google scholar and pubmed. Various research articles and case reports were reviewed and grouped into different levels of intervention; at the female genital system, at the spinal cord and the brain. This study has evaluated all the possible etiologies and suggested the possible treatments and management strategies for the disorder. This study has thrown striking limelight on all the potential causes leading to PGAD, its potential line of treatment, and the management strategy. This study is based on the case reports found till date, but there is still a paucity in data, the number of reported cases is less due to a possible social stigma associated with the disease. The present investigation demands extensive research in the topic as this is a cause of social concern leading to psychological, emotional and nervous breakdown.

Keywords: Arousal, Disorder, Genital, Persistent

INTRODUCTION

Persistent genital arousal disorder is currently not understood well and is recently recognized. It’s first case was diagnosed in 2001.1 PGAD generally occurs in women.1 The condition can affect women of any age group. It has been compared to priapism in men.1

In 2003, "persistent genital arousal" was considered for inclusion with regard to the International Consultation on Sexual Medicine (ICSM). In 2009, "persistent genital arousal dysfunction" was included in its third edition.1 PGAD is not included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the International Classification of Diseases (ICD-10), which may be due to the disorder requiring further research.1 PGAD is diagnosed rarely and is not well understood, there is a paucity in the knowledge of the disease awareness, there are various factors for its rarity. Experts have not clinically confirmed the incidence of PGAD, as many people with the condition feel too embarrassed or ashamed to seek medical help. Medical negligence can also be one of the causes of its misdiagnosis, as it might be confused with hypersexuality. PGAD is commonly confused with hyper-sexuality, but these two are different sexual disorders. Hypersexuality is linked to heightened sexual desires, while PGAD can occur with or without sexual stimulus.1
PGAD is very rare. Although online surveys have indicated that hundreds of women may have PGAD.² There are various research articles and case reports on the topic, but there are no approved etiology or treatment guidelines yet. This review article is aimed to evaluate the current knowledge of the disease and the various treatments that have been used successfully, to draw out a possible etiology, treatment guidelines and management strategy from the same.

Prior reports in the Gynecology and sexual medicine literature have described persistent genital arousal disorder as a syndrome of unprovoked, excessive, and frequently unremitting sexual arousal that causes distress and interferes with quality of life.²

Persistent genital arousal disorder (PGAD) was initially called as persistent sexual arousal syndrome but renamed later as in the case of persistent genital arousal disorder, genital arousal is usually not associated with sexual desires or sexual thoughts before the symptoms of the disorder.

There are currently no FDA-approved treatment guidelines or management strategy for the disorder. The symptoms of the disorder occur in the presence and even in the absence of sexual stimulation / sexual desire / sexual thoughts or fantasy of any form and is typically not relieved by orgasm, alternatively the patient may receive multiple orgasms for hours, days, months or even years. The patient with the disorder of PGAD can encounter spontaneous orgasms not resulting in mitigation of the sexual arousal, on the other hand, the orgasm may momentarily mitigate symptoms, but the symptoms may reappear in the later hours. The painful symptoms of the disorder can affect women for several days, months or even years.

There are five Diagnostic criteria for diagnosing a case of PGAD that are used currently, the following are

- Persistently aroused genitalia
- Arousal is unrelated to desire
- Arousal is triggered by both sexual and nonsexual Stimuli
- Symptoms are intrusive and unwelcome
- Arousal remains despite orgasm or requires multiple orgasms to diminish.

PGAD can lead to psychological implications as PGAD not only causes continued sexual arousal leading to pain and stress, but also causes the inability of the patient to perform routine tasks. There are a few studies which indicated PGAD being a cause of depression and even suicides.³ There is a plethora of psychological manifestations that may develop in a patient of PGAD due to constant discomfort, irritation, stress and pain. These psychological manifestations include many psychological diseases like- anxiety, depression, panic attacks, general distress, frustration, irritation, guilt, general discomfort, insomnia and suicides.³ According to a research study, that compared PGAD subjects to non-PGAD subjects, patients with PGAD were significantly more likely to be depressed (55% vs. 38%) and to report panic attacks (31.6% vs. 14.6%).³ Women with history of chronic, untreated or even incurable PGAD may eventually lose their interest in sexual activity or sexual pleasure and their association of orgasm may be linked to hopeful relief of pain from the disorder rather than a pleasurable experience from the act of sex. Therefore, this study is of extreme importance, as PGAD alters not only sexual health but is also responsible for affecting psychological health of women.

**REVIEW OF LITERATURE**

A thorough review of literature was done by reviewing all the research articles of Persistent Genital Arousal Disorder and case reports which described successful treatment of patients with PGAD. They were searched using keywords like ‘persistent’, ‘genital’, ‘arousal’, ‘disorder’, ‘treatment’, ‘case’, ‘report’ on platforms of google scholar and Pubmed.

The various case reports were thoroughly read and categorized into groups. Possible etiology, treatment guideline and management strategy were framed from all the case reports found on all the sources till date.

There are several case reports which have used different successful treatments that point to a possible etiology and treatment strategies for the patients of PGAD.

The results found are categorized in groups of

1. **Peripheral neurological pathology**

One of the research study, used Botulinum toxin Therapy on the dorsal pudendal nerve in the periclitorial region in order to block the dorsal nerve of the clitoris.⁴ The authors presented 2 cases, in which application of Botulinum toxin resulted in improvement of the symptoms of PGAD.⁴ According to the study, Botulinum toxin type A treatment protocol is seen as a promising application for the PGAD.⁴

Another study used Chronic pudendal nerve neuromodulation, according to the research study, pudendal nerve neuromodulation, can be an effective treatment for decreasing frequency of PGAD symptoms and providing symptomatic relief.⁵

Another study used neurolysis of the dorsal branch of pudendal nerve as an effective treatment for PGAD.⁶ Eight women were included in this study.⁶ They were followed more than 26 weeks since surgery.⁶ Seven of these women had the surgery bilaterally while one woman with unilateral decompression had a unilateral surgery of the dorsal branch of pudendal nerve and each of these had an excellent result, meaning mitigation of the
arousal symptoms, and the ability to resume normal sexual intercourse along with no major surgical complications.6

2. Peripheral vascular pathology

There are also case reports of vascular etiology associated with PGAD. One such case report described, a patient with Pelvic Congestion Syndrome presenting as persistent genital arousal disorder.7 In this case, A 62-year-old woman presented with a 5-month history of persistent genital arousal.7

The researchers did a Doppler ultrasound and Magnetic ultrasound imaging (MRI) which demonstrated varices in the pelvis, the vaginal wall, perineum, inguinal region, and anterior abdominal wall.7 A Suspected pathology of left ovarian vein was diagnosed which was found dilated, therefore, they performed a coil embolization of the dilated vein, which resolved the symptoms.7 This case suggested a vascular pathology of the ovarian vein.7

3. Peripheral localized pathology

Another case report described a postmenopausal woman who presented with symptoms of PGAD which she had from the past 6 months.8 Careful examination revealed a tender, firm, mobile, left-sided mass that appeared to have compress the dorsal nerve of the clitoris, causing pudendal nerve entrapment.8 Complete excision of the mass resulted in full resolution of her symptoms over several weeks.8

Another recent case report, of three girls treated a case of PGAD, which was diagnosed with vestibular erythema, on vulvoscopy/examination.9 They all had resolution from the symptoms of PGAD, by vestibular anesthesia with application of topical benzocaine (20%) , lidocaine (8%)/ tetracaine (6%) applied at the hart’s line laterally and the hymen medially.9

Another recent study has shown a case of PGAD and clitorodynia occurring due to a closed compartment syndrome.10 During the examination, there were adhesions found between glans clitoris and the adjacent skin. The researchers did a dorsal slit procedure with removal of adhesions that reduced the symptoms of PGAD in the patient.10

In another case report, two cases were described with severe labial swelling associated with symptoms of PGAD.11 These were diagnosed with a pathological condition of hyper mobility syndrome- Ehlar Danlos.11 Patients with hypermobility syndrome exhibit an increased ratio of type III collagen to type I collagen, causing tissue laxity and venous insufficiency.11 Abnormal collagen may lead to gynecologic manifestations, including unexplained profound labial edema, pelvic organ prolapse in the absence of risk factors, and possibly persistent genital arousal.11

4. Peripheral manual physical therapy

A case report of a pregnant woman was diagnosed with symptoms of PGAD, disease awareness was provided and a manual therapy treatment was provided to decrease muscle hypertonus near the pudendal nerve, and home intervention was suggestion.12 The patient reported 1 week later with complete resolution of her symptoms.12 This study provided a simple, manual treatment of PGAD.12 The possible pathology in this case was due to the pudendal nerve.12

5. Spinal pathology

This study identified meningeal cyst as the cause of PGAD.13 This study identified 11 patients with PGAD out of a cohort of 1,045 with surgically treated symptomatic spinal meningeal cysts.13 Out of the 11 patients, Tarlov cysts were found in eight patients, two had a meningeal diverticulum, and one had an ectatic spinal sac cyst.13 In this case series of 11 women with PGAD and sacral nerve root compression by a meningeal cyst, 91% had elimination or improvement of persistent genital arousal disorder after surgical decompression of the cyst.13 This supports a causal role for such cysts in some cases of PGAD.13 Although eight out of eleven patients had Tarlov cyst, but Tarlov cysts are not the only type of meningeal cyst that were found in the sacrum that led to PGAD.13 They all shared that the meningeal cysts were causing sacral nerve root compression.13 It therefore seems that the presence of sacral nerve root compression is more important than the particular type of meningeal cyst involved.13 The researchers of the case series concluded that PGAD was present along with other sacral radiculopathy symptoms in all 11 patients, implying that PGAD is also a form of sacral radiculopathy.13 prior publication in 2012 also identified that several patients with persistent genital arousal disorder had Tarlov cysts.14

Another recent research study, showed the use of Minimally invasive spinal surgery (MIS) for the treatment of PGAD, who had lumbosacral disc herniation and annular tears who went under endoscopic discectomy surgery, as a successful treatment.15

6. Psychological pathology

A case study of a 71-year-old female, who suffered from PGAD, was provided with hypnotherapy, in 9 sessions of hypnotherapy, the follow up indicated that the patient’s symptoms of depression, sleep disturbance, and marital interference were significantly alleviated, while quality of life improved.16 This showed a possible treatment of PGAD, by hypnotherapy. A case report of a 52-year-old having PGAD was given couple therapy with cognitive behavioral treatment techniques, initially once per week for 18 months, then at longer intervals.17 Later, decrease in patient’s anxiety and urge to masturbate; also, less tension with partner was found.17
7. Central pathology

There are various drugs that have been used as treatment for PGAD, effectively. While, there have been reports of few drugs and their withdrawal causing PGAD.18

One research study showed, case series of five women who believe they developed PGAD either after withdrawing from selective serotonin re-uptake inhibitor (SSRI) anti-depressants or while using them.19 This study concluded that use of, and withdrawal from certain drugs acts as a causation factor for development of PGAD.19 As serotonin is an inhibitor of female sexual arousal, withdrawal of Selective serotonin re-uptake inhibitor (SSRI), causes a central serotonin deficiency, as serotonin is an inhibitor of sexual arousal, rapid serotonin deficiency causes continued sexual arousal, uninhibited by serotonin.18 Although, SSRI abrupt withdrawal can lead to PGAD, but PGAD can be treated with SSRI’s as well, as SSRI’s increase central serotonin and therefore inhibit sexual arousal.

A case report in the journal of clinical psychopharmacology, depicted a case of 57-year-old woman, married, nonsmoker, and history of binge drinking; comorbid depression and anxiety, with 8-week history of symptoms, who was initially on therapy of citalopram, was discontinued of it and given -Lorazepam 1 mg/d and duloxetine 30 mg/d, with paroxetine tapered off; Symptoms improved over 2-week inpatient admission; mood and anxiety also improved; no PGAD symptoms were found at follow-up.19

Treatment with Duloxetine and pregabalin- Another research study used these drugs in the Treatment of two women suffering from PGAD with duloxetine and pregabalin.20

In both women, the treatment proved to be very successful.20 One of them experienced full remission (Duloxetine) and the other one experienced substantial improvement (pregabalin), over a period of time.20 can be inhibited by pregabalin.20 A case report used Varenicline, as an effective treatment for PGAD. In this case report, the case of a 49-year-old woman with lifelong PGAD who was prescribed varenicline for smoking cessation and who subsequently experienced amelioration of PGAD symptoms was reported.21 Based on the pharmacological mechanism of action of varenicline and the observation of its effectiveness in this case of PGAD, the researchers hypothesized 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 hyper stimulated central dopamine release.21 This study indicated a central dopamine pathophysiology of PGAD.

Another unique case report described a 65-y-old woman, diagnosed with Parkinson disease at 60-y-old present with Restless genital symptoms for 3 y; the symptoms only occurred during evenings and nights and triggered by sitting or lying down.22 The patient was treated with Pramipexole 0.25 mg at night.22 The patient experienced improved symptoms within a few days; benefits lasted for 9 months, until symptoms became resistant to increases in dose.22

Another case report, suggested a case of PGAD occurring due to the use of trazodone in a young eumenorrheic woman.23

Another case report, from Mysore, India, indicated an enhanced improvement in PGAD, due to the used of leuprolide, an anti-androgen.24 According to the case report, the patient was initially started with, antidepressants- clomipramine and fluoxetine, along with local application of a local anesthetic- lignocaine gel and pelvic floor exercises, application of anesthetic lignocaine gel and pelvic floor exercises, but the improvement was significantly enhanced by adding injection of leuprolide along with the ongoing line of treatment already provided.23 As, Female arousal is greatly related to the female sex hormones, Leuprolide acts as an agonist at pituitary gonadotropin-releasing hormone receptors.24 It indirectly downregulates the secretion of gonadotropins-luteinizing hormone and FSH leading to hypogonadism and reducing the symptoms of PGAD.24

Another research study in the trial Journal of Psychosomatic Obstetrics & Gynecology did a case series of PGAD using Clomipramine for treatment-resistant persistent genital arousal disorder.25 Female sexual arousal occurs by hypothalamus and limbic system; therefore, clomipramine can work as an effective line of treatment for PGAD.

Another research study used Zolpidem for the treatment of PGAD. Zolpidem is a Non-Benzodiazepine Indirect GABA A Receptor Agonist. The researchers concluded a successful experience with low doses of zolpidem (1 e 2.5 mg q 6 hours) in more than 10 PGAD patients.26

A research study reported a unique case in which the genital arousal was exacerbated by drowsiness and the initiation of sleep suggesting a central activation rather than a peripheral cause.27 Various treatments were tried on the patient, Of the treatments tried only Risperidone was found effective allowing the subject to sleep throughout the night without disturbance and according to the subject had significantly reduced the aggravation of the arousal during the day.27

Another case report depicted A case of a patient who was a 32-y-old woman, who was suffering from bipolar disorder, taking lithium, quetiapine with no response, was later given venlafaxine.28 The symptoms of PGAD began when she reached a dose of 300mg/dl of venlafaxine.28 Lowering the dose of venlafaxine relieved the symptoms.28
Another research used Electroconvulsive therapy for the treatment of PGAD, the patient had Bipolar disorder, due to which he was given an Electroconvulsive therapy, which eventually resolved her PGAD.\textsuperscript{29} After the fourth ECT, the patient's PGAD symptoms abated meticulously.\textsuperscript{29} With each ECT treatment, PGAD symptoms immediately disappeared, relapsing slowly over time until the next ECT was administered.\textsuperscript{29} The patient in total received a total of 30 treatments of ECT.\textsuperscript{29} The pathology behind the treatment is that ECT is known to induce cerebral excitatory and inhibitory neurotransmitter changes after acute and chronic administration.\textsuperscript{29} As, Sexual arousal is stimulated by the action of hypothalamic and limbic neurotransmitters, ECT helped in resolving the symptoms of PGAD.\textsuperscript{29} The researchers of the study hypothesized the following: (i) bipolar disorder led to central hyperactive dopamine release, an important component in the pathophysiology of her PGAD; (ii) central serotonin deficiency after selective serotonin-reuptake inhibitor (SSRI) withdrawal resulted in a lack of inhibition of sexual excitement; (iii) ECT resulted in lowering of the hyper stimulated central dopamine release; and (iv) ECT led to an increase in sexual inhibition by stimulating serotonin activity.\textsuperscript{29}

Another research study in the field of neuroscience, depicted a case of a woman with typical PGAD symptoms and orgasmic seizures that were found to be related to a specific epileptic focus.\textsuperscript{30} the researchers performed a EEG/MEG and fMRI spontaneous activity study during genital arousal symptoms and after the chronic administration of 300 mg/day of topiramate. From MEG data an epileptic focus was localized in the left posterior insular gyrus (LPIG).\textsuperscript{30} FMRI data evidenced that sexual excitation symptoms with PGAD could be correlated with an increased functional connectivity (FC) between different brain areas: LPIG (epileptic focus), left middle frontal gyrus, left inferior and superior temporal gyrus and left inferior parietal lobe.\textsuperscript{30} The reduction of the FC observed after antiepileptic therapy was more marked in the left than in the right hemisphere in agreement with the lateralization identified by MEG results.\textsuperscript{30}

Treatment completely abolished PGAD symptoms and functional hyper connectivity.\textsuperscript{30} The functional hyper connectivity found in the neuronal network including the epileptic focus could suggest a possible central mechanism for PGAD.\textsuperscript{30}

A case report of successful treatment of PGAD with transcranial Magnetic stimulation of a 29-year-old female who presented with symptoms of PGAD.\textsuperscript{31} The researchers decided to treat her mood and pelvic pain symptoms with TMS.\textsuperscript{31} They treated her pelvic pain with inhibitory TMS (2000 pulses at 1 Hz at 90% MT) bilaterally on the motor strip in the area of the pelvis on the homunculus.\textsuperscript{31} For her BDD, They eschewed excitatory treatment of the left DLPFC (dorsolateral prefrontal cortex) and stimulated the right DLPFC (1200 pulses of 1 Hz at 100% MT).\textsuperscript{31} After 50 TMS sessions over 3 months, her Montgomery–Åsberg Depression Rating Scale (MADRS) score de-creased from 32 to 16.\textsuperscript{31} Her pelvic pain and PGAD symptoms were virtually in remission.\textsuperscript{31} Spontaneous orgasms had completely ceased.\textsuperscript{31} This shows a central pathological link of PGAD and a possible treatment of Transcranial Magnetic Stimulation for treatment of PGAD.\textsuperscript{31}

8. Dietary pathology

This case report of a 44 old year female, who presented to the gynecologist presenting with the symptoms of PGAD (from the past 5-6 months which included increased pelvic tension, not associated with an increase in desire that required her to self-stimulate to orgasm approximately 15 times daily), during general history examination of the patient, patient reviled her dietary regimen included soy intake in excess of 4 pounds per day that began approximately 1 month prior to the onset of symptoms.\textsuperscript{32} Treatment consisted of supportive counselling and dietary modification.\textsuperscript{32} At the 3-month follow-up visit, the patient's menstrual difficulties and sexual complaints resolved.\textsuperscript{32}

9. Association with restless leg syndrome and overactive bladder disorder\textsuperscript{33}

In a case series study in 18 Dutch women, the study showed that the majority of women experienced PGAD during early menopause without pre-existing psychiatric disorders and laboratory abnormalities.\textsuperscript{33} Most women had difficulties in depicting the quality of the genital sensations.\textsuperscript{33} These were described in various terms and were diagnosed as dyesthesias and paresthesia’s.\textsuperscript{33} Their intensity was most severe during sitting. A few women reported PGAD during pregnancy and premenstrual.\textsuperscript{33} The majority of women also reported preexistent or coexistent restless legs syndrome (RLS) and overactive bladder syndrome (OBS).\textsuperscript{33} These strongly associated morbidities point into the direction of a clinical cluster, which harbors PGAD or PGAD plus these typical other disorders.\textsuperscript{33} Notably, as in RLS and OBS, it appeared that daily treatment with clonazepam 0.5-1.5 mg was effective in 56% of PGAD women.\textsuperscript{33} Also, oxazepam 10 mg and trazodone 50 mg elicited PGAD -reducing effect.\textsuperscript{33} According to the research, PGAD seems to belong to a highly associated disease cluster including morbidities, which share an imperative urge to suppress dyesthesias and paresthesia’s by firm manipulative actions. PGAD-or as proposed by this case series study was referred as restless genital syndrome (RGS) in the context of its strong association with restless legs is probably the expression of a non-sexually driven hyperexcitability of the genitals and subsequent attempts to overcome it by genital manipulations.\textsuperscript{33} This study also incorporates that not only SSRIs but also serotonin and norepinephrine reuptake inhibitor (SNRI) may induce PGAD, that activation of the sympathetic system is involved in PGAD, and that pelvic varices may induce PGAD.\textsuperscript{33} This
Another case report described a 56-y-old woman who suffered from PGAD and overactive bladder for 42 years. She was treated with TENS (placed 2 cm medial to tuber ischiadicum); later, 90% decrease of genital sensations, spontaneous orgasm, restless leg, and overactive bladder was found.

A case report described a case of 61 years who presented with genital sensations of imminent orgasm associated with engorgement of clitoris and labia and increased vaginal lubrication; The patient was treated with TENS (placed bilaterally on pubic bone); Later 100% decrease of genital sensations and overactive bladder was found.

### DISCUSSION

This review article points to possible etiology and pathology of the persistent genital arousal disorder. We have grouped possible etiologies into different groups and provided with possible treatment guidelines for the same.

The various possible etiologies leading to the condition of PGAD are:

1. **A Pathological Condition at the level of female Genital System**

   Focusing the female genital system, the disorder PGAD can arise due to 3 factors; neurological, localized and vascular condition.

   Beginning from a peripheral neurologic condition, it is a sensory pathology, mostly involving the pudendal nerve (S2-S4). Pudendal nerve is a sensory nerve that supplies the vulva of the female genital system, most importantly the clitoris and the G-spot which are the most sensitive parts of the female genital system and are responsible for their arousal and stimulation. Pudendal nerve later goes to the sacral plexus and joins the spinal cord. There have been successful treatments that have relieved the patients of PGAD; importantly treating the pudendal nerve disorder, e.g., use of Botulinum Toxin in pudendal nerve in the treatment, use of chronic pudendal neuromodulation for the treatment, neurolysis of dorsal branch of pudendal nerve, and PGAD, therefore treating the dilated vessel will lead to mitigation of the symptoms.

   Also, it could also be due to a localized mass causing compression of the nearby sensory structures, e.g., Pudendal nerve causing PGAD, this can be treated by complete excision of the mass, or it could be due to a condition causing vestibular erythema, it can be successfully treated with local application of topical benzocaine (20%), lidocaine (8%) tetracaine (6%), or a condition associated with closed compartment syndrome, a surgery to treat the adhesions can lead to complete resolution of the symptoms. There has also been positive association with localised mass occurring due to a systemic disorder like- Ehler Danlos, as it affects the collagen system of the body, it can affect structures in the female genital system as well. This suggests a complete physical examination of the female genital system along with vulvoscopy, to diagnose any female genital disorder and treating the same. Additionally, manual therapy has also shown improvement in the condition of PGAD.

![Figure 1: Indicates possible pathological condition at different levels, this has been concluded from the data recorded in the study; OBS- Overactive Bladder Syndrome, RLS- Restless Leg Syndrome.](image)

2. **At the level of Spinal Cord**

A Pathological Condition at the level of Spinal Cord-Pudendal nerve [S2-S4], takes it’s root branches from the sacral plexus of the spinal cord, a pathological condition that would compress the root could be a possible cause of PGAD, most commonly reported are, Tarlov Meningeal cyst, Others are meningeal diverticulum and ecstatic meningeal cysts. From a neurological perspective, it
seems logical that sacral nerve root compression by a meningeal cyst could be causally related to PGAD. Anatomically speaking, the dermatomes of the lower sacral nerve roots cover the perineal area and they play a major role in sexual function. Treatment of these cyst may lead the patient completely resolved of her symptoms.  

Another cause leading to PGAD at the level of spinal cord - found in the case reports was lumbosacral disc herniation or/ and annular tears, these were possibly causing nerve entrapment/ compression causing PGAD, treating these disorder by endoscopic surgery- Minimally invasive spinal surgery (MISS), this can be done after careful examination of spinal cord to diagnose the pathology and the level of pathology at the spinal cord and then performing the surgical method to alleviating the PGAD.  

3. Central pathological condition - which could be due to

Psychologically induced - just like many diseases are psychologically induced, PGAD can be psychologically induced as well. Sexual arousal is greatly linked to the psychological aspect of the female; therefore, it can be treated by Psychological support including hypnotherapy, placebo effect medicines, couple therapy with cognitive behavioral treatment techniques, or psychotherapy. Central pathology of overactive central sympathetic outflow and neurotransmitters. Centrally, sexual arousal is linked to central sympathetic outflow and the hypothalamic and limbic outflow of release of various neurotransmitters that stimulate and inhibit female sexual arousal.

There are Stimulatory dopamine, noradrenaline, melanocortin, and oxytocin, as well as inhibitory serotonin, cerebral opioids, and endocannabinoids. A pathological condition that causes the hyper-excitability of these neurons can lead release of these hormones and lead to PGAD, therefore drugs that will lead to the decreased release of stimulatory hormones (eg. dopamine), lead to the decreased symptoms of PGAD, while increase in the release of inhibitory hormones (eg. serotonin), helps in decreasing the symptoms of PGAD. Neurotransmitter pathology of the hormone serotonin - which could be due to the withdrawal of SSRI, or causing central serotonin deficiency, as serotonin is an inhibitor of sexual arousal, sudden central serotonin deficiency could lead to continuous sexual arousal, many of the cases found were related to abrupt withdrawal of SSRI’s leading to PGAD, also, using drugs which increase central serotonin can lead to mitigation of the symptoms of PGAD, as well.  

While, there are few SSRI and SNRI that are useful for treatment of PGAD as well, eg. duloxetine and Pregabalin. The pharmacology and physiology behind it is Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor, it is commonly used as an antidepressant and for neuropathic pain. Due to it’s action by increasing serotonin, it can lead to inhibition of sexual arousal, also, due to it’s action at the dorsal horn of the spinal cord allows duloxetine to strengthen the serotonergic and adrenergic pathways involved in descending inhibition of pain, this acts at the sensory pathway, which is majorly involved in the PGAD pathology. As for Pregabalin- Pregabalin is a 3-isobuty1 derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic, and analgesic activities.

Although the exact mechanism of action is unknown, pregabalin selectively binds to alpha2delta (A2D) subunits of presynaptic voltage-dependent calcium channels (VDCCs) located in the central nervous system (CNS). Binding of pregabalin to VDCC A2D subunits prevents calcium influx and the subsequent calcium-dependent release of various neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, and substance P, from the presynaptic nerve terminals of hyperexcited neurons; synaptic transmission is inhibited and neuronal excitability is diminished. Pregabalin does not bind directly to GABA-A or GABA-B receptors and does not alter GABAuptake or degradation. Pregabalin is an inhibitor of neuronal activity used for therapy of neuropathy and as an anticonvulsant.

In, PGAD, there is a possibility of hyper excitable state of neurons, that lead to a continuous sexual arousal, which can be inhibited by pregabalin. The other hormone related to central pathology is dopamine- Hypothalamic Dopamine release causes sexual stimulation by dilating peripheral blood vessels for genital arousal, this hypothalamic dopamine release is one of the stimulating causes of genital arousal and therefore, drugs to reduce/ regulate dopamine release could be useful in the treatment of PGAD, eg. Varenicline, is a partial agonist of the α2β1 subtype of nicotinic cholinergic receptor.  

Its 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, also, The hypothalamic dopamine release in the medial pre-optic area is a major controller of sympathetic outflow, activated in sexual instances to dilate peripheral blood vessels for genital arousal and facilitate sexual desire.

Another drug affecting dopamine hormone was Pramipexole, a patient with Parkinson’s disorder has a dopamine acetylcholine balance disorder and as PGAD is also associated with dopamine hormone, treating a patient of Parkinson’s, with Pramipexole treated the patient with PGAD, as well, proves a strong dopamine pathology in PGAD as well. There is another report, which reported a use of trazodone, causing PGAD. Trazodone is a serotoninergic modulating antidepressant that is used in
therapy of depression, aggressive behavior and panic disorder.

The pharmacological mechanism of trazadone's antidepressant action in man is not fully understood. In animals, trazadone selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor, 5-hydroxytryptophan. Possible manifestation of PGAD, due to trazadone, could be due to serotonin pathway, but the topic requires more research. As well as leuprolide, that is used for treating PGAD, which occurred due to overactive female hormones causing PGAD, along with clomipramine. Zolpidem, a FDA-approved fast-acting non-benzodiazepine indirect GABA- A receptor agonist, potentiates GABA release and in turn modifies the benzodiazepine binding site.24-26

![Image](image_url)

Figure 2: Depicts the central sympathetic flow, the association with OBS and RLS, it’s possible line of treatment, the neurotransmitter release and their possible line of treatment. OBS- overactive bowel disease; RLS- restless Leg syndrome.

The brain dopamine neurons are inhibited by GABA neurons, with small axons contacting dopamine cell bodies shutting down dopamine transmission, keeping it in check when activated.26 Benzodiazepines are used clinically to diminish dopamine release by activating GABA release in adjacent neurons, although the effect takes longer to produce and has more severe side effects than zolpidem, therefore zolpidem is of better value is in reducing dopamine release.26

Zolpidem acts to knock out dopamine and release serotonin from inhibition. If PGAD is occurring due to a hypo functioning GABA system in the hypothalamus allowing dopamine to run uninhibited, then zolpidem is hypothesized to normalize GABA release, reduce dopamine and allow serotonin increase reducing PGAD symptoms.26 Another drug used effectively was-Risperidone.27

Risperidone is primarily used for bipolar disorder patients, but it acts on several of the receptors on nerves including dopamine, serotonin, and alpha 2 adrenergic receptors and therefore can be helpful in a central pathological cause of PGAD. If there is a history of high dose of venlafaxine, dose reduction can also lead to mitigation of PGAD symptoms; Venlafaxine is an SSRI and reducing the dose of it, helps reducing symptoms.28

There was a case treated with Electroconvulsive therapy as well, which treated serotonin and dopamine release in combination.29 Another central cause can be due to a brain injury or an epileptic foci; also, alternatively Transcranial Magnetic stimulation, can also be tried for a central pathological condition.30,31

Additionally, A case reported has also shown increased soy intake to be associated with symptoms of PGAD, this can be treated by reducing the dietary soy intake and taking general care of the diet of the patient.32 This points to a thorough general history examination of the patient and reducing the dietary soy intake if found responsible for the cause of PGAD.

The pathological condition causing over activity of central sympathetic outflow causing PGAD was found to be associated with OBS and RLS - this was treated effectively with clonazepam, oxazepam and tramadol, this can also be treated effectively with TENS at a peripheral level.33-35

Management Strategy: We hereby conclude that a PGAD patient should first be examined for peripheral causes of PGAD. For detecting a peripheral cause, a complete physical examination, vulvoscopy and a nerve stimulation test should be performed along with thorough general examination to examine a dietary cause and later be suspected for a spinal examination using Magnetic Resonance Imaging (MRI) or a central pathological cause. The study of Thorne, C and Stuckey, B corroborates with our management study where they proposed a careful general and systemic examination of the patient before pointing a central or psychological cause.8

This study has thrown striking limelight on all the potential causes leading to PGAD. Its potential line of treatment, a treatment guideline for different cases of PGAD and the management strategy. Our study is based on the case reports found till date, but there is still a paucity in data, the number of reported cases is less due to a possible social stigma associated with the disease.

The present investigation demands extensive research in the topic as this is a cause of social concern leading to psychological, emotional, nervous breakdown.
Table 1: Indicating the Pathology found during the diagnosis of the patient and potential line of treatment for it based on the case reports found; here - OBS- Overactive bowel disease and RLS- Restless Leg disorder.

<table>
<thead>
<tr>
<th>Pathology causing PGAD</th>
<th>Potential Line of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neurological Pathology</td>
<td>a. Botulinum toxin therapy</td>
</tr>
<tr>
<td>Peripheral Neurological Pathology</td>
<td>b. Chronic Pudendal Neuromodulation</td>
</tr>
<tr>
<td>Peripheral Neurological Pathology</td>
<td>c. Neurolysis of Pudendal nerve</td>
</tr>
<tr>
<td>Peripheral Neurological Pathology</td>
<td>d. Manual physical therapy</td>
</tr>
<tr>
<td>Peripheral Vascular Pathology</td>
<td>Coil Embolization of the affected vessel</td>
</tr>
<tr>
<td>Peripheral a. (Localized Mass)</td>
<td>a. Complete excision of the mass</td>
</tr>
<tr>
<td>Peripheral a. (Localized Mass)</td>
<td>b. Local anesthesis</td>
</tr>
<tr>
<td>Peripheral a. (Localized Mass)</td>
<td>c. Dorsal slit procedure, remove adhesions</td>
</tr>
<tr>
<td>Spinal Pathology - Meningeal cyst</td>
<td>Removal of the cyst</td>
</tr>
<tr>
<td>Spinal Pathology - Lumbosacral Herniation/annual tears</td>
<td>Minimal Invasive spinal surgery (MISS)</td>
</tr>
<tr>
<td>Central Pathology - Psychologically induced</td>
<td>Hypnotherapy, Cognitive Behavioraltherapy, couple therapy.</td>
</tr>
<tr>
<td>Central neurotransmitter pathology- history of SSRI use-</td>
<td>withdrawal of SSRI’s like- citalopram, trazodone. Psychotherapy drugs safe to use- lorazepam, fluoxetine, duloxetine, paroxetine, pregabalin, clomipramine.</td>
</tr>
<tr>
<td>Central Neurotransmitter Pathology- Also associated with Depression/anxiety</td>
<td>Give SSRI/SNRI’s like- lorazepam, fluoxetine, duloxetine, paroxetine, pregabalin, clomipramine.</td>
</tr>
<tr>
<td>Central Neurotransmitter Pathology- associated with Smoking addiction</td>
<td>Varenicline</td>
</tr>
<tr>
<td>Central Neurotransmitter Pathology- also associated with Bipolar disorder</td>
<td>Risperidone, IF history of high dose of venlafaxine( reduce dose), Electroconvulsive therapy</td>
</tr>
<tr>
<td>Central Neurotransmitter pathology- also associated with parkinsonism</td>
<td>Pramipexole</td>
</tr>
<tr>
<td>Central Pathology with epileptic foci</td>
<td>Antiepileptic drugs like topiramate</td>
</tr>
<tr>
<td>Central pathology with hormonal overactivity</td>
<td>Leuprolide</td>
</tr>
<tr>
<td>Central sympathetic outflow overactivity -PGAD associated with OBS and RLS</td>
<td>Oxazepam, Clonazepam, Tramadol, TENS (2 cm medial to tuber ischiadium) TENS (B/L to pubic bone)</td>
</tr>
<tr>
<td>Central pathology also associated with insomnia</td>
<td>Zolpidem</td>
</tr>
<tr>
<td>Central pathology due to high intake of soy</td>
<td>Reduce dietary soy intake</td>
</tr>
<tr>
<td>Central pathology</td>
<td>Can be treated with Transcranial Magnetic Stimulation</td>
</tr>
</tbody>
</table>

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REFERENCES


