Persistent Genital Arousal Disorder (PGAD) in Women: Mental or Body

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Persistent genital arousal disorder (PGAD) (formerly PSAS) is a rare, unwanted and intrusive sexual dysfunction associated with excessive and unremitting genital arousal and engorgement in the absence of sexual interest.

PGAD is extremely frustrating and can lead to suicidal ideation and attempts.

The persistent genital arousal usually does not resolve with orgasm.
Persistent Genital Arousal Disorder: during PGAD episode

Homuncular genital representation
Normal clitoris projection
PGAD attack
Increased peripheral pudendal nerve sensory afferent input

Central sexual arousal reflex center that is overly excited and under inhibited
Pain and Orgasm Share Common Neurologic Pathways – Lateral Spinothalamic Tract
Pain and Orgasm Share Common Neurologic Pathways – Lateral Spinothalamic Tract

The spinothalamic tract is a sensory pathway originating in the spinal cord.

The spinothalamic tract transmits afferent information to the thalamus about pain, temperature, itch and crude touch.

The types of sensory information transmitted via the spinothalamic tract are described as “affective sensation” - the sensation is accompanied by a compulsion to act.

For instance, an itch is accompanied by a need to scratch, and a painful stimulus makes us want to withdraw from the pain.
Female Sexual Response Cycle

Adapted from Masters WH, Johnson VE. Human Sexual Inadequacy. Little Brown; 1970.
1. PGAD is not so rare—I personally have spoken with and/or cared for well over 100 women and men with PGAD. I have asked healthcare providers at numerous sexual meetings to raise their hands if they have cared for individuals with PGAD and under most situations, approaching 1 in 4 or 5 providers have managed such patients.

2. PGAD can be cured—We have several patients diagnosed with PGAD who are no longer suicidal or bothered/distressed after treatment(s).

3. **PGAD seems to be caused BOTH by excess peripheral pudendal nerve stimulation from irritated genital, pelvic tissues and from a central sexual reflex that is under excess central excitation and limited central inhibition.**

4. PGAD may be acquired later in life after living many years with no hint of PGAD symptoms.

5. PGAD can occur at a very young age; some people report persistent genital arousal all their lives and do not know any other form of sexual arousal.
Persistent Genital Arousal Disorder (PGAD)

It takes a lot of courage to tell the world I have PGAD. It is something we don’t talk about. It’s a secret. If someone were to find out, we could be ridiculed and sexually harassed for the rest of our lives. Some of us don’t even tell our spouses due to the fact that we’re afraid that they will leave us.

PGAD can last for hours or days with no relief; it is unrelenting and unwanted. It causes a lot of suffering and is often associated with social withdrawal and suicidal thoughts and plans—at one time I had plans. I am very lucky to be standing here today. I was bed ridden. I could not ride in a car; the thought of even getting in a car was unthinkable, as the vibration from driving would stimulate the PGAD. I couldn’t wear tight clothing or even underwear. I wore only dresses so nothing would touch me and aggravate my PGAD. I couldn’t carry out my regular household duties, cooking, cleaning, washing clothes. Just walking would trigger my PGAD. It is embarrassing and humiliating. I had to be near a bathroom at all times. It caused me to not want to live.
<table>
<thead>
<tr>
<th>Persistent Genital Arousal Disorder (PGAD)</th>
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<td>There are no recognized safe and effective evidence-based treatments</td>
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<td>Most physicians are uninformed and unaware of PGAD</td>
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<td>No animal models of PGAD yet exist</td>
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<td>Primary versus acquired</td>
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<td>Biopsychosocial pathophysiology –</td>
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<td>Psychologic – especially STRESS</td>
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<td>Pharmacologic Causes</td>
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PGAD is likely always secondary to the SUM of TWO underlying pathophysiologies:

- Increased peripheral pudendal nerve sensory afferent input
- Central sexual arousal reflex center that is overly excited and under inhibited
Persistent Genital Arousal Disorder (PGAD)

The central sexual reflex center of the brain FALSELY INTERPRETS the excess peripheral sensory information as sexual arousal - leading to the spontaneous arousal and orgasm and short refractory period post-orgasm.

This is the unusual PGAD combination - 1) too much peripheral input and 2) not enough central inhibition.
Persistent Genital Arousal Disorder (PGAD)

In PGAD there are often concomitant secondary symptoms (may be related in part to associated high tone pelvic floor dysfunction):

- Bladder (urinary frequency, urinary urgency) problems
- Bowel (irritable bowel) problems
- Restless leg problems
Persistent Genital Arousal Disorder (PGAD)

PGAD symptoms include:

Persistent perception that the clitoris, labia, vagina are engorged and throbbing and are fully sexually aroused - even though there is no sexual stimulation

Physical examination locally does not usually show local clitoral, labial or vaginal engorgement – despite the presence of PGAD
Persistent Genital Arousal Disorder (PGAD)

Treatment of PGAD is INDIVIDUALLY BASED:

1. REDUCE the excess peripheral sensory input - conservative treatments, surgical treatments

2. INCREASE inhibitory regulation of the uninhibited central sexual reflex center

Successful PGAD management utilizes ALL the strategies - to keep the PGAD condition manageable - so PGAD patients can have a life going forward
### Medical/Biologic Causes Pudendal Nerve Stimulation/Irritation

| 1. | Altered pre-menopausal hormone integrity – Hormonally Mediated PVD |
| 2. | Altered menopausal hormone integrity – Vulvovaginal Atrophy |
| 3. | Increased nerve fiber density - genetic susceptibility leading to elevated levels of nerve growth factor substances |
| 4. | An injury to, or irritation of, the pudendal nerves that transmit pain and other sensations |
| 5. | Abnormal response of tissues to Candida infection, or recognized allergies or non-specific allergies |
| 6. | Dermatologic conditions: lichen sclerosus or lichen planus |
| 7. | Vulvar granuloma fissuratum |
| 8. | Peri-urethral glans pathology |
| 9. | Desquamative Inflammatory Vaginitis |
| 10. | Bartholin cyst |
| 11. | Clitorodynia |
| 12. | Pelvic Congestion Syndrome |
| 13. | Endometriosis |
| 14. | Pelvic Organ Prolapse |
| 15. | Interstitial Cystitis |
| 16. | Referral from Hip Disease |
| 17. | High tone pelvic floor dysfunction |
Most commonly caused by hormonal contraceptives (may not resolve just by stopping OCPs.)
Other causes include: menopause, oophorectomy, hormonal control of endometriosis or hirsutism, breast-feeding, infertility treatments, treatment of breast cancer

Diffuse vestibular tenderness of the entire vestibule

Ostia of glands are frequently erythematous

The vestibule may have a diffuse pallor with superimposed erythema

Low estradiol, low free testosterone, very high SHBG
Hormonally Mediated Provoked Vestibulodynia

Treatment:
Stop hormonal contraceptives
Systemic testosterone – ideal calculated free testosterone 0.8 ng/dl
Local to vestibule estradiol 0.02%/testosterone 0.1% in methylcellulose BID
Expect no improvement for 6 weeks, 30-40% by 12 weeks

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Dryness and insufficient moisture
Diminished blood flow
Dyspareunia
Itching
Burning sensation
Soreness
Loss of elasticity
Thinning of the vaginal tissue and alteration of keratinization

Mucosal defects including petechiae, microfissures, ulceration and inflammation
Shortening, fibrosis, obliteration of vaginal vault and/or
Narrowing of vaginal entrance
Smoothing of fornix, flattening of vaginal rugae

Epithelium well-estrogenized, multi-layered with good blood supply, superficial cells rich in glycogen

Estrogen-deficiency atrophy with marked thinning of epithelium, blood supply reduced and loss of glycogen

N=919
Menopause Management for Female Sexual Dysfunction

FIVE KEY BASELINE HORMONAL STRATEGIES

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<td>Prolactin Antagonant</td>
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<td>Other: Adderall, Ritalin</td>
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<td>Vasodilators (Systemic, Local)</td>
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Acquired Neuro-Proliferative Vestibulodynia

Women report onset of symptoms after severe or recurrent candidiasis or allergic reaction\(^1,2\)

Polymorphism in genes coding for IL-1ra, IL-1\(\beta\)\(^2,3\)

Decreased INF-\(\alpha\)\(^3\)

Elevated TNF, IL-1\(\beta\), IL-6, IL-8, Heparanse\(^3\)

Increased mast cells in mucosa\(^4\)

Persistent inflammation can lead to a proliferation of C-afferent nociceptor\(^4\)

Neuroproliferative Vestibulodynia

S-100 Immunostain

29-year-old control
Only a few nerve cell bundles are detectable (×25)

Patient with vestibulodynia
Abundant proliferation of nerve fibers (×25)

Involvement of Heparanase in the Pathogenesis of Localized Vulvodynia.
Bornstein, Jacob; Cohen, Yitzhak; Zarfati, Doron; Sela, Shifra; Ophir, Ella
DOI: 10.1097/pgp.0b013e3181400211

FIG. 1. A ×600 Giemsa stain depicting the mast cells subepithelially in a specimen from localized vulvodynia.
Neuroproliferative Vestibulodynia

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Fig. 2. A x400 (A) and x600 (B) CD117 (C-kit) stain depicting mast cells. They are located subepithelially, among other inflammatory cells, in a specimen from localized vulvodynia.

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Fig. 3. Heparanase expression. x400 (A) and x600 (B). Positive cytoplasmic staining is seen in the subepithelial layer, close to the epithelial basement membrane.
Neuroproliferative Vestibulodynia

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**FIG. 4.** x400 (A) and x600 (B) staining for PGP 9.5. The nerve fibers are seen intruding into the epithelium to more than half its depth.

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<th>Characteristic</th>
<th>Score (0-3)</th>
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<th>2-Sided <em>p</em></th>
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<td></td>
<td>Mean ± SD</td>
<td>Median</td>
<td>Range</td>
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<td>No. mast cells (Giemsa stain)</td>
<td>2.14 ± 0.378</td>
<td>2.0</td>
<td>2-3</td>
<td>0.14 ± 0.378</td>
<td>0.0</td>
<td>0-1</td>
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<tr>
<td>Heparanase expression</td>
<td>2.71 ± 0.488</td>
<td>3.0</td>
<td>2-3</td>
<td>0.14 ± 0.378</td>
<td>0.0</td>
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<td>Subepithelial innervation (PGP 9.5)</td>
<td>2.0 ± 0</td>
<td>2.0</td>
<td>2-2</td>
<td>0.71 ± 0.488</td>
<td>1.0</td>
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<td>Intraepithelial innervation (PGP 9.5)</td>
<td>2.0 ± 0</td>
<td>2.0</td>
<td>2-2</td>
<td>0.14 ± 0.378</td>
<td>0.0</td>
<td>0-1</td>
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*Wilcoxon rank sum test (Mann-Whitney *U* test).

**TABLE 1.** Comparison of semiquantitative scores in localized vulvodynia and controls.
Neuroproliferative Vestibulodynia
VESTIBULAR ANESTHESIA TEST
6 weeks post-op
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"TENS" - Transcutaneous Electrical Nerve Stimulation.
Pudendal Nerve Blocks
Pudendal Nerve Blocks
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Candida Infection
Genital herpes is a sexually transmitted disease caused by a herpes virus.

The disease is characterized by the formation of fluid-filled, painful blisters in the genital area.

*Herpes may be spread by vaginal, anal, and oral sexual activity. It is not spread by objects (such as a toilet seat or doorknob), swimming pools, hot tubs, or through the air.*

Genital herpes is a disease resulting from an infection by a herpes simplex virus.

*There are eight different kinds of human herpes viruses. Only two of these, herpes simplex types 1 and 2, can cause genital herpes*
### Medical/Biologic Causes: Pudendal Nerve Stimulation/Irritation

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Lichen Sclerosus (LS)
Erosive Lichen Planus
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INTROITAL DYSPAREUNIA
Vulvar granuloma fissuratum
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Desquamative inflammatory vaginitis

Intensely inflammatory vaginitis of unknown etiology. Finding on wet mount- pH >5.0, +++++WBCs, +++parabasal cells

Leukorrhea causes a secondary dermatitis because of inflammatory cytokines

Treatment: compound of hydrocortisone 10%; estradiol 0.02%; and clindamycin 2% in a vaginal cream base – versabase

Use every other day for one month or indefinitely
With this strategy, those with DIV are 85% cured 15% use it indefinitely

Use diflucan 150 mg once per week if needed
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Medical/Biologic Causes Pudendal Nerve Stimulation/Irritation

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Pelvic Congestion Syndrome Presenting as Persistent Genital Arousal: A Case Report

Catherine Thorne, MBBS,* and Bronwyn Stuckey, FRACP*†‡

Figure 1 Magnetic resonance imaging scan with contrast enhancement shows extensive varices involving the entire vaginal wall, contiguous with the prominent parametrial veins. Varicosities are also seen in the anterior abdominal wall and in the anterior thigh.

Figure 2 Venogram of the left ovarian vein shows retrograde flow and pelvic varices before embolization (left) and after embolization using stainless steel coils and 3% ethoxysclerol (right).
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Common sites for endometrial growths in red:
- Ovary
- Rectum
- Uterus
- Bladder

Normal endometrial lining

Uterus
Left Tube and Ovary
Right Tube and Ovary
Endometriosis
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Vaginal Mesh Extrusion

Vaginal inspection

Vaginal endoscopic view

Shah HN, Badlani GH. Indian J Urol 2012
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Hypertonic Pelvic Floor Muscle Dysfunction

Increased tone causes a decrease in blood flow and oxygen to the muscles of the pelvic floor. This leads to a build up of lactic acid.

Symptoms include: generalized vulvar pain or burning, tenderness where the muscle insert (4,6,8 o’ clock on the vestibule) which causes severe introital dyspareunia, urinary symptoms (frequency, hesitancy, incomplete emptying) constipation, hemorrhoids, and rectal fissures

Physical exam reveals erythema where the muscles insert at the vestibule, multiple trigger points, muscles weakness and an inability to hold a sustained contraction.
“TARLOV” CYST

Cerebro-Spinal Fluid (CSF)
Tarlov cysts

Sagittal
Tarlov cysts

Sagittal

Frontal
T2-weighted MRI image of L.A.'s Tarlov cyst at S2

Injection needle inserted into L.A.'s Tarlov cyst. Cyst is partially empty in this CT image with black air above and small fluid below. The same needle was used to inject fibrin glue inside the cyst for treatment.
Increased peripheral pudendal nerve sensory afferent input

Central sexual arousal reflex center that is overly excited and under inhibited
High Excitation, Low Inhibition Sexual Dysfunction

**SEX THERAPY**
- Strategies to reduce anxiety
  - Conservative measures such as heating pad, warm bath, yoga and acupuncture

**PHYSICAL THERAPY**
- Pelvic floor relaxation strategies to reduce stress or anxiety that is associated with skeletal muscle pelvic floor relaxation

**Pharmacologic Agents That Decrease Neurotransmission**
- (Local Anesthesia, Tricyclic Antidepressants, Calcium Channel Blocking Agents, Sodium Channel Blocking Agents, Anticonvulsant Agents)
  - Lidocaine – topical 1-5%
  - TCA – Amitriptyline – 25 – 150 mg
  - TCA – Nortriptyline – 25 – 100 mg
  - TCA – Desipramine – 25 – 300 mg
  - Ca+ - Gabapentin – 100 – 2400 mg
  - Ca+ – Pregabalin – 25 – 300 mg
  - Na+ – Carbamazepine – 100 – 400 mg
  - Na+ – Oxcarbazepine – 150 – 2400 mg
  - Lamotrigine – 25 – 200 mg

**Non-Pharmacologic Strategies That Decrease Neurotransmission**
- TENS/Inferential Stimulation
- Sacral Neuromodulation – Interstim
- Pudendal Neuromodulation – Interstim
- Pudendal Nerve Block – local anesthesia and steroid
- Electroconvulsive Therapy (ECT)

**DOPAMINE ANTAGONIST**
- Varenicline Tartrate 0.5 mg – 2 mg/day

**Hyperthyroidism**
- Methimazole 5 – 60 mg

**Cannabinoid**
- Dronabinol – 2.5 – 20 mg

**Opioid Agonist**
- Tramadol 25 – 200 mg
- Tapentadol 25 – 400 mg
- Hydrocodone bitartrate and acetaminophen – 5/500
- Oxycodone and Acetaminophen – 2.5/325 – 10/325

**Serotonin and Norepinephrine Reuptake Inhibitor**
- Serotonin Reuptake Inhibitor and 5 HT1A Receptor Partial Agonist
  - SNRI – Duloxetine - 20 – 120 mg
  - SNRI – Venlafaxine – 75 – 225 mg
  - SNRI – Desvenlafaxine – 50 – 100 mg
  - SRISRPA – Vilazodone – 10 – 40 mg

**Vascular Causes**
- Arterial Venous Malformation – Embolization
- Congestion Syndrome - Embolization

**Neurologic Causes**
- Cerebral space occupying lesion, CVA
- Spinal Cord injury, trauma, surgery

**Pharmacologic Causes**
- DISCONTINUE UNDER SUPERVISION:
  - Trazodone
  - Anti-psychotics - chlorpromazine
  - Anti-coagulants – heparin
  - Anti-hypertensives – alpha-blockers
  - Recreational drugs – cocaine
Severe 10/10 PGAD - Pulsating throbbing genital arousal sensations

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PGAD after Peripheral Treatment

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Persistent Genital Arousal Disorder (PGAD)

Effective treatment of PGAD consists of attention to both the peripheral problems and the central problems.

PGAD is a dynamic condition - there will be times where the persistent genital arousal symptoms are worse.

Hopefully with logical, rational biopsychosocial treatments, the persistent genital arousal symptoms will be more often better.