

The Use of Pramipexole to Treat Persistent Genital Arousal Disorder: A Case Report



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ABSTRACT

Introduction: Persistent Genital Arousal Disorder (PGAD) is defined as “spontaneous, intrusive, and unwanted genital arousal (tingling, throbbing, pulsating) in the absence of sexual interest and desire” and traditionally causes marked distress, embarrassment and shame. PGAD may be caused by starting, discontinuing, or making adjustments in certain antidepressants or other medications.

Aim: To report the case of a 36-year-old woman with PGAD, likely due to changes in her psychiatric medications, who was treated with pramipexole and experienced improvement in her PGAD symptoms.

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

Main Outcome Measure: Improvement in PGAD symptoms.

Results: Patient reported improvement in her symptoms by “90%” on a low dose of pramipexole, although higher doses exacerbated her symptoms.

Conclusions: It is likely that an effective treatment window exists for the treatment of PGAD with drugs that possess the ability to exert their control of dopaminergic transmission. This includes direct acting receptor agonists like pramipexole, which produce feedback inhibition. Limitations to their efficacy then involve co-treatments that counteract their ability to exert a dampening effect on hyperstimulated dopamine transmission. It is recommended that clinicians be aware of drugs taken by patients to treat psychiatric disorders that could induce PGAD symptoms, drugs recently discontinued where a rebound effect could lead to PGAD symptoms, and drug mechanisms that could counteract the effect of treatments for PGAD. **Lynn BK, Grabenhorst C, Komisaruk BR, et al. The Use of Pramipexole to Treat Persistent Genital Arousal Disorder: A Case Report. Sex Med 2021;9:100372.**

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Key Words: Persistent genital arousal disorder, Restless genital syndrome, Pramipexole, Dopamine

Persistent Genital Arousal Disorder (PGAD) is defined as “spontaneous, intrusive, and unwanted genital arousal (tingling, throbbing, pulsating) in the absence of sexual interest and desire” and causes marked distress, embarrassment and shame according

to a consensus statement from the Fourth International Consultation on Sexual Medicine.¹ It is unrelieved or worsened by orgasm and may have severe psychological consequences including isolation or suicidal ideation. PGAD is different from hypersexuality in that it occurs in the absence of desire whereas hypersexuality is characterized by high desire for sexual activity. Despite a sensation of engorgement, physical engorgement is usually not visualized. In addition, some women experience spontaneous orgasms, not related to sexual activity, that they find “disturbing, distracting and uncomfortable”. Symptoms may be worsened by stress, anxiety, visual stimuli or physical stimuli. Physical stimuli may be sexual or nonsexual, like the vibrations felt when riding in a car (See Goldstein et al. for a comprehensive review).²

PGAD was first recognized as a condition in 2001. Leiblum & Nathan first reported on a series of 5 women with the disorder

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and named it persistent sexual arousal syndrome.² The name was changed to persistent genital arousal disorder to reflect that the arousal is confined to the genitals in the absence of subjective arousal. Based on limited data, PGAD is thought to occur in approximately 1% of women.

ETIOLOGY

The etiology of PGAD is unclear. It may be the end result of a variety of different conditions, psychological and/or physiological. Physiologically, it may be central or peripheral. Peripherally, PGAD may be due to neuropathy or radiculopathy. It has been linked to meningeal cysts, especially Tarlov cysts, which irritate the pudendal and pelvic nerve root components of the cauda equina.² Disc impingements, annular tears, facet cysts and spinal stenosis have also been implicated in its development.^{3,4,5} Women with pudendal neuropathy may have symptoms of PGAD.² Several case reports have linked PGAD to starting or discontinuing selective serotonin reuptake inhibitors (SSRIs) or SNRIs.² It has also been linked to the use of trazodone, amitriptyline, pramipexole and lamotrigine. Psychologically, anxiety, and stress seem to worsen PGAD.²

We present here a case report of a 36 year old woman who developed PGAD symptoms related to adjustments in her antidepressant/antianxiety medications. Her symptoms ultimately improved with the use of pramipexole, a dopamine D3-prefering receptor agonist typically used to treat Parkinson's Disease and Restless Leg Syndrome. Pramipexole has been used in the past to treat PGAD.⁶ Raj et al report on a case of PGAD that was successfully treated with a combination of pramipexole and leuprolide. Pramipexole has also been reported to be associated with the development of PGAD in another case report in a woman with Parkinson's syndrome.⁷

CASE REPORT

A 36 year old female presented to a sexual medicine clinic with symptoms of PGAD in March of 2018. Informed consent was obtained from the patient for this case report. She described feeling arousal in the genital area that was so severe that sometimes she couldn't walk. She also described urinary urgency, frequency and nocturia. Her symptoms had started one year prior after she was discharged from the hospital following an admission for adjustment of her psychiatric medicines including weaning her off alprazolam, which she took for anxiety. Before her admission, she had been on multiple psychiatric medications including fluoxetine, bupropion, venlafaxine, trazodone, amitriptyline and vilazodone. Her psychiatrist felt it was important to stop the multiple medications to "start fresh regarding her medications". The patient thinks she may have been taking other medications that she could not recall. She specifically noticed arousal symptoms after stopping fluoxetine and vilazodone.

During her admission, she was started on lurasidone 20 mg and titrated up to 40 mg. She was discharged on this medication. After hospitalization, she was placed on quetiapine which was ultimately discontinued, and she was started on desvenlafaxine.

She initially sought treatment for arousal symptoms with her gynecologist who started her on ethinyl estradiol and/or etonogestrel ring and a topical estrogen cream. The ring worsened her symptoms "times 20" and the cream did nothing for her symptoms. She then presented to a sexual medicine clinic. At that time, her PGAD symptoms seemed to be the most intense at night. She did not experience any lower back or extremity pain, numbness, tingling, or weakness. She denied a history of trauma or motor vehicle accidents. She had had a c-section 9 years ago. She was taking trazodone and tramadol. The tramadol provided some relief. Her exam showed no abnormal findings. She was weaned off the trazodone, continued on tramadol, referred to pelvic floor physical therapy, to urogynecology for urinary symptoms, and an MRI was ordered.

In April of 2018 she returned with improvement of urinary symptoms at night while using tramadol. Physical therapy did not alleviate her symptoms, although it helped with her urgency and frequency. A bilateral pudendal block was performed in the office. The pudendal block did not alleviate her symptoms.

In June of 2018 the patient returned after starting levomilnacipran for her anxiety that seemed to worsen her PGAD symptoms "by five times". She was switched to sertraline and she discontinued the tramadol because it was no longer effective. She tried varenicline and zolpidem and neither alleviated her symptoms.

In July of 2018 she saw the urogynecologist and was started on mirabegron.

In March of 2019, an x-ray of the abdomen pelvis was unremarkable. Her MRI showed degenerative disc and joint disease at L3-4 and L4-5 with possible hemangiomas seen at L2 and L3. No Tarlov cysts, annular tears or bulging discs were seen.

In April of 2019 the patient saw a pain specialist who performed a right pudendal nerve block. She returned about 8 weeks later without improvement and the pain specialist performed a bilateral pudendal nerve block. In September of 2019 she underwent a fluoroscopically guided caudal epidural steroid injection with no improvement.

She returned to the sexual medicine clinic in November of 2019. Her husband had found an article in which PGAD had been successfully treated with pramipexole. She was started on pramipexole at a dose of 0.125 mg TID. In January of 2020, she reported that pramipexole had slightly improved her symptoms. Her pramipexole was increased to 0.125 mg BID with 0.250 mg at night. At this dose her symptoms worsened, so she returned to 0.125 mg TID.

The patient followed up in the sexual medicine clinic in May of 2020. After being on the pramipexole for 6-7 months, she reported that her symptoms were "so much better" and her

feelings of arousal had decreased by 90%. There was no change in the quality of her sensations. Prior to starting the pramipexole she rated her symptoms as a 5 during the day and 10 at night. After starting pramipexole, she rated her symptoms as 0-2 during the day and 4 at night. She was not sexually active because she was worried that it would trigger her symptoms or worsen them. The patient reports that in 2021, the pramipexole is still alleviating her symptoms.

DISCUSSION

This case report illustrates the complications that polypharmacy can have in both the etiology and treatment of PGAD. The patient was on a number of drugs to treat depression and anxiety, many of which have neurochemical side effects that involve hypothalamic mechanisms that control genital blood flow.

Pramipexole is a selective agonist of the dopamine D2, D3, and D4 receptors⁸ with a longer sustained action at these receptors relative to other dopamine agonists. At first glance, it seems paradoxical that a dopamine agonist should reduce PGAD symptoms, given the role of dopamine in the medial preoptic area and elsewhere in mediating genital blood flow and linking it to subjective sexual arousal and desire.⁹ However, subchronic treatment with pramipexole reduces both phasic dopamine release in mesolimbic terminals (e.g., nucleus accumbens) and reduces dopamine cell firing by 40%,^{8,10} due to inhibitory feedback caused by direct agonist action that is sustained. The net effect is reminiscent of the “takeover” of dopamine cell firing with varenicline via actions at cholinergic receptors.¹¹ In both cases, the disruption of phasic dopamine cell firing and release may reduce or eliminate the feelings of PGAD.

So why was varenicline not effective in this patient? It is likely that the timing of her other treatments played a role. Her PGAD symptoms emerged when she discontinued SSRI treatment with fluoxetine and vilazodone. Discontinuance of SSRI treatment releases brain dopamine systems from chronic inhibition by serotonin,⁹ which in some individuals causes an increase in phasic dopamine release in the medial preoptic area that either induces genital blood flow or results in PGAD-like feelings of genital engorgement.¹² Although varenicline may have worked at that time, we note that she was subsequently on levomilnacipran at the time she tried varenicline. Levomilnacipran is a selective serotonin and noradrenaline reuptake blocker (SNRI) that elevates both serotonin and noradrenaline concentrations in the central nervous system, but also leads to an increase in dopamine concentrations due to its inhibition of noradrenaline reuptake.¹³ This may have counteracted the effect of varenicline. We note that the patient was taken off levomilnacipran before pramipexole was prescribed, which is likely why it worked.

CONCLUSIONS

It is likely that an effective treatment window exists for the treatment of PGAD with drugs that possess the ability to exert

their own control of dopaminergic transmission. This includes varenicline, which promotes a lower but sustained release of dopamine from axon terminals, and direct acting receptor agonists like pramipexole, which produce feedback inhibition. Limitations to their efficacy then involve co-treatments that counteract their ability to exert a dampening effect on hyperstimulated dopamine transmission. It is recommended that clinicians be aware of drugs taken by patients to treat psychiatric disorders that could induce PGAD symptoms, drugs recently discontinued in which a rebound effect could lead to PGAD symptoms, and drug mechanisms that could counteract the effect of treatments for PGAD.

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REFERENCES

- McCabe M, Sharlip I, Atalla E, et al. Definitions of sexual dysfunctions in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J Sex Med* 2009;6:1479–1486.
- Goldstein I, Komisaruk BR, Pukall CF, et al. International society for the study of women’s sexual health (ISSWSH) review of epidemiology and pathophysiology, and a consensus nomenclature and process of care for the management of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD). *J Sex Med* 2021;8:665–697.
- Yue JJ, Telles C, Schlösser TP, et al. Do presence and location of annular tear influence clinical outcome after lumbar total disc arthroplasty? A prospective 1-year follow-up study. *Int J Spine Surg* 2012;6:13–17.
- Soldatos T, Chalian M, Thawait S, et al. Spectrum of magnetic resonance imaging findings in congenital lumbar spinal stenosis. *World J Clin Cases* 2014;2:883–887.
- Gu YT, Cui Z, Shao HW, et al. Percutaneous transforaminal endoscopic surgery (PTES) for symptomatic lumbar disc herniation: a surgical technique, outcome, and complications in 209 consecutive cases. *J Orthop Surg Res* 2017;12:25.
- Raj R, Bhagat N. Pramipexole with leuprolide: a treatment strategy for PGAD. *Int J Basic Clin Pharmacol* 2017;6:1828–1832.
- Elkins G, Ramsey D, Yu Y. Hypnotherapy for persistent genital arousal disorder: a case study. *Int J Clin Exp Hypn* 2014;62:215–223.

8. Chernoloz O, El Mansari M, Blier P. Sustained administration of pramipexole modifies the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in the rat brain. *Neuro-psychopharmacology* 2009;34:651–661.
9. Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506–1533.
10. Pes R, Godar SC, Fox AT, et al. Pramipexole enhances disadvantageous decision-making: lack of relation to changes in phasic dopamine release. *Neuropharmacology* 2017;114:77–87.
11. Korda JB, Pfaus JG, Goldstein I. Persistent genital arousal disorder: 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.
12. Goldstein I, Komisaruk BR, Pukall CF, et al. International society for the study of women's sexual health (ISSWSH) review of epidemiology and pathophysiology, and a consensus nomenclature and process of care for the management of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD) *J Sex Med*, submitted.
13. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder: a review. *Neuropsychiatric Dis Treat* 2015;11:125–135.