Persistent Genital Arousal Disorder (PGAD): Case Report of Long-Term Symptomatic Management with Electroconvulsive Therapy

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ABSTRACT

Introduction. This is the second case report of a woman with bipolar disorder type I who noted the onset of persistent genital arousal disorder (PGAD) symptoms after abrupt cessation of paroxetine. With the worsening of PGAD symptoms, she developed severe depression and suicidal thoughts, resulting in her undergoing electroconvulsive therapy (ECT) as management.

Aim. To describe a case of PGAD and develop hypotheses to explain the beneficial actions of ECT on PGAD based on 4 years of ECT administration.

Methods. Patient self-report after obtaining consent, as well as literature review.

Results. After the fourth ECT, the patient's PGAD symptoms abated serendipitously. She was placed on ECT on demand for the treatment of her PGAD. With each ECT treatment, PGAD symptoms immediately disappeared, relapsing slowly over time until the next ECT was administered. The patient has, thus far, received a total of 30 treatments of ECT. Side effects continue to be minimal and include brief short-term memory loss, headache, and muscle aches.

Conclusion. ECT is known to induce cerebral excitatory and inhibitory neurotransmitter changes after acute and chronic administration. Sexual arousal is stimulated by the action of hypothalamic and limbic dopamine, noradrenaline, melanocortin, and oxytocin, and inhibited by serotonin, cerebral opioids, and endocannabinoids. Based on the patient's bipolar disorder, the mechanism of action of ECT and the observation of ECT effectiveness on her PGAD, we hypothesize 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 hyperstimulated central dopamine release; and (iv) ECT led to an increase in sexual inhibition by stimulating serotonin activity. Further research in the central control of sexual arousal is needed. **Korda JB, Pfaus JG, Kellner CH, and Goldstein I. Persistent Genital Arousal Disorder (PGAD): Case report of long-term symptomatic management with electroconvulsive therapy. J Sex Med 2009;6:2901–2909.**

Key Words. Persistent Genital Arousal Disorder; Persistent Sexual Arousal Syndrome; Electroconvulsive Therapy; Dopamine Release

Introduction

Little is known about the etiology and pathophysiology of persistent genital arousal disorder (PGAD), first described in 2001 [1–20]. Women who present with PGAD typically have feelings of persistent, spontaneous, intrusive, unrelenting, and unwanted physical arousal such as throbbing, pulsating, pounding, engorgement, and/or pressure/discomfort in the genital tissues,

including the clitoris, labia, vagina, perineum, and/or anus. The occurrence of these arousal symptoms is unrelated to conscious thoughts of sexual desire or sexual interest. For many women with PGAD, the sexual arousal symptoms are associated with significant bother and distress [2,4,5]. PGAD may be categorized as a primary, lifelong, or secondary, acquired condition. Research has shown that PGAD is often associated with depression and panic attacks, and that women meeting all the criteria of PGAD seem to be more likely to show certain psychological patterns, in particular, of obsessive–compulsive nature [7]. Potential biological etiologies are vascular (e.g., pelvic arterio-venous malformations, ovarian venous incompetence) [4,12], hormonal (e.g., hormone deficiencies) [1,4], central, and/or peripheral neurological (e.g., CNS trauma, epilepsy, pudendal nerve entrapment) [4,7,9,13,14,16], and pharmacological (e.g., use or withdrawal of certain antidepressants) [4,8,11]. However, some cases of PGAD seem to be idiopathic [4,6,7,9,11].

Therapeutic strategies for women affected by PGAD are limited, but include both psychological and biological treatments. Treatment options include symptomatic strategies such as topical anesthetic agents [13], and target-oriented strategies such as psychological interventions [4,21], discontinuation of the triggering agent [1,10], pharmacological therapy [4,11,13], and surgical intervention in women suffering from PGAD secondary to vascular or neurological co-morbidities [12].

Herein we report the follow-up of a patient with bipolar disorder type II suffering from secondary PGAD who has been treated successfully with electroconvulsive therapy (ECT). A previous case report published in the psychiatric literature involved patient follow-up for a total of 9 months with emphasis on her depression and techniques of ECT but did not provide any hypothesis as to how ECT influenced her PGAD [14]. This current case report extends her follow-up to 4 years, from the beginning of her treatment with ECT, and introduces hypothetical explanations for the beneficial actions of ECT in her particular case of PGAD.

Case Report

Prior to ECT

The patient was first diagnosed with clinical depression at the age of 24 and treated with a tricyclic antidepressant (protryptyline) for about 9 years with no significant side effects. She was already married at that time and experiencing no sexual problems, reporting her sexual life to be satisfying and fulfilling. She gave birth to her two children at age 29 and 32 without any complications. In her mid-30s, her antidepressant medication was changed to maprotiline, a tetracyclic antidepressant that increases the level of central noradrenaline. Her medication was subsequently changed to bupropion because she became anorgasmic on maprotiline. Her orgasmic capacity returned and she described her orgasmic function to be as good as it was prior to maprotiline treatment.

Around the age of 42, the patient entered menopause but did not experience distressing symptoms. Diagnostic procedures were not performed to understand why she went into premature menopause. During menopause, she noticed that achieving orgasm and becoming lubricated during sexual arousal became slightly more difficult; however, she had no problems with her sexual desire and she did not experience any pain during intercourse. "*My sex life was normal, and wonderful.*" During the menopausal transition, she developed hypothyroidism and went on thyroid replacement with levothyroxine. Diagnostic evaluation failed to determine the cause of her hypothyroidism.

She stayed on the buproprion for years, but because she was still suffering from depression, her medication was changed to paroxetine, a selective serotonin-reuptake inhibitor (SSRI). With paroxetine, her depressive symptoms improved rapidly, but she again experienced orgasmic difficulties. At that time, she was diagnosed with bipolar disorder type II, and the paroxetine was abruptly stopped and changed to lamotrigine, an anti-convulsant.

After the abrupt discontinuation of paroxetine, she began to experience unwanted genital arousal including pulsing, tingling, genital engorgement, swelling and pressure, not related to sexual desire, excitement, thoughts, or fantasies. During those episodes of unwanted genital arousal there was an associated sense of mild vaginal/vulvar lubrication. She often felt very distressed, ashamed, isolated and "absolutely miserable." As part of the arousal, she experienced discomfort and pain (throbbing, sharp, burning). She reported an increased severity of her persistent genital arousal during exposure to heat, physical exercise, driving, or horseback riding. She could decrease the intensity of her complaints by local cooling of the area with ice packs, a topical anesthetic creme (*Pramoxine*®), and oral analgesics (*Paracetamol*®). "*For me, uncontrolled full-blown PGAD symptoms are so intensely*

distracting that they 'want' to destroy my capacity to function, to live a normal, outwardly directed life." Concomitantly, alterations of her micturition began. It felt like "*a block to pee*," she stated. She felt difficulty initiating micturition, a very slow urine stream, dysuria, incomplete emptying of her bladder, an increase in micturition frequency especially at night when she had nocturia three to four times, and strained urination. She also reported coincident symptoms of a symmetrical facial dystonia in the area of the zygomatic muscles. Medical evaluation, including an assessment of thyroid status, failed to detect a potential metabolic basis for her PGAD symptoms. Several therapeutic medical interventions failed to improve her symptoms during the subsequent 18 months, including valproic acid, phenylephrine, nortriptyline, baclofen, and quetiapine.

Two years after the initial occurrence of her persistent genital arousal, at the age of 50, she was evaluated at a sexual medicine clinic. To assess possible biological and/or psychological causes of her sexual health complaints, she underwent the standard sexual medicine diagnostic paradigm consisting of assessment of her complaints by validated questionnaires, interviews with a sexual medicine physician and a psychologist, physical examination, quantitative sensory testing, Duplex-Doppler-ultrasound, and blood tests. Psychological evaluation revealed some of the known PGAD-associated factors such as depression and anxiety, and ruled out other often-associated factors including obsessive–compulsive symptoms, panic attacks, and sexual victimization [7]. Physical examination, quantitative sensory testing, and Duplex-Doppler-ultrasound were performed, and some of the biological etiologies of PGAD such as arterial and venous vascular, and/or neurological pathologies, were ruled out. Her blood test results, however, revealed low values of DHEA, testosterone, estradiol, and progesterone, as well as elevated FSH and LH. (Table 1). She was diagnosed with PGAD secondary to SSRI withdrawal. The androgen deficiency was treated with dehydroepiandrosterone and testosterone. She elected not to undergo systemic estradiol treatment, but was placed on local vestibular and vaginal estradiol treatment. She reported that her orgasmic ability improved significantly, but her PGAD symptoms remained.

For the first time in her history of depression, she experienced suicidal thoughts and inability to function. "*Many things I cared about were neglected because of my PGAD.*" After lack of efficacy of several conservative, medical therapeutic options, and severe depressive symptoms, she was referred to a university-based Department of Psychiatry, and electroconvulsive therapy (ECT) was suggested as primary treatment for depression with suicidal ideation. At the time of her first ECT, her Hamilton Depression Rating Scale score was 26 and she was 52 years old.

Table 1 Patient's hormone blood results at first visit before hormonal therapy

	Value	Reference range	Reference range postmenopausal
TSH	1.55 mIU/mL	0.47–4.68	
LH	24 mIU/mL		5–52.3
FSH	49.7 mIU/mL		23–116.3
Prolactin	5.5 ng/mL		1.8–20.3
Estradiol (E2)	20 pg/mL		27–161
Progesterone	0.3 ng/mL		0.0–0.7
DHEA-S	42 μg/dL	45–320	
Total testosterone	8 ng/dL	20–76	
SHBG	35 nmol/L	6–112	
Calculated free testosterone	0.137 ng/dL	0.6–0.8	

The patient has been married to her current partner for almost 30 years and describes him as loving, caring, understanding, and very supportive of her in any situation. "*We had a wonderful sex life. I loved sex and felt fulfilled. PGAD ruined it.*" The stability and intimacy of their relationship, however, was never severely threatened by her sexual health complaints.

Post ECT

She had an acute course of six bilateral ECT. After the sixth ECT, the symptoms of depression and suicide had completely resolved. In addition, serendipitously, the symptoms of PGAD also disappeared completely. Her Hamilton Depression Rating Scale score decreased to 1. She was placed on low-dose paroxetine (10 mg) because it was known to be effective in abatement of her depressive symptoms, along with low-dose valproic acid (250 mg), and observed.

After experiencing a gradual relapse and return of depressive and suicidal symptoms as well as PGAD symptoms, she was started on maintenance ECT. Maintenance ECT consisted of one ECT every 2 weeks for a total of 3 months, followed by one ECT every 4 weeks and then one ECT every 5 weeks. Notably, her PGAD resolved after each ECT. Likewise, voiding symptoms immediately improved. Maintenance ECT was eventually spread out to one ECT per year. Her PGAD symptoms always returned gradually. It took weeks

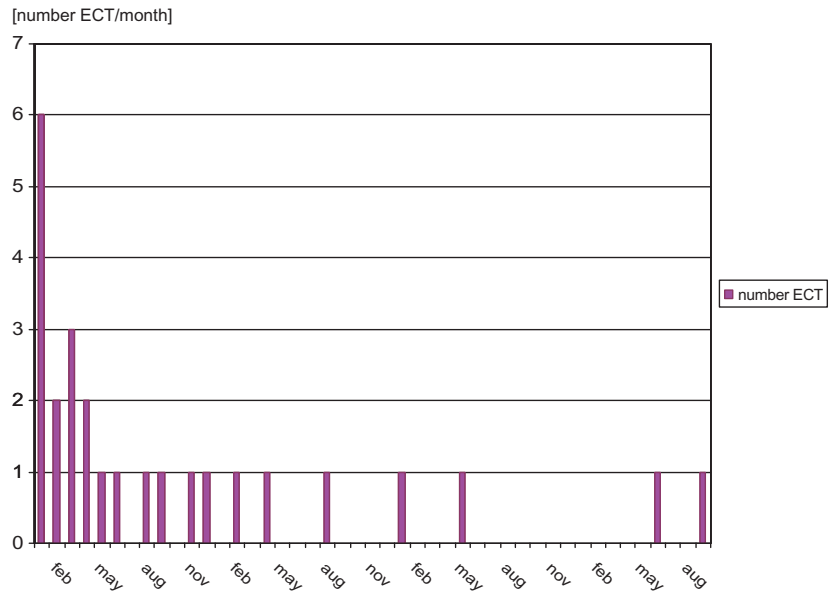

Figure 1 Time course of ECT. [number ECT/month]. Patient was treated with ECT over a period of 42 months. Each column represents 1 month. Starting with the left column, the month her ECT regime started, she received a total of six ECTs in that month. In the following month, she received two treatments, in the third month two ECTs, etc. The longer the treatment duration, the longer her remission time was.

for the intensity (starting around 20–30% of the intensity prior to the ECT) to increase to 60–70%, at which time she would schedule another ECT. Over a 4-year period, she has received a total of 30 ECT treatments. (Figure 1).

In the past 4 years, she felt a shift in PGAD symptom localization. The arousal feeling has relocated more to her perineal region, the anus, and rectum, while her vagina, vulva, and clitoris seemed to have become less involved. Because of the shift in localization, the triggers have also seemed to change. For example, one new trigger for the symptoms of persistent arousal associated with physical contact was wiping after defecation.

During her last relapse, the PGAD symptoms exacerbated quickly and it was hard for her to function. She had suicidal thoughts for the first time in years, and after not sleeping for two nights ("*I slept with an ice pack between my legs*") she underwent an emergency ECT. The day after the treatment, her PGAD symptoms abated over the day along with her suicidal thoughts. Her voiding difficulties persisted that time for a few days longer and then finally resolved. Her facial dystonia remains unchanged after the ECT, so she is taking baclofen, an agonist to the gamma-aminobutyric acid (GABA) B receptor that successfully diminishes her muscular discomfort.

"*This is powerful memory: the PGAD feeling is not normal pleasurable sexual arousal but far along the spectrum toward actual genital pain. This I experienced fully just before this last ECT as deep, central pelvic (vulvovaginal) pain, intense and persistent throbbing pain with a bizarre sexual edge. Now it is just gone*" (07/2008). After this last ECT, however, she experienced a "spooky" feeling "like a bad trip," which took several days to disappear. She has also experienced a partially reversible loss of geographic and personal memories common to ECT treatment that worried her because of her professional responsibilities. Currently, she is free of any PGAD feelings.

Discussion

The serendipitous ability of ECT to ameliorate symptoms of PGAD in this case study prompted us to further examine both the case and the potential effects of ECT that may be related to this amelioration. In turn, this information allows us to speculate about the physiological mechanisms that may underlie PGAD, a syndrome that currently is not well understood in terms of etiology.

Sexual arousal in women and men is under the control of both the autonomic and central nervous systems and is controlled by excitatory and inhibitory mechanisms [22]. Neurotransmitters like dopamine (DA), noradrenaline (NA), melanocortin, and oxytocin compose the excitatory system and act on the limbic system and hypothalamic regions [23]. The incertohypothalamic and mesolimbic DA systems appear to play a crucial role. Animal studies in female rats showed that during sexual arousal, dopamine is released in the nucleus accumbens (NAcc) [24,25], a region of the limbic system involved in the control of attention to

reward-related stimuli and dopamine agonists increase vaginal blood flow in female rabbits. Inhibition of sexual excitement and arousal in female rats is mediated by serotonin (5-hydroxytryptamine; 5-HT), cerebral opioid, and endocannabinoid activity in the frontal cortex, NAcc, lateral hypothalamus, mPOA and the ventral tegmental area [23,25,26]. The 5-HT and DA systems are interconnected and mutually inhibitory in terms of their neurotransmitter release [23,27]. However, 5-HT release can be associated both with a decrease and increase in DA release, depending on the location of innervation [23]. An intact DA system is required for the release of 5-HT in the NAcc [27]. We note that the melanocortin receptor agonist bremelanotide increases vaginal blood flow and sexual desire in women [28], and increases measures of sexual desire in female rats [29] by a selective stimulation of DA release in the mPOA [30]. DA activity in the mPOA is critical for genital blood flow in male rats [31], and is likely the mechanism by which bremelanotide stimulates genital blood flow in both women and men.

Various animal and human models suggest a cyclical dysregulation in DA transmission in bipolar disorder that mediates episodes of mania and melancholia. It is believed that there is an increase of DA transmission in the manic phase [33–37]. Accordingly, administration of levodopa, a DA precursor, leads to hypomanic episodes in bipolar patients [38]. Research has shown that central nervous system stimulants like cocaine (that increases extracellular concentrations of DA) also induce manic symptoms [39]. Berk et al. [33] discuss the potential role of DA as a switching agent in bipolar disorder. In the manic phase, it is believed that the hyperdopaminergic activity activates negative feedback mechanisms to decrease DA, and therefore, induce a hypodopaminergic state with resultant depression. It is known that there is a relationship between low DA activity in the NAcc and depression. Disruption of DA function within the NAcc of animals was shown to cause anhedonia, and several animal models demonstrated the involvement of limbic DA in depression, supporting the hypothesis of mesolimbic DA deficiency in depressed patients [40]. Depletion of synaptic DA concentration results in sleep disturbance, decreased locomotion, hypophagia, and reduced sexual activity in rats, symptoms that are similarly observed in depressed patients [33]. It is hypothesized that the depressive phase in bipolar disorder is characterized by a hypodopaminergic state [33].

Sudden withdrawal of selective serotonin-reuptake inhibitors, as occurs in sudden SSRI discontinuation syndrome, can be a possible pharmacological cause of PGAD [4,8,11]. Our patient developed feelings of PGAD after sudden withdrawal of paroxetine, which is the most potent inhibitor of serotonin-reuptake among SSRIs currently available. In fact, withdrawal from paroxetine is reported to cause the highest prevalence of a sudden SSRI discontinuation syndrome compared to other SSRIs, caused by its short half life (T1/2 = 20 hours), as well as its high potency [41]. A temporary deficiency of synaptic 5-HT with abrupt withdrawal of an SSRI is thought to be the cause. In addition to the reduced amount of synaptic 5-HT, 5-HT receptors are down-regulated and remain in their relatively hypoactive state for days to weeks after sudden SSRI withdrawal [41].

Considering that sexual excitement is mediated by either activation of excitation or loss of inhibition, we hypothesize that in this PGAD patient with bipolar disorder, there are two possible explanations for her developing PGAD. One factor might be the loss of inhibition of sexual excitement because of 5-HT deficiency, induced by the discontinuation of SSRI [25,26]. The second factor might be enhanced DA turnover in the mPOA or NAcc associated with her bipolar disorder leading to hyperstimulation of sexual excitement and arousal [32,33]. Consistent with the hypothesis of excess DA resulting in the development of PGAD, we recently described a case in which a woman suffering from lifelong PGAD noted a loss of PGAD symptoms while being treated with varenicline tartrate for smoking cessation. Varenicline is a partial agonist of $\alpha 2\beta 4$-nicotininc acetylcholine receptors (nAChRs), and acts to decrease extracellular DA levels in the NAcc, an area that is known to be crucial for attention to reward-related stimuli [42]. A similar effect may occur in the mPOA, which, as noted above, is known to control autonomic outflow and genital blood flow in female rats [43,44]. Another case supporting the link between PGAD and DA excess was recently described in which treatment with the DA receptor antagonist risperidone decreased genital engorgement in a postmenopausal woman suffering from PGAD [13]. Other authors hypothesize that in women being treated with SSRIs, elevated atrial natriuretic peptide (ANP) levels may lead to genial vasocongestion and edema via increased vascular endothelial permeability and vasodilatation, resulting in manifestation of PGAD [11]. Notable is the link between certain psychologi-

cal conditions and the development of PGAD. Leiblum et al. hypothesize that the symptoms of depression and anxiety facilitate the onset of persistent genital arousal, creating a vicious circle by endorsement of negative feelings that may maintain persistent genital arousal via psychological and physiological mechanism (e.g., increased autonomic nervous system activity, cognitive narrowing) [7].

Although lamotrigine, the medication the patient was placed on after discontinuation of the SSRI, acts as a sodium-channel blocker with anticonvulsive and mood-stabilization properties, it is impossible to know what influence it might have had on development of her PGAD symptoms, although it has been shown to decrease midbrain DA cell firing in rats by over 80% [45].

ECT is well established as an effective and safe first and second-line therapy for major depression and some other psychiatric diseases since the 1930s. Patients with cardiovascular, neurological, and hormonal conditions, or on certain medications, need careful evaluation and treatment [46]. Substantial co-morbidities associated with ECT are cognitive impairments, in particular, memory effects resulting in antegrade and retrograde amnesia, and verbal learning [47,48]. Repetitive ECT has provided reliable and long-lasting improvement of PGAD symptoms in our patient. What are the possible mechanisms underlying the effects of ECT in this patient? ECT is known to induce cerebral regional neurotransmitter changes after acute and chronic administration; however, the findings are not consistent. Some studies have reported either an increase or no change after ECT in major metabolites of DA, NA, or 5-HT [49,50], while others demonstrated reduced levels of these major metabolites following ECT [51]. Glue et al. [52] reported increased concentrations of NA and DA in the frontal cortex of rats, but unchanged DA content in the striatum, followed by a small rise in NA and a fall in DA in the NAcc. In several studies, it was hypothesized that in certain subgroups of humans, depending on environmental or other influencing factors [53], ECT reduced DA hyperactivity [54] as brain-derived neurotrophic factor (BDNF) was shown to be elevated [55,56]. BDNF is a neurotrophic factor expressed in the CNS and is crucial for the brain development, survival, and maintenance of neuronal functions and synaptic plasticity. It is hypothesized that hyperdopaminergic activity is suppressing the synthesis of BDNF and ECT might raise the BDNF level by reducing DA activity [55,56].

Another possible mechanism for the alleviation of PGAD symptoms after ECT treatment in our patient might be an amplification of inhibition of her sexual excitement and arousal. The capability of repeated ECT to increase both 5-HT neurotransmission and density of 5-HT receptors was shown in both animal and human studies [56,57]. It is also known that ECT increases the availability of tryptophan, the precursor for 5-HT, and can, therefore, increase central 5-HT activity [58]. Other potent inhibitors of sexual arousal are endogenous opioids. Repeated ECT is known to mediate an increase in the release of endogenous opioids [59]. Considering the propensity of 5-HT and opioid activity to suppress sexual excitement [23], those actions may have contributed to the positive outcome of ECT in our patient. Important to consider in this context is the role of opioids in analgesia and memory. Wasan et al. were able to demonstrate analgesic effects of ECT secondary to endogenous opioid release independent of its improvement of depression in patients with chronic pain syndrome and major depression [59]. Of interest in this context is a placebo-controlled study by Prudic et al., in which the authors were able to demonstrate the role of endogenous opioid systems in ECT-induced memory impairment [60]. It might be speculated that the increase in endogenous opioids secondary to ECT ameliorated PGAD symptoms in our patient by acting on three different systems known to be influenced by opioids: (i) suppression of sexual excitement; (ii) enhancement of the analgetic mechanism; and (iii) alteration of cognitive function/memory.

The relationship between lower urinary tract symptoms, as experienced by our patient, and PGAD, is not clear, but there is growing anecdotal and scientific evidence for a connection between feelings of micturition urgency and persistent genital arousal as recently described by Waldinger and colleagues [16]. Notably he describes an intriguing high prevalence of restless leg syndrome (RLS) in women diagnosed with PGAD. Our patient has been affected by RLS since her 30's, treating it successfully with magnesium. Our findings support Waldinger's hypothesis of PGAD being part of a clustered disease entity with a common pathogenesis. It is likely that the links between RLS, PGAD and micturition urgency is through a high tone pelvic floor dysfunction.

Since repetitive ECT treatment reduced PGAD symptoms in this patient, we hypothesize that

lowering hyperstimulated central DA and increasing inhibiting mediators like 5-HT and/or endogenous opioids resulted in restoration of a balance of stimulating and inhibiting mediators and, therefore, more normal sexual arousal.

Conclusion

In conclusion, we report the case of a woman with PGAD and bipolar disorder who underwent ECT for treatment of depression and suicidal ideation. During treatment, her PGAD symptoms serendipitously resolved. To date she has received 30 ECT treatments over a 4-year period. We review the potential explanations for the positive therapeutic effect of ECT on PGAD. We hypothesize that: (i) the bipolar disorder led to central hyperactive dopamine release, which is an important component in the pathophysiology of PGAD in this patient; (ii) central 5-HT deficiency associated with an SSRI discontinuation syndrome resulted in a lack of inhibition of the sexual excitement; (iii) ECT resulted in lowering of this hyperstimulated central dopamine release; and (iv) ECT led to an increase in sexual inhibition by stimulating 5-HT activity. As in all interventions in humans, treatment options associated with the least risk, cost and irreversibility should be considered first line treatments. Second-and third-line therapies should only be utilized based on individual risk-benefit considerations, therefore, ECT might be utilized as a third-line treatment in women with refractory PGAD and suicidal tendency. Further research is needed to understand the impact of ECT in women with PGAD.

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