## Pregabalin as a probable cause of thrombocytopenia: Presentation of two clinical cases and review of literature

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To the editor:

Pregabalin (PGB) is a psychoactive drug, approved by the FDA (Food and Drugs Administration) for neuropathic pain associated with peripheral diabetic neuropathy, for postherpetic neuralgia, for epilepsy as combined therapy in adults with partial seizures and for fibromyalgia.[1] PGB has also been approved by the European Medicines Agency (EMA) for the treatment of generalized anxiety disorder.[2-4] A number of studies have demonstrated the efficacy of this drug in other conditions such as benzodiazepine and alcohol dependency,[5-7] post-traumatic stress disorder[8] or social phobia disorder.[9] Clinical use of the drug is also common outside the approved indications, such as treatment of insomnia and a range of different anxiety disorders.[10-12] Prescription is therefore both promising and controversial, due to issues such as toxicity or potential abuse in patients at risk of substance dependency.[13]

### Description of cases

Two patients with severe anxiety-related conditions under treatment with PGB, both developing thrombocytopenia, and whose platelet counts returned to baseline a few days after suspension of the drug, are presented.

Case 1: Fifty-seven year old woman diagnosed with bipolar disorder, admitted with a severe mixed anxiety-related episode. Her medical history only included asthma. Her usual treatment consisted of PGB 300 mg/day, Clonazepam 6 mg/day, Duloxetine 120 mg/day and valproic acid 1,000 mg/day. The patient's physical examination on admission was normal. The blood count revealed low platelet count, 117x103/mm$^3$ (normal range 150-450x103/mm$^3$). The remaining blood parameters were normal. Serum valproic acid level was 50.4 mg/mL.

Upon review of prior blood tests, thrombocytopenia was found to have been present for the previous three years. Valproic acid was ruled out as the cause of thrombocytopenia, as onset occurred six months prior to introducing the drug. PGB was therefore suspended due to etiological suspicion, continuing treatment with Valproate. One week after suspension of PBG, the patient's platelet count had increased to 297x103/mm$^3$.

Case 2: Thirty-five year old male patient, admitted with severe obsessional hypochondriac thoughts and compulsive muscle spasms associated with severe anxiety of six months' evolution. He had received a number of different diagnoses: body dysmorphic disorder, borderline personality disorder and obsessive-compulsive disorder. He presented no medical history of significance except low body weight in the physical examination. His usual treatment was Fluoxetine 20 mg/day and Clonazepam 1.5 mg/day. Blood tests conducted on admission were normal (platelets: 235x103/mm$^3$). After admission, his medication was adjusted, switching the previous one to escitalopram 10 mg/day and PGB 150 mg/day. After 15 days there was a clear decrease in platelet count to 164x103/mm$^3$ and an increase in transaminase enzymes (ALT 68 IU/L and AST 43 IU/L). All other parameters remained without alterations. Two days later further blood testing confirmed a platelet count of 127x103/mm$^3$. Given that PGB was the suspected cause of the thrombocytopenia and escitalopram the suspected cause of the transaminase increase, both drugs were withdrawn. Five days after withdrawal of therapy a recovery of platelet counts up to 164x103/mm$^3$ and normal levels of transaminase enzymes were observed. The platelet count continued to increase gradually up to 285x103/mm$^3$ at three weeks.

Application of the Adverse Drug Reactions Probability Scale[14] resulted in a score of 7 for both cases, suggesting that thrombocytopenia was probably an adverse effect of PGB.

### DISCUSSION

According to Pfizer Laboratories, the distributors of PGB, the most common adverse drug reactions are dizziness and drowsiness.[1,2] As regards adverse hematological effects, neutropenia and low leukocyte levels are rare (1 in 1,000 to 10,000 patients); however a drop in platelet count occurs more frequently (1 in 100 to 1,000 patients)[1,2].

The overall controlled clinical trial database shows that 2% of patients receiving placebo, and 3% of those receiving PGB experienced a clinically significant decrease in platelet count. In randomized controlled trials, PGB was not associated with increased bleeding[1]. As of June 2013, a detailed search of medical literature identified just one reported case of severe thrombocytopenia (platelet count under 20x103/mm$^3$) possibly caused by PGB. The drug was prescribed for a 91-year old female with several conditions and polymedicated at a dose of 50 mg/day during treatment for osteoarthritis.[15]

Despite the low prevalence rate reported for PGB-induced thrombocytopenia, we detected two cases at the same hospital in less than one year. This suggests that this adverse event may be underestimated or under-diagnosed, being incorrectly attributed to another underlying condition and/or concomitant medication.

Indeed, thrombocytopenia may have been related to drugs other than PGB in the two cases presented here. Valproic acid may cause low platelet counts in 1 to 10% of patients.[16] Vasudev et al. found a prevalence of thrombocytopenia of approximately 5% in 126 patients receiving valproic acid.[17] The same study found a significant inverse correlation between serum valproate levels and platelet count in women (but not in male patients); a cut-off point of 80 mg/mL of valproic acid was associated with a low platelet count in female patients.[17] In the first case, the concentration of valproic acid was lower than this (50.4 mg/mL), and thrombocytopenia was already present at the time valproic acid therapy was initiated. The thrombocytopenia was detected in the blood tests after the introduction of PGB, and once interrupted this latter, the platelet count returned to normal. In the second case, thrombocytopenia was detected after the simultaneous introduction of PGB and escitalopram, and the number of platelets began to recover after interruption of both drugs. Although we cannot be certain about the drug associated with this adverse effect, literature contains only anecdotal accounts connecting escitalopram and thrombocytopenia.[18,19]

Given that thrombocytopenia places patients at risk of serious bleeding, early diagnosis is essential. In the cases presented here, other non-pharmacological causes of thrombocytopenia were ruled out, such as infectious diseases or systemic disorders. Anti-platelet antibodies testing was not available at our laboratory: this test could have helped to confirm the causal relationship of the drug with thrombocytopenia. In principle the prognosis for drug-induced thrombocytopenia is good, once the causal compound is withdrawn, as was demonstrated in both cases.

## CONCLUSION

Although drug-induced thrombocytopenia is uncommon, it can have serious consequences which can be prevented by identification and withdrawal of the causal drug. It is therefore important for doctors to have a general understanding of this condition and of the drugs most likely to cause a drop in platelet levels, in order to avoid its association.

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## Factitious disorder with psychotic symptoms and seizure in adolescence: A case report

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To the editor:

Factitious disorder (FD), firstly described as Munchausen syndrome by Asher has been discussed in the literature since the last century.[1] FD is characterized by the falsification of psychological or physical symptoms that are associated with the identified deception. Intentionally produced clinical problems can include depression, suicidal thoughts, seizures, dizziness and blacking out.[2] As we know, there has been limited information except for few case reports about FD with psychological symptoms in the pediatric literature.[3-5] In this report, we aim to present an adolescent case of FD with psychotic symptoms and non-epileptic seizures.

## CASE

A. was a 14-year-old adolescent girl and referred to our outpatient clinic with abdominal pain, seizures, hitting to her own head, staring and freezing at one point, and seeing imagines lasting for a year. She had applied to different hospitals and physicians for many times after the initiation of her complaints. She had been followed with various prediagnoses including epilepsy, and atypical psychosis. Although she had received different medications such as antiepileptics, antipsychotics and antidepressants, she had not benefited; even the severity and variety of her complaints increased.

Family history revealed cerebral palsy, epilepsy, mental retardation and diabetes in her sibling, diabetes in her father, and admittance to psychiatry clinic in her mother. With regard to the family relationships, her parents have interested much more in their little child, who had chronic disease; A. has been relatively ignored. After the beginning of her symptoms, her parents' attention to her has been increased.

Since we failed to obtain favorable result from ambulatory monitoring of A., we decided to monitor her as inpatient. When she was told that the conditions of the clinic do not allow staying with a companion, she was pleased. Mental examination of the present case showed that her associations were stable; her affect was inconsistent with her content of thought. She was laughing inappropriately. She was easily bringing up her content of thought. The patient expressed that she suspects of strangers and she has delusion of persecution such as going to be harmed or killed. She had also delusion of reference thought such as news speakers are mentioning about her. She has never committed suicide before, but when she was questioned about her thoughts concerning suicide, she negligently told she is thinking to do. She had visual and auditory hallucinations such as voices ordering her to kill herself or someone else, or images such as red-black flying objects and flying tigers. No memory or orientation defect was detected. During clinical follow-up, colorful and brisk seizures predominated the clinical appearance. Psychotic complaints were decreased, but appeared mostly during examination. On the first night, she was found in her bed as strained, looking puzzled and confused, and talking to herself. This seizure lasted for about 20 seconds. On her evaluation just after the seizure, she was conscious, cooperated and oriented. She expressed that she did not remember the seizure. She had a second seizure on the second day. During this seizure, she was laughing in a puerile tone, speaking to herself, covering her ears, clapping, and hitting to her head. She responded when her name was called during the seizure. After seizure that lasted about 5 minutes, the patient healed by saying, "okay, it's over, I came around". She repeated that she did not remember the seizure. After seizure, she was conscious, cooperated and oriented but, the patient suddenly began to cry and display anxious affection. She was asking in a crying manner to the health staff around "you are not going to kill me, are you?", and telling that stabbing herself would be the first thing after discharge from hospital. During family interview, her parents told that A. had attacks when she was ordered to "get ill". On the third day of her hospital stay, treatment team ordered to A. "get ill". She had a seizure similar to the previous one. On her examination during the seizure, it was observed that she was watching and following medical inspector's hand during the procedures of cornea and Babinski reflexes. Her neurological and laboratory examinations were unremarkable. Results of electro-encephalogram, cranial MRI examination were within the normal limits. As the result of detailed examinations, and consultation with pediatric neurology, we excluded the diagnoses of psychosis and epilepsy. Seizures were considered to be non-epileptic psychogenic. Policlinic visits were planned for A. with the diagnoses of FD.

## DISCUSSION

In general hospital practice, FD is a clinical condition that is not well known by the healthcare providers. The prevalence of FD has been reported to be 1.8% among pediatric inpatients, whereas it has been reported to be

0.03% among pediatric outpatients.[6,7] History of multiple hospitalizations, symptoms with unknown etiology, unimproving symptoms despite appropriate treatment, continuously variable symptoms, medical knowledge above average, exaggerated or fake histories, inconsistency between clinical picture and medical findings, voluntariness for all kind of diagnostic procedures are the common characteristics observed in the patients with FD.[8] Risk factors for FD include presence of a chronic medical disease, presence of a psychiatric disease in relatives, and witnessing severe medical diseases in other family members.[6]

Although the FD has been officially recognized in the DSM for 30 years, the diagnostic validity and classification of FD is still controversial.[9] In the DSM-5, a new category and new criteria for FD has been constituted. Accordingly, it was recategorized in the somatic symptom and related disorders.[2] The DSM-5 criteria for FD focus on the objective identification of falsification of illness symptoms and the absence of obvious external rewards but not requiring determination of the patient's underlying motivation.

The differential diagnosis includes a variety of medical and psychiatric conditions such as conversion disorder (CD) and malingering. FD with neurological symptoms is distinguished from CD by evidence of deceptive falsification of symptoms.[2] As we directly observed her feigning seizure symptoms while the neurological examination during the seizure and we had sufficient evidence of deceptive falsification the patient was diagnosed as FD, rather than CD. Another significant evidence favouring FD, rather than CD is her intentionally fabrication of seizure symptom when she was instructed to be gotten ill. FD is distinguished from malingering by the absence of obvious rewards (e.g. money, time off work).[2] However, it is emphasized that there is less or more external reward for pediatric or adolescent FD cases and thus differentiating FD from malingering is more difficult particularly in pediatric cases versus adults. The diagnosis must be made based on the prominence of the external reward and whether it is forefront or not in the clinical picture.[10] In this present case, no remarkable external reward was out of question as is in malingering. Although increase of attention by other family members because of the illness might be seemed as an external reward, it was disproportional with the severity of symptoms.

In this case, the following factors supported the diagnosis of FD; being ruled out the other likely causes of seizures and psychotic symptoms based on the examinations; exaggerated symptoms particularly during examination; absence of definite diagnosis despite recurrent admission and hospitalizations; increased in the number, type and severity of symptoms despite appropriate treatments; being voluntary for hospitalization; deliberately produced symptoms by the patient to attract attention by adopting sick role; and presence of organic and psychiatric diseases in family medical histories.

In conclusion, FD should exactly be considered in the differential diagnosis of epilepsy and psychotic disorder in children and adolescents. Suspicion of FD is the key point for diagnosis. A multidisciplinary approach is required in the diagnostic and treatment processes. FD should be considered particularly in patients with inconsistency between complaints and examination findings, with lower level of anxiety than expected despite severe disease picture, and without definite diagnosis despite recurrent hospital applications and/or hospitalizations.

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