

## Case report Ενδιαφέρουσα περίπτωση

### Zolpidem related persistent genital arousal disorder: An interesting case

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The present paper is describing a case of persistent genital arousal disorder that developed to a 55-year-old woman, shortly after the initiation of zolpidem. Persistent genital arousal disorder (PGAD) is a clinical entity that appears with a relatively low frequency in women, and is characterized by persistent or recurrent, unwanted and bothersome feelings of genital arousal, which often do not resolve with orgasm and are not associated with sexual desire (sexual interest, thoughts or fantasies). Women who experience PGAD often have feelings of shame, guilt and distress. Although its exact etiology remains unclear, various etiological factors have been proposed, central or peripheral, which may be psychological, vascular, dietary, pharmacological or neurological. Additionally, its presence has been associated to restless legs syndrome and overactive bladder syndrome. Likewise, multiple therapeutic interventions have been proposed and tried in patients with PGAD, either pharmacological (SSRIs, SNRIs, antiandrogens, benzodiazepines, antipsychotics, anticonvulsive agents) or other (ECT, physiotherapy, psychotherapy, nerve stimulation). Zolpidem is a non-benzodiazepine indirect GABA A receptor agonist, which has lately been used as a therapeutic agent for PGAD in some cases. Nevertheless, in our patient, receiving zolpidem for insomnia seemed to be timely connected to the onset of PGAD symptomatology. The aim of the present paper is to highlight the need for more research into the possible factors that may contribute to PGAD.

**Key words:** Persistent genital arousal disorder, persistent sexual arousal syndrome, sexual side-effects, drug side-effects related to sexual function, zolpidem.

#### Introduction

Persistent genital arousal disorder (PGAD), also known as persistent sexual arousal syndrome (PSAS), is a relatively rare condition that affects

women and is characterized by unremitting genital arousal in the absence of conscious feelings of sexual desire.<sup>1,2</sup> More specifically, PGAD may include all or some of the following symptoms: spontaneous, intrusive, and unwanted signs of

physiologic sexual arousal (e.g. genital fullness and sensitivity, tingling, throbbing, pulsating), which do not resolve on their own or even after orgasmic experience and may persist for hours or days, in the absence of sexual interest and desire and unrelated to subjective feelings of sexual arousal (the awareness of subjective arousal is typically, but not invariably, unpleasant), triggered by sexual or non-sexual stimuli, while causing at least moderate distress since they are considered unwanted and intrusive.<sup>3,4</sup>

It is still unclear whether its etiology is central or peripheral, since due to its low frequency most of the literature on the topic is based on case reports, suggesting multiple etiologies as well as therapeutic interventions.<sup>5-9</sup> More specifically, regarding possible etiologies, psychological entities (e.g. history of sexual abuse, comorbidity with depression or anxiety), vascular changes (e.g. pelvic congestion syndrome), dietary explanations (such as high intake of soy products), meningeal cysts (e.g. Tarlov cysts), central (e.g. epilepsy) or peripheral neurologic causes (e.g. small-fiber neuropathy theory), relationship with restless legs syndrome, as well as several pharmacologic agents (their initiation as well as their cessation), have been discussed by several authors in the literature.<sup>5,6,10,11</sup> In any case, most commonly, PGAD is a distressing condition, which may even lead to social isolation or suicidal ideation.<sup>8</sup>

Multiple therapeutic interventions have been proposed, but since no specific cause identification exists, similarly no therapeutic algorithm exists. Nevertheless, multiple treatments have been reported in the literature, such as electroconvulsive therapy, pelvic floor physiotherapy, nerve stimulation, psychotherapeutic interventions, as well as various oral medications such as SSRIs or SNRIs, antiandrogens (e.g. leuprolide), anticonvulsive agents (e.g. pregabalin), benzodiazepines (e.g. clonazepam) and antipsychotics (e.g. risperidone, quetiapine).<sup>5-8,12</sup>

Zolpidem is a non-benzodiazepine indirect GABA A receptor agonist. Its sedative-hypnotic and anticonvulsive activities seem to be due to its action on  $\alpha 1$ -GABA A receptors and not on the

rest of GABA A receptors ( $\alpha 2$  or  $\alpha 3$ ).<sup>13</sup> There is no reported connection so far between zolpidem and PGAD, except for the fact that it has recently been used in low doses (<2.5 mg) as a therapeutic agent,<sup>14-17</sup> perhaps by blocking dopamine transmission (dopamine neurons are inhibited by GABA neurons) and thus the inhibition of serotonin release, allowing serotonin to increase and reducing PGAD symptoms.<sup>15-17</sup>

Here we discuss a case of a woman presenting with symptoms of persistent genital arousal disorder, after the initiation of zolpidem, which was prescribed for the treatment of insomnia.

### Case history (table 1)

The patient is a 55-year-old Caucasian female, mother of two children (31-year-old male and 29-year-old female, both born by natural labors) and married for 32 years, while she is working as a cleaning lady for the last 27 years for a private cleaning company. Regarding her medical history, she has never had any major operation, or had taken any medication for a long period of time –neither in the past nor during the period of her assessment– for any organic or psychiatric cause.

Three months before presenting to Eginition hospital, she reported visiting her internist, because she was experiencing gradual worsening of her sleeping habits (less sleeping hours, followed by fatigue during the daytime). This condition kept getting worse, until 15 days before her visit to Eginition hospital when she felt that she could hardly sleep for more than 3 or 4 hours in the night, sometimes intermittent sleep, while some of the nights she felt like she had hardly slept at all. Additionally, she recalls poor quality and amount of sleep, and fatigue. She does not recall any stressful event or condition preceding this period. Then she began receiving valerian for 15 days with poor response and –following her internist's advice– she also began receiving zolpidem 10 mg before bedtime. Poor response is reported during the first two nights and only during the third night did she manage to sleep for some hours. At the same time, at the third day of zolpidem intake, she reports feelings of tension and mild anxiety,

**Table 1.** The course of symptoms of PGAD and the applied treatments, before and after the visit in the Sexual Disorders Treatment Unit of Eginition Hospital.

3 months before	15 days before	7 days before	1st visit (Eginition hospital)	1 week after (2nd visit, private practice psychiatrist)	3 weeks after	4 weeks after	2 months after
Insomnia, fatigue	Worsening of insomnia Valerian initiation but no sleep improvement	Zolpidem initiation PGAD after the 3rd day, zolpidem cessation but PGAD remains	Quetiapine initiation (50 mg, twice daily) PGAD stops	Quetiapine cessation due to side effects and olanzapine initiation, 5 mg before bedtime	No changes No PGAD	↓Olanzapine (2.5 mg before bedtime) No PGAD	No changes No PGAD

along with symptoms of persistent genital arousal disorder. More specifically, she describes genital swelling, pulsating, tingling and sensitivity, without nipple fullness or swelling that did not subside on their own. Genital arousal did not resolve with orgasmic experience, was unrelated to external stimuli or subjective sense of arousal, was triggered by non-sexual stimuli and was described as unwanted and intrusive, causing important degree of distress.

PGAD symptomatology lasted for a week, even though zolpidem intake was ceased immediately. At the end of this week, she visited the emergency outpatient clinic of Eginition hospital and was directly referred to the special outpatient clinic of psychosexual disorders. Psychiatric evaluation included clinical assessment and administration of the Mini International Neuropsychiatric Interview.<sup>18</sup> She did not meet criteria for any psychiatric disorder, neither during the time of the evaluation, nor in the past and she did not reveal any sexual trauma. Her personality traits did not meet the criteria for any personality disorder. Regarding her sexual function during this period and in the past, it never seemed to be problematic or dysfunctional in any domain. At the same time, she underwent a gynecologic exam, along with a basic laboratory investigation, which did not reveal anything abnormal. After the clinical evaluation, it was explained to her that her symptoms could be attributed to an identified disorder named PGAD. Since atypical antipsychotics have been discussed in the literature and have been used as therapeutic agents for PGAD,<sup>5,6</sup> the patient was advised to start receiving quetiapine 25 mg twice a day and was advised to gradually increase the daily dose to 100 mg. Remission of the above-mentioned symptoms took place when quetiapine was increased to 50 mg twice a day. After a week of the cessation of the symptoms, she visited a psychiatrist in private practice, who stopped quetiapine due to its sedative action during the day, which the patient could not tolerate. Alternatively, he advised her to receive olanzapine 5 mg daily, before bedtime. The symptoms of PGAD never appeared again, and the patient continuously re-

ceives olanzapine, now 2.5 mg before bedtime, reporting satisfying sleep duration and quality. Provided that she remains asymptomatic, olanzapine will eventually be withdrawn.

## Discussion

The etiology of PGAD remains enigmatic. Nevertheless, as mentioned above, psychological, vascular, dietary, neurological, as well as pharmacological factors have been discussed by the literature as possible contributors to this disorder. Among other drugs, the use or withdrawal of antidepressants has been connected to the onset of persistent genital arousal symptomatology. Regarding PGAD induced after SSRI antidepressant withdrawal, possible mechanisms are either local vulval vasodilation<sup>19</sup> or the return to baseline sexual desire and genital arousal, which were suppressed during SSRI medication.<sup>20</sup> On the other hand, antidepressant initiation and particularly nefazodone, citalopram, bupropion, paroxetine, venlafaxine, trazodone and fluoxetine have been reported to trigger PGAD symptomatology.<sup>5,6,21-23</sup> Proposed mechanisms include increased clitoral volume and vasoengorgement (especially with trazodone),<sup>23</sup> increased angiogenesis that follows antidepressant medication,<sup>21</sup> but still the exact mechanism that antidepressants may trigger PGAD remains unclear.

Could the initiation of zolpidem play a role in the PGAD onset in our patient, since there was a timely connection between initiation and PGAD onset? Recent case reports<sup>14-17</sup> have proposed zolpidem as a therapeutic agent for PGAD. In these cases, zolpidem was administered in low doses (0.5–2.5 mg, up to 4 times daily) either alone or along with other drugs (tramadol) and seemed to reduce PGAD symptomatology. The proposed mechanism was decreasing the inhibition of serotonin release by blocking dopamine transmission.<sup>15-17</sup> On the other hand, as noted above, the increase of serotonin has been associated with the trigger of PGAD symptomatology, probably due to vasoengorgement or angiogenesis, induced by antidepressants.<sup>5,6,21,23</sup> It is important to note that the patient has also received valerian for 15 days, at the same time that

she initiated zolpidem. Valerian has a mechanism of action similar to that of benzodiazepines, since it has an affinity for GABA A receptors, with a high amount of GABA present in the valerian extract itself.<sup>24</sup> Therefore, the dose of GABA A receptor agonist that our patient received, might exceed 10 mg per day that she initially received through zolpidem.

Regarding pharmacokinetics, the drug-metabolizing enzymes cytochrome P450 3A4 (CYP3A4), 2D6 (CYP2D6) and 1A2 (CYP1A2) seem to be mainly involved in the metabolism of zolpidem.<sup>25</sup> *In vitro* studies assessing valerianic acid have not revealed significant effects upon CYP3A4 or other P450 isoforms.<sup>26</sup> However, valerian *in vivo* may moderately increase drug C<sub>max</sub> (of the drug which is metabolized using the CYP3A4 isoform), when typical doses are used, although this increase is considered clinically insignificant.<sup>27</sup> Interestingly enough, endocrine factors seem to also be associated with CYP3A4 metabolism, since low plasma concentrations of free testosterone may contribute to lower CYP3A4 activity, and therefore explain up to 50% higher zolpidem plasma levels in women.<sup>28</sup> Therefore, in the present case, although of small relevance, the gender, as well as pharmacokinetics of zolpidem and valerian may have also been slightly involved in PGAD symptomatology.

The present paper discusses the observations of a single case only and obviously the results cannot be generalized. Additionally, we must point out the following limitations: neither a baseline hormone profile nor an imaging examination took place when the patient first presented with PGAD symptoms, which are proposed by the literature to be included in the baseline assessment.<sup>5,6</sup> Therefore, our observations should be interpreted with caution. This is the first case to imply that there could be a connection between high doses of zolpidem or when zolpidem is combined with another GABA A receptor agonist and PGAD symptom onset. More research is needed to verify if there is such an action and identify the probable underlying mechanism. This could lead to a better insight into possible factors that are associated with the trigger of this interesting disorder.

# Σχετιζόμενη με τη ζολπιδέμη διαταραχή επίμονης σεξουαλικής διέγερσης: Μια ενδιαφέρουσα περίπτωση

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Σκοπός της παρούσας εργασίας είναι η περιγραφή μιας περίπτωσης επίμονης γεννητικής σεξουαλικής διέγερσης που παρουσιάστηκε σε μία γυναίκα 55 ετών, ύστερα από την έναρξη λήψης ζολπιδέμης. Η διαταραχή επίμονης σεξουαλικής διέγερσης (ΔΕΣΔ) είναι μια κλινική οντότητα που εμφανίζεται με χαμηλή συχνότητα στις γυναίκες, και χαρακτηρίζεται από επίμονα ή επαναλαμβανόμενα, ανεπιθύμητα και ενοχλητικά ερεθίσματα γεννητικής διέγερσης, τα οποία συνήθως δεν υποχωρούν με τον οργασμό και δεν σχετίζονται με σεξουαλική επιθυμία (σεξουαλικό ενδιαφέρον, σκέψεις ή φαντασιώσεις). Οι γυναίκες που παρουσιάζουν ΔΕΣΔ μπορεί να έχουν αισθήματα ντροπής, ενοχής ή δυσφορίας. Παρά το γεγονός ότι η ακριβής αιτιολογία δεν είναι ξεκάθαρη, πολλοί αιτιολογικοί παράγοντες έχουν προταθεί, κεντρικοί ή περιφερικοί, και μπορεί να είναι ψυχολογικοί, αγγειακοί, διατροφικοί, φαρμακολογικοί ή νευρολογικοί. Επιπρόσθετα, η παρουσία του έχει συσχετισθεί με το σύνδρομο ανήσυχων ποδιών και το σύνδρομο υπερδραστήριας κύστης. Αντίστοιχα, έχουν προταθεί και δοκιμαστεί πολλές θεραπευτικές παρεμβάσεις, είτε φαρμακευτικές (SSRIs, SNRIs, αντιανδρογόνα, βενζοδιαζεπίνες, αντιψυχωσικά, σπασμολυτικοί παράγοντες) είτε άλλες (ECT, φυσικοθεραπεία, ψυχοθεραπεία, νευροδιέγερση). Η ζολπιδέμη είναι ένας έμμεσος μη-βενζοδιαζεπινικός GABA A αγωνιστής, ο οποίος έχει πρόσφατα χρησιμοποιηθεί και για τη θεραπεία της ΔΕΣΔ. Παρόλ' αυτά, η λήψη ζολπιδέμης από την ασθενή μας για την αντιμετώπιση αϋπνίας, φάνηκε να σχετίζεται χρονικά με την έναρξη συμπτωματολογίας ΔΕΣΔ. Σκοπός του παρόντος άρθρου είναι η ανάδειξη της ανάγκης διεξαγωγής περαιτέρω μελετών προκειμένου να αναδειχθούν οι παράγοντες που σχετίζονται με τη ΔΕΣΔ.

**Λέξεις ευρετηρίου:** Διαταραχή επίμονης σεξουαλικής διέγερσης, σύνδρομο επίμονης σεξουαλικής διέγερσης, σεξουαλικές παρενέργειες, παρενέργειες φαρμάκων σχετιζόμενες με τη σεξουαλική λειτουργία, ζολπιδέμη.

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