

# Anorgasmia during pregabalin add-on therapy for partial seizures

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**ABSTRACT** – Anorgasmia is the inability to reach orgasm during sexual intercourse, and, although it is believed that around 90% of anorgasmia problems are related to psychological issues, the use of serotonergic drugs, including antidepressants and atypical antipsychotics, is a common cause of situational anorgasmia. Pregabalin is a new antiepileptic drug, structurally related to gabapentin, and commonly used as adjunctive therapy for partial epilepsy and treatment of neuropathic pain in adults. Herein, we describe three men with epilepsy, who experienced severe anorgasmia after pregabalin add-on treatment.

**Key words:** anorgasmia, pregabalin, sexual dysfunction

Anorgasmia is the inability to reach orgasm during sexual intercourse, even with appropriate stimulation. In males, the condition is often related to delayed ejaculation, typically causing sexual frustration. It is estimated that around 90% of anorgasmia problems are related to psychological issues, although sexual dysfunction (SD) can also be caused by different medical problems, such as diabetic neuropathy, pelvic trauma, multiple sclerosis, spinal cord injury, complications from genital surgery, and hormonal imbalances, or be iatrogenic in origin (Rowland *et al.*, 2010). Although the relationship between older antiepileptic drugs (AEDs) and SD has long been known (Calabrò

*et al.*, 2011), the sexual side effects of new AEDs (table 1), such as erectile dysfunction (ED) and anorgasmia, have been rarely described (Calabrò, 2011a). In particular, a few reports suggest that new AEDs, including topiramate (Holtkamp *et al.*, 2005; Calabrò *et al.*, 2009; Coebergh and Waldinger, 2012), oxcarbazepine (OXC) (Calabrò *et al.*, 2010), levotiracetam (LEV) (Calabrò and Bramanti, 2013), gabapentin (GBP) (Clark and Elliott, 1999; Kaufman and Struck, 2011), and pregabalin (PGB) (Hitiris *et al.*, 2006) may cause SD through complex and poorly understood pathomechanisms, possibly involving, beyond sexual hormonal changes, an imbalance

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**Table 1.** AED-related sexual dysfunction.

Sexual side effects	
<b>Old AEDs</b>	
enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital)	hyposexuality, erectile dysfunction, delayed ejaculation, anorgasmia
valproic acid	retrograde ejaculation
<b>New AEDs</b>	
topiramate	erectile dysfunction, anorgasmia
oxcarbazepine	anorgasmia, ejaculatory failure, retrograde ejaculation
lamotrigine	hypersexuality
levetiracetam	loss of libido, hypersexuality
zonisamide	erectile dysfunction
gabapentin	anorgasmia
pregabalin	erectile dysfunction, delayed ejaculation, anorgasmia

in central nervous system neurotransmission with regard to dopamine and serotonin rate. Herein, we describe three male individuals with epilepsy presenting with clear drug-related anorgasmia after pregabalin add-on treatment.

## Case studies

### Patient 1

A healthy 35-year-old man had partial seizures with secondary generalisation since the age of 10 years. Family history was unremarkable, however, he had a history of febrile convulsions. General and neurological examinations were normal as well neuropsychological testing, while brain MRI showed left mesial temporal sclerosis. Interictal EEG showed frequent focal epileptiform discharges from the left fronto-temporal region. His seizures remained refractory despite treatment with OXC (up to 1,800/day) and valproate (up to 2,000/day). After PGB was gradually titrated at a dosage of 300 mg/day, he progressively started complaining of delayed ejaculation and anorgasmia, which caused severe sexual dissatisfaction. His sexual history was unremarkable and he had never experienced similar SD before. He denied using other medications, alcohol, or substances of abuse. Moreover, urological evaluation and blood sexual hormonal profile, as well as psychiatric examination, were within the normal range. Thus, PGB was gradually withdrawn and lacosamide introduced up to 400 mg/day with com-

plete restoration of the patient's sexual performance. At two years of follow-up, sporadic partial seizures without SD were reported.

### Patient 2

A 24-year-old man was evaluated in our epilepsy centre following episodes of complex partial seizures without generalisation. Family history was positive for epilepsy (his uncle and one of his cousins were affected by undetermined epilepsy), whereas personal history was unremarkable. EEG showed interictal sharp waves over the right anterior temporal region. Neurological examination and brain MRI were normal. Treatment with carbamazepine was started and gradually titrated up to 1,800/day with moderate seizure control. Thus, since the patient had a concomitant generalised anxiety disorder, PGB was introduced and seizures disappeared when a dosage of 300 mg/day was reached. Nonetheless, the patient progressively complained of severe anorgasmia, followed by loss of libido and, sometimes, secondary erectile dysfunction. Medical and sexual history, as well as general, psychiatric and urological examinations, were normal. The patient was not taking any other medication, alcohol or illicit drugs. Haematological tests, including a complete sexual hormonal panel, as well as urological examination, were within the normal range. Thus, PGB was gradually withdrawn and LEV introduced up to 3,000 mg/day with no other reported seizures or sexual problems at 12 months of follow-up.

### Patient 3

Following a brain trauma, an otherwise healthy 28-year-old young man experienced several complex partial seizures, sometimes followed by secondary generalisation. Neurological examination, as well as brain MRI, were normal. EEG revealed moderate slow activity and epileptiform discharges over the right fronto-temporal region. The patient was started on OXC up to 1,600/day, with improvement in his seizure control (2-4 seizures/month). However, as PGB was added, although the patient was nearly seizure-free, he progressively started to complain of anorgasmia, which caused distress within the relationship and high levels of sexual dissatisfaction. Sexual history, psychological and urological evaluation, as well as blood tests (including hormonal levels), were unremarkable. Thus, PGB was gradually withdrawn and LEV introduced, up to 2,000 mg/day, with a remarkable improvement in seizure control and complete restoration of the patient's sexual performance at 18 months of follow-up.

### Discussion

Although the use of serotonergic drugs, including antidepressants and atypical antipsychotics, is a common cause of situational anorgasmia in both men and women, anorgasmia related to new AEDs has been rarely reported (Serretti and Chiesa, 2011). Conversely, emerging evidence shows that GBP-related anorgasmia could be an overlooked and under-reported problem (Calabrò, 2011b). Since GBP and PGB are similar with regards to structure and mechanism of action, it is also possible that PGB-induced SD may be underestimated.

To this end, Hitiris *et al.* (2006) reported the cases of five men who experienced mild-to-moderate erectile dysfunction for the first time when treated with the new antiepileptic drug PGB as add-on therapy. Notably, all patients were taking part in randomised clinical trials or open-label studies with the drug. Indeed, in the placebo-controlled trials of PGB in epilepsy patients, erectile dysfunction was reported by 11 (3.0%) men taking PGB and three (1.9%) with placebo. Moreover, the same authors, in their interesting study, showed that erectile dysfunction was reported by 71 of a total of 2,428 male patients (around 3%) who received the new AED across all PGB placebo-controlled trials for all indications, whereas only 8 of 1,099 male patients (0.7%) who received placebo experienced erectile dysfunction. Sexual dysfunction was not reported by female patients with epilepsy receiving treatment with PGB during the epilepsy trials. Interestingly, we have recently described a 35-year-old

man, affected by post-traumatic epilepsy, who experienced severe delayed ejaculation, sometimes with anorgasmia, secondary to PGB monotherapy.

Our patients presented with anorgasmia, very likely, as a direct effect of PGB add-on treatment. Indeed, the onset and termination of anorgasmia was closely related in time to the exposure to PGB, moreover, all other potential causes of sexual dysfunction were ruled out.

PGB is a new AED licensed in Europe and US as adjunctive therapy for partial epilepsy and treatment for neuropathic pain in adults. It is structurally related to GBP and both drugs bind to the  $\alpha_2\delta$  subunit of voltage-dependent calcium channels and, thereby, modulate the release of a range of neurotransmitters (Sills, 2006). Orgasm refers to the subjective experience of pleasure associated with somatic phenomena occurring during ejaculation, such as the rhythmic contractions of the genital and reproductive organs, cardiovascular and respiratory changes, and the release of sexual tension. Interestingly, orgasm is achieved only in the expulsion phase of the ejaculation process when both sympathetic and parasympathetic cerebral tension-releasing processes occur together, due to the multifaceted neural networks between spinal and supraspinal (particularly hypothalamic) centres (Argiolas and Melis, 2003; Rowland *et al.*, 2010). Human sexual response involves a complex interplay between many neurotransmitters including dopamine, serotonin, norepinephrine, acetylcholine,  $\gamma$ -aminobutyric acid, oxytocin, opioids, and nitric oxide, as well as neuromodulators. In particular, whereas dopamine appears to promote sexual desire and arousal, serotonin has an inhibitory effect on sexuality, especially on orgasm (Argiolas and Melis, 2003). Because of the wide distribution of calcium channels in the central and peripheral nervous systems, it is likely that they control neuronal, and thus sexual, function at many sites. Therefore, the inhibition of calcium currents induced by PGB (as well as by GBP) may lead to a decrease in neurotransmitter release and attenuation of postsynaptic excitability. Since excitatory transmission is necessary for sexual arousal and, consequently, for achieving orgasm, it is possible that PGB may exert a negative effect on sexuality by reducing central nervous system excitatory transmission (*via* calcium channel inhibition) and by unbalancing the dopamine/serotonin ratio.

In conclusion, given that individuals with epilepsy may not spontaneously complain of sexual dysfunction, physicians should always discuss sexual issues with their patients since sexual dysfunction, including anorgasmia, related to AEDs may continue to be an overlooked and underestimated problem, even with new AEDs. □

## Disclosures.

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