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CASE REPORT

Pregabalin-induced sexual disinhibition

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Introduction. Sexual side effects have rarely been reported secondary to treatment with Pregabalin, a structural analogue of the inhibitory neurotransmitter gamma amino butyric acid (GABA).

Method. We present the case of AB, a 27-year-old single man with a diagnosis of recurrent depressive disorder who was prescribed pregabalin to alleviate the significant anxiety symptoms he was experiencing.

Results. A significant amelioration in anxiety symptoms was attained; however, he developed the adverse effects of acute sexual disinhibition and increased libido. These adverse effects were temporally related to treatment with pregabalin and reduced with dose reduction of this agent.

Conclusions. To date, limited published data are available relating such a reaction to pregabalin. A greater clinical recognition of this association between pregabalin and sexual disinhibition, would allow clinicians to intervene at an earlier stage of this adverse effect and potentially as in this case, management may only require dose reduction rather than treatment discontinuation.

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Key words: Pregabalin, recurrent depressive disorder, sexual disinhibition.

Introduction

Pregabalin, a structural analogue of the inhibitory neurotransmitter γ amino butyric acid (GABA) is approved for the treatment of epilepsy, neuropathic pain and generalised anxiety disorder. Whilst sexual side effects have rarely been reported secondary to treatment with this agent, a number of case reports have described either increased libido or reduced sexual dysfunction secondary to pregabalin treatment (Jerome, 2007; Oulis *et al*. 2008; Bucur & Jeczmien, 2011; Osman & Casey, 2014). We describe here the case of a 27-year-old single man with a diagnosis of recurrent depressive disorder and comorbid anxiety who developed significant sexual disinhibition secondary to treatment with pregabalin.

Case

In 2015, AB, a 27-year-old single unemployed man with a diagnosis of recurrent depressive disorder was admitted as a voluntary patient to the Department of Psychiatry in University Hospital Galway for management of on-going and deteriorating depressive symptoms in the context of his second depressive episode. His symptoms had been present for a 6-month period, occurred without an identifiable precipitant and despite a number of alterations in psychotropic medications as an outpatient (as detailed below); no amelioration in depressive symptomotology was noted. Symptoms of anxiety were not initially present but both cognitive and physical symptoms became evident ~2 months after the onset of depressive symptomotology and these continued to deteriorate until his hospital admission. On admission, he fulfilled International Classification of Diseases (ICD)-10 diagnostic criteria for a severe depressive episode without psychosis. Symptoms included a pervasive low mood, anhedonia, fatigue, diurnal mood variation (morning exacerbation of low mood), amotivation, reduced concentration, initial insomnia, early morning wakening poor self-esteem and poor self confidence. He experienced decreased libido but no sexual dysfunction. Whilst he experienced fleeting thoughts that life was not worth living, he had no passive death wish and denied suicidal ideation or intent. In addition to the above symptoms, he also experienced prominent anxiety including both cognitive symptoms of worry and several physical symptoms including muscular tension in his head, neck and back, nausea and abdominal churning, diaphoresis, tremulousness, and shortness of breath. AB described feeling persistently sad and frustrated by his on-going symptomotology. He described his symptoms of fatigue, insomnia and 'nervousness' as most problematic.

His medications on admission consisted of escitalopram 20 mg mane and quetiapine 300 mg nocte (to

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relieve anxiety and insomnia). Treatment trials prior to admission of the antidepressants venlafaxine, mirtazapine, sertraline and agomelatine all at maximum therapeutic or close to maximum therapeutic dosages were associated with no clinical benefit of note. In addition, trials of olanzapine and clonazepam at low-to-medium dosages had minimal effects on reducing his anxiety symptoms.

Prior to the index presentation, AB had one severe depressive episode in 2012, which required psychiatric inpatient hospital admission, with his mood successfully treated with the antidepressant venlafaxine XL at a dose of 150 mg daily. Anxiety symptoms were not previously present during periods of euthymia or this previous depressive episode. He has no previous history of self-harm. He has no past history of experiencing any significant medical conditions, sexual disorders and has no history of harmful use or dependence on alcohol or engaging in using any psycho-active substance. A first-degree relative has a history of recurrent depressive disorder, without significant anxiety symptoms and has not required any period of inpatient treatment to date.

With regards to his personal and social history, the patient was a full-term normal delivery, attained all developmental milestones appropriately and denied any early childhood adversity. He performed well academically and has attended third- and fourth-level education. He did not have a diagnosis and did not fulfil ICD-10 criteria for a personality disorder.

He has a close circle of friends but due to his mental health difficulties had little contact with them for several months and had left his most recent employment due to mood disturbance. He had not engaged in a sexual relationship for 3 years (although he had some brief non-sexual relationships) and prior to this admission described a low libido for 4–5 months (associated with somatic features of depressive episodes rather than secondary to psychotropic agents). He did not experience sexual dysfunction in the last 4–5 months in that he was able to have erections and ejaculate, however, described reduced number of sexual fantasies.

Organic causes of mood disorders were excluded by routine haematological screening including testing for thyroid function. A toxicology screen on admission was negative for alcohol and a range of psycho-active substances. One week following inpatient admission, due to his on-going anxiety symptoms, he was commenced on pregabalin 50 mg BD, which was increased to 100 mg BD after 10 days. Within 2–3 days on this increased dosage, amelioration in anxiety symptoms was evident, both objectively and subjectively. However, acute behavioural changes became evident, including the use of explicit sexual language to mental health staff and patients, with this also observed by staff when he was engaged in telephone conversations with family and friends. He was noted to discuss topics of a sexual nature including preferences regarding sexual relations (e.g. that he would like to engage in sexual relations with actresses or presenters on television) with both male and female patients. AB was noted to make comments towards female patients and towards staff regarding their appearance and ask them inappropriate questions about their relationship history. He admitted to masturbating frequently (e.g. three to four times per day), albeit always in a private location, which was out of character for him, even prior to the onset of any depressive symptoms. He was not fully clear if he had a compulsive urge to engage in masturbation. He denied elated mood and did not present with other putative hypomanic or manic symptoms including reduced sleep pattern, pressure of speech, increased flow of thoughts, grandiose ideation. AB acknowledged that he was using explicit sexual language that would not be unusual for him, albeit did not appear significantly concerned by this behavioural change. Collateral history from family and friends corroborated this presentation and objectively an elated mood or other features of elated mood were not present including other reckless behaviours, abnormalities in thought form, stream or content.

Three weeks into his inpatient admission, his mood objectively was euthymic and subjectively he described his mood as 'good' with improvements in a range of biological symptoms including sleep, energy levels and concentration and cognitive symptoms including self-esteem.

Due to the presence of these sexual side effects, and their temporal relationship with pregabalin treatment, the dose of pregabalin was reduced to 50 mg BD (1 week after commencement of the 100 mg BD dosage) with a gradual improvement but not disappearance in sexual disinhibition noted in that he was observed to engage in less use of explicit sexual language, although such language did remain, and he admitted to on-going 'excessive' masturbation as described above. His other psychotropic treatments (escitalopram 20 mg mane and quetiapine 300 mg nocte) continued to be prescribed without alteration in dose. No additional agents such as benzodiazepines were prescribed throughout AB's admission.

Following discharge from hospital, AB continued to report an increased sexual drive and increased libido and engaged in numerous sexual relationships, which were significantly out of character for him (including when in a euthymic state). He also admitted to watching pornography on one occasion, which again was out of character for him. His pregabalin prescription was further reduced to his current dose of 25 mg BD 3 weeks

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post-discharge, which resulted in a significant reduction in sexual disinhibition (e.g. less use of sexual language, and less engagement in sexual relationships with females he was not familiar with) but continued relief from anxiety symptoms. He has remained euthymic following discharge from hospital. Both AB and his family report no further sexual disinhibition over the last 6 months since his dose of pregabalin was reduced to 25 mg BD. His sexual disinhibition caused significant concern to family and friends prior to treatment reduction and amelioration in this adverse effect. AB stated that this sexual disinhibition was of concern to him, and had a deleterious effect on relationships with some family members and friends, who were embarrassed by his behaviours. He believed that some sexual thoughts at that time were quite intrusive and occurred often without any warning. Whilst initially not distressed by his increased sexual disinhibition, he stated that 'it was not me' and would not like to experience such symptoms again. His treating mental health team on his most recent review noted his mood to be euthymic, with no evidence of significant anxiety and no sexual disinhibition, which has been further corroborated following discussions with his community mental health nurse, who maintains contact with both AB and his family.

Discussion

Pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid] is a structural analogue of the inhibitory neurotransmitter GABA and is approved for the treatment of epilepsy, neuropathic pain and generalised anxiety disorder (Baldwin & Ajel, 2007; Finnerup & Jensen, 2007; Vranken *et al*. 2008). It is believed to exert its anxiolytic effects through binding in a state-dependent manner to the α-2-δ sub-unit of voltage-gated calcium channels in over-excited pre-synaptic neurones, reducing the release of excitatory neurotransmitters such as glutamate and substance P and increasing GABA concentrations in a number of brain regions including the neocortex, amygdala and hippocampus (Hill *et al*. 1993; Li *et al*. 2011).

Although typically well tolerated, infrequent adverse effects of pregabalin include euphoria, insomnia, confusion, restlessness, irritability, increased thoughts of self-harm, erectile dysfunction and reduced libido (Frampton, 2014). In 2005, the United States Deputy Administrator of the drug enforcement authority positioned pregabalin into Schedule V of the Controlled Substances Act due to limited available information regarding abuse potential. However, concerns with regards to pregabalin and abuse potential have subsequently been documented, predominantly in patients with a preceding diagnosis of alcohol or substance dependence (Leonhart, 2005; Schwan *et al*. 2010; Yargic & Ozdemiroglu, 2011).

Data pertaining to an association between pregabalin and increased libido or sexual disinhibition is limited. A previous case report noted a 2-day period of enhanced sexual desire and excitement following an intentional overdose of pregabalin due to its euphoric-inducing qualities (2250 mg/day) (Osman & Casey, 2014). The patient reported aphrodisiac-like qualities, with increased sexual interest and sexual arousal without associated erectile or ejaculatory dysfunction. Self-reported increased libido following treatment with pregabalin has also been detailed in two cases following treatment with pregabalin for 3 and 4 weeks, respectively (Bucur & Jeczmien, 2011). These cases, similar to our case, reported isolated increased libido without the addition of other associated symptoms of elated mood or hypomania after similar treatment duration. Data pertaining to the management of these cases was not provided.

Pregabalin has also been utilised in a number of cases for the management of sexual dysfunction including selective serotonin reuptake inhibitor (SSRI)-related sexual dysfunction (Oulis *et al*. 2008). Pregabalin has also been reported to ameliorate vulvodynia, a chronic pain syndrome affecting the female genital organs, reducing pain and impaired psychosocial functioning, potentially secondary to the neuropathic qualities of pregabalin (Jerome, 2007).

The mechanism of action of sexual adverse effects associated with pregabalin has not been elucidated to date. Published information on other GABA promoting agents, namely benzodiazepines have reported paradoxical or disinhibitory reactions, including sexual disinhibition and acute excitement, in patients with pre-existing impulse control problems or neurological disorders (Paton, 2002).

It is unlikely that other pharmacological agents employed contributed to AB's presentation, due to the temporal relationship in time of symptomotology with treatment with pregabalin, the amelioration in sexual disinhibition noted with treatment reduction and that no other pharmacological agent was introduced or changed in dose during AB's hospital admission or after discharge from hospital. In addition, limited evidence exists for quetiapine-induced sexual disinhibition, with previous reports either noting such as association in the context of mania (Pacchiarotti *et al*. 1993) or when other pharmacological agents were also implicated (Lam *et al*. 2007). Similarly, SSRIs such as escitalopram have been associated with sexual disinhibition, but such an adverse effect has also most likely resulted from an associated SSRI-induced hypomania or mania (Greil *et al*. 2001).

There are a number of limitations with this study. It is plausible that an alleviation of both depressive and

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anxiety symptoms including an improved self-esteem could have contributed to the patients' presentation. The effect of other management strategies such as group occupational therapy activities and supportive psychotherapy attained from nursing staff as an inpatient cannot be fully out-ruled as contributing to ABs presentation.

In conclusion, relatively low-dose pregabalin in this case was associated with prominent sexual disinhibition and increased libido, in the absence of elated mood or other concomitant features of hypomania or mania. Treatment reduction alleviated this adverse effect, without full drug discontinuation been required. Further research is warranted, perhaps using a case control study design to ascertain the frequency of this adverse effect and potential appropriate management strategies, given potential biases inherent in case report data.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this case report was not required by the local Research Ethics Committee. The participant gave written informed consent for the publication of this case report.

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