

Persistent Genital Arousal Disorder: Successful Treatment with Duloxetine and Pregabalin in Two Cases

Susanne Philippsohn, MD and Tillmann H. C. Kruger, MD

Department of Psychiatry, Social Psychiatry, and Psychotherapy, Clinical Psychology, Hannover Medical School, Hannover, Germany

DOI: 10.1111/j.1743-6109.2011.02518.x

ABSTRACT

Introduction. Persistent genital arousal disorder (PGAD) is a rare condition in women that causes a lot of suffering. The pathophysiology is not well understood and an approach promising effective treatment has not been established so far.

Aim. This study aims to make colleagues aware of two treatment options, which proved to be successful in one case each and which might be worth further investigation.

Main Outcome Measures. Subjective distress from unwanted sexual arousal, unwanted orgasms, and pain in the genital area.

Methods. Treatment of two women—36 and 41 years old—suffering from PGAD with duloxetine and pregabalin, respectively.

Results. In both women, the treatment proved to be very successful over a long period of time. One of them experienced full remission (duloxetine) and the other one experienced substantial improvement (pregabalin), over a period now lasting for more than a year.

Conclusion. Pregabalin and duloxetine, in particular, should be further investigated as possible medication for the treatment of PGAD. **Philippsohn S and Kruger THC. Persistent genital arousal disorder: Successful treatment with duloxetine and pregabalin in two cases. J Sex Med **;**:**-**.**

Key Words. Persistent Genital Arousal Disorder; PGAD; Persistent Sexual Arousal Syndrome; Unwanted Genital Arousal; Restless Genital Syndrome; Duloxetine; Pregabalin

Introduction

Persistent genital arousal disorder (PGAD) is probably a rare condition that was first described in the modern scientific literature by Modell 1989 and defined by Leiblum and Nathan in 2001 [1,2]. It is characterized by unwanted genital arousal that occurs in the absence of sexual desire, that is, without any subjective sense of sexual excitement, and that does not easily subside. It usually causes a lot of suffering and is often associated with social withdrawal and even suicidal thoughts. Theories exist regarding causes, triggers, and pathophysiology but nothing is known for sure [3–5]. Consequently, no therapy has been established so far, and treatment is difficult. In this light, we describe here two patients who were suc-

cessfully treated as well as the rationale that led us to try out duloxetine and pregabalin. Both patients gave written consent to publishing their case histories.

Case Reports

Case 1

A 36-year-old woman presented with a permanent thumping or stabbing pain in her clitoris, usually low in intensity, 1–2 out of 10 on the visual analog scale (VAS). About once in 2 weeks up to three times a week, she was awakened at night by the rhythmical contractions of an orgasm with subsequent severe pain in her clitoris (VAS 8) lasting for several hours, while clitoris and labia were enlarged as they are directly after deliberate sexual

activity. No subjective arousal accompanied the nightly orgasms. There were no trigger mechanisms for the orgasms. This symptomatology had started 4 years earlier with an increased urge to urinate (but without change in the frequency of urination), followed by initially mild symptoms in the clitoris a few months later, and finally resulting in the above-mentioned disorder. The urge to urinate led her to consult a urologist who first diagnosed cystitis, afterwards a bladder polyp. Treatment of these with antibiotics and surgery, respectively, did not improve the symptoms.

Psychological exploration revealed no signs of a mental illness except for emotional pressure as a consequence of the distressing bodily symptoms. There was no history of sexual assault. Physical examination of pelvic and abdominal muscles, including trigger points as described by Rosenbaum, indicated heightened muscle tension in the perineal area without any indication of vaginismus [6,7]. Both legs showed varices. There was no restless legs syndrome. Blood count, gynecological ultrasound, and magnetic resonance imaging of the pelvis displayed no pathological findings. The patient had already tried several analgesics (paracetamol, ibuprofen, and metamizole) without any success. Local anesthetic gel applied a few times to the clitoral area had brought only minimal relief. Other medications were not used.

Because of the combination of urinary urge and persistent genital arousal disorder, which we discussed as a possible consequence of neuropathy, duloxetine was chosen for treatment, beginning with 30 mg, titrated up to 60 mg once daily in the morning [4]. Duloxetine is a serotonin and norepinephrine reuptake inhibitor, which has been approved for stress urinary incontinence (in Europe), pain associated with diabetic neuropathy, and depressive disorders. Within 1 week, the nightly orgasms disappeared completely, and the permanent pain diminished considerably. After 4 months of treatment, there was no longer any pain. Her sexual life was not affected, either before or during pharmacological treatment. At the time of writing, after some 13 months of treatment, the effect of treatment has not faded so far.

Case 2

A 41-year-old woman received amitriptyline (30 mg), a tricyclic antidepressant, because of a single depressive episode in response to the death of a near friend. After about 10 days of taking

amitriptyline, she got a constant feeling that her trousers had become very tight and that her private parts were swollen. After her next sexual encounter with her husband, she instantly developed a feeling of urinary urge and genital arousal for a few hours, which she perceived to be almost painful. During the following weeks, the symptoms became more constant. Sexual intercourse led to temporary relief, as did distraction and cold showers. Masturbation and driving a car aggravated the symptoms. Stopping the intake of amitriptyline after about 2 months did not change anything. Over a period of several weeks, the symptoms worsened so much in intensity and constancy that the patient developed suicidal thoughts. She tried a low dosage of the atypical antipsychotic quetiapine (25 mg) in the evening for a few weeks, which led to a reduction of the symptoms by 20%.

Further psychological exploration revealed that bodily reactions to psychological pressure were a common pattern in her life. There was no history of sexual assault. Gynecological examination produced no pathological results. Vaginal ultrasound showed pelvic varices. There was no restless legs syndrome. No further examinations were carried out because the patient refused them.

Because of the onset of symptoms during intake of amitriptyline, the patient was not willing to try any other antidepressant (such as duloxetine) for treatment. Due to disturbed sleep, she then took 0.5–1.0 mg clonazepam, a benzodiazepine, in the evening. This medication improved sleep moderately; however, PGAD remained unchanged. Because of the painful component of the symptomatology, it was then decided to administer pregabalin, an anticonvulsant drug approved for epilepsy, neuropathic pain, and generalized anxiety disorder, 75 mg in the morning and 100 mg in the evening. All symptoms diminished considerably within 2 weeks and returned in only a mild form for a few days preceding menstruation or under considerable psychological pressure, both of which the patient said she could handle. Importantly, discontinuation of pregabalin for a period of about 2 weeks brought the symptoms back in full force. Because of the patient's known pattern of bodily reaction to psychological pressure, she additionally started psychodynamic psychotherapy in order to overcome her friend's death and to diminish general daily stress. This brought further relief over time but no complete disappearance of the illness. As in the first case, the symptoms have not worsened again over the period of treatment, which in the meanwhile has lasted for 14 months.

Discussion

Various pathophysiological mechanisms have been discussed in recent years. Leiblum et al. prefer a psychological approach in the sense that “the tendency to be both anxious and depressed contributes to greater worry about the existence of spontaneous genital arousal” and so “PGA may be maintained by anxiety” [8]. Leiblum and Chivers elaborate a circle of maintenance in which “thoughts regarding the meaning of unwanted genital responses or morality of the individual experiencing them may be related to the persistence of attention to genital sensations; anxiety, associated with these thoughts may increase attention and catastrophic thinking regarding unwanted sexual arousal” [9]. Waldinger and Schweitzer found a large overlap of PGAD with overactive bladder and restless legs in their sample [10]. They concluded from their findings that PGAD may be because of neuropathy, probably affecting the sensory small fibers ($A\delta$ - and the C-fibers) of the pudendal nerve [4,11]. With regard to our first case, we primarily hypothesized the PGAD to be of somatic etiology, such as neuropathy, because no mental disorder or other psychological abnormalities were detected. In the second case, we assumed the etiology of the disease to be mixed—somatic and psychological [1,10]. These considerations led us to administer the above mentioned drugs, discussed more specifically in the following paragraphs.

In the first case, duloxetine was given. It is a combined serotonin and norepinephrine reuptake inhibitor. One possible mechanism by which duloxetine may have accounted for the clinical benefits in this case is by enhancing the tone of descending inhibitory pain nerve fibers in the brain and spinal cord, which seems to be mediated by, and dependent on, both serotonin and norepinephrine (reviewed in [12]). This inhibition can be augmented by duloxetine as described in painful diabetic neuropathy, fibromyalgia, and pain associated with major depressive disorders [12]. Because this patient did not show any signs of a depressive or anxiety disorder—one pathophysiological mechanism proposed by Leiblum and Chivers—we assume that the major benefit as documented here was primarily induced by the analgesic effects of duloxetine and not by its antidepressant or anxiolytic properties [9]. In addition, serotonergic drugs such as duloxetine exhibit inhibitory effects on sexual function most probably via 5-HT_{2A} - and 5-HT_{2C} -receptor agonism in the

brain [13–15]. In this case, such a mechanism may have accounted for the disappearance of the nightly orgasms within 1 week. In other words, increased inhibition may have accounted for a normalization of the balance of inhibitory and excitatory factors, however, without evoking concrete sexual side effects such as orgasmic dysfunction as seen in 33% of patients taking duloxetine [13,14]. Finally, duloxetine may have had effects on the spinal cord level. Whereas the described facilitatory neuromodulatory effect of duloxetine on pudendal motor neurons controlling urethral pressure may not have accounted for the benefit here, it is quite possible that there were inhibitory effects on sacral and/or thoracolumbar neurons generating genital sexual arousal and orgasm [14,16,17]. The specific mechanism of action remains speculative; however, serotonin and norepinephrine receptors have been identified for somatic (pudendal nerve, S2–4), sympathetic (Th11 to L2), and parasympathetic efferent nuclei (S2–S4) as well as afferent fibers of the spinal cord (reviewed in [17]), arguing for an increasing inhibitory and/or sympathetic tone.

In the second case, the patient refused treatment with another antidepressant drug such as duloxetine. Clonazepam moderately improved sleep but did not significantly affect PGAD. Therefore, pregabalin was administered additionally. Pregabalin is an anticonvulsant drug that has also received approval for neuropathic pain and generalized anxiety disorder. Pregabalin is a γ -Aminobutyric acid (GABA) analog without an active effect on the GABA receptor, however, binding with the auxiliary subunit ($\alpha_2\delta$ -protein) of voltage gated calcium channels. It thereby functions as a presynaptic modulator of overexcited neurons and may reduce synaptic release of glutamate and other neurotransmitters [18]. In neuropathic pain, primary sensory afferent neurons are damaged, which results in hyperexcitable dorsal root ganglia, increased pain transmitter release in the spinal cord, and central sensitization [18]. Based on the theory that there is a neuropathic or neuronal contribution to the pathogenesis of PGAD, pregabalin can be assumed to be effective in reducing pain in this case by modulation of specific pain neurons. This is in contrast to the case report of Waldinger et al., where pregabalin did not show any benefit [4]. Discontinuation of pregabalin in our case brought back all symptoms immediately, which indicates that it was highly effective here. As pregabalin is not known to have specific antidepressant properties, it is

unlikely that it acted via improvement of depressive symptoms. Moreover, this subject showed no sign of an anxiety disorder that might also have responded to pregabalin treatment. Therefore, we assume that pregabalin was beneficial here primarily because of its analgesic effects or by some kind of modulation of overexcited neurons. Nevertheless, it is possible that the initial depressive symptomatology was a trigger of PGAD in this woman. With regard to the timely connection between amitriptylin medication and PGAD onset, we cannot rule out that amitriptylin has contributed in some way to PGAD.

Conclusion

Under the assumption that, in these two cases, PGAD might be a specific form of neuropathy, or neuropathy combined with psychological distress, duloxetine and pregabalin were administered. Both of these pharmacological approaches resulted in long-term reduction (pregabalin), and even complete remission (duloxetine), of this highly distressing condition. Because of limited experience and knowledge of these drugs in PGAD, different modes of action may have accounted for the clinical benefit including analgesic, modulatory, and sexual inhibitory effects. These observations warrant further investigation of duloxetine and pregabalin in PGAD.

Acknowledgments

Tillmann H. C. Kruger would like to thank the European Society of Sexual Medicine for receiving the grant for Medical Research 2008.

Corresponding Author: Susanne Philippsohn, MD, Department of Psychiatry, Social Psychiatry and Psychotherapy, Clinical Psychology, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany. Tel: +49 511 532 2631; Fax: +49 511 532 8407; E-mail: philippsohn.susanne@mh-hannover.de

Conflict of Interest: None.

Statement of Authorship

Category 1

(a) Conception and Design

Susanne Philippsohn; Tillmann H. C. Kruger

(b) Acquisition of Data

Susanne Philippsohn

(c) Analysis and Interpretation of Data

Susanne Philippsohn; Tillmann H. C. Kruger

Category 2

(a) Drafting the Article

Susanne Philippsohn; Tillmann H. C. Kruger

(b) Revising It for Intellectual Content

Susanne Philippsohn; Tillmann H. C. Kruger

Category 3

(a) Final Approval of the Completed Article

Susanne Philippsohn; Tillmann H. C. Kruger

References

- Modell JG. Repeated observations of yawning, clitoral engorgement, and orgasm associated with fluoxetine administration. *J Clin Psychopharmacol* 1989;9:63–5.
- Leiblum SR, Nathan SG. Persistent sexual arousal syndrome: A newly discovered pattern of female sexuality. *J Sex Marital Ther* 2001;27:365–80.
- Goldmeier D, Mears A, Hiller J, Crowley T. Persistent genital arousal disorder: A review of the literature and recommendations for management. *Int J STD AIDS* 2009;20:373–7.
- Waldinger MD, de Lint GJ, Venema PL, van Gils AP, Schweitzer DH. Successful transcutaneous electrical nerve stimulation in two women with restless genital syndrome: The role of adelta- and C-nerve fibers. *J Sex Med* 2010;7:1190–9.
- Brotto LA, Bitzer J, Laan E, Leiblum S, Luria M. Women's sexual desire and arousal disorders. *J Sex Med* 2010;7:586–614.
- Rosenbaum TY. Physical therapy evaluation of dyspareunia. In: Goldstein AT, Pukall CF, Goldstein I, eds. *Female sexual pain disorders: Evaluation and management*. Oxford: Wiley-Blackwell Publishing; 2009:27–31.
- Rosenbaum TY. Physical therapy treatment of persistent genital arousal disorder during pregnancy: A case report. *J Sex Med* 2010;7:1306–10.
- Leiblum S, Seehuus M, Goldmeier D, Brown C. Psychological, Medical, and Pharmacological Correlates of Persistent Genital Arousal Disorder. *J Sex Med* 2007;4:1358–66.
- Leiblum SR, Chivers ML. Normal and persistent genital arousal in women: New perspectives. *J Sex Marital Ther* 2007;33:357–73.
- Waldinger MD, Schweitzer DH. Persistent genital arousal disorder in 18 Dutch women: Part II. A syndrome clustered with restless legs and overactive bladder. *J Sex Med* 2009;6:482–97.
- Waldinger MD, Venema PL, van Gils AP, Schweitzer DH. New insights into restless genital syndrome: Static mechanical hyperesthesia and neuropathy of the nervus dorsalis clitoridis. *J Sex Med* 2009;6:2778–87.
- Bellingham GA, Peng PW. Duloxetine: A review of its pharmacology and use in chronic pain management. *Reg Anesth Pain Med* 2010;35:294–303.
- Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. *J Sex Med* 2007;4:917–29.
- Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506–33.
- Korda JB, Pfaus JG, Kellner CH, Goldstein I. Persistent genital arousal disorder (PGAD): Case report of long-term symptomatic management with electroconvulsive therapy. *J Sex Med* 2009;6:2901–9.
- Boy S, Reitz A, Wirth B, Knapp PA, Braun PM, Haferkamp A, Schurch B. Facilitatory neuromodulative effect of duloxetine on pudendal motor neurons controlling the urethral pressure:

- A functional urodynamic study in healthy women. *Eur Urol* 2006;50:119–25.
- 17 Jost W, Marsalek P. Duloxetine: Mechanism of action at the lower urinary tract and Onuf's nucleus. *Clin Auton Res* 2004;14:220–7.
- 18 Bauer CS, Rahman W, Tran-van-Minh A, Lujan R, Dickenson AH, Dolphin AC. The anti-allodynic alpha(2)delta ligand pregabalin inhibits the trafficking of the calcium channel alpha(2)delta-1 subunit to presynaptic terminals in vivo. *Biochem Soc Trans* 2010;38:525–8.