CNS Neurosciences & Therapeutics

LETTER TO THE EDITOR

CNS Neuroscience & Therapeutics

Pregabalin in the Treatment of Refractory Bipolar Disorders

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Received 16 October 2011; revision 21 November 2011; accepted 30 November 2011

doi: 10.1111/j.1755-5949.2011.00289.x

Oulis et al. [1] reported the case of a 29-year-old woman with an acute manic episode in whom, after obtaining a partial response with quetiapine, complete remission was achieved after adding 300 mg/day of pregabalin (PGB). The patient remained euthymic 9 months later with PGB plus quetiapine. The authors consider the hypothesis of an antimanic effect of PGB.

We set out below the case of a patient with a long-standing Bipolar Disorder (BD) and manic episodes resistant to the usual treatments but who, surprisingly and by chance, has had a very positive response to a combined treatment with sodium valproate and PGB.

The PGB-valproate combination has led to complete and sustained remission of manic symptoms, illness awareness, and reduction in alcohol and caffeine consumption.

"Mr A" is a 46-year-old graduate with a history of psychiatric disorders since the age of 20, associated with harmful hashish and cocaine use. He subsequently suffered a major depressive episode with severe psychomotor retardation and no awareness of his illness. Ever since, he has had recurrent hypomanic episodes associated with inflated self-esteem, no awareness of his illness, behavioural disinhibition, expansiveness and loss of feeling for family and friends. In 2006, while in a hypomaniac state, he started to use cocaine; he then developed a manic episode which led to admission to a psychiatric hospital for 8 weeks. His clinical condition included euphoria, megalomanic ideas, hyperactivity, insomnia, and lack of awareness of his illness. The patient failed to benefit from multiple trials with typical and atypical anti-psychotics (haloperidol up to 30 mg/day; perfenazine up to 32 mg/day; Fluphenazine decanoate i.m. 25 mg/month), beginning with lithium carbonate and sodium valproate. He was discharged before complete remission, in a persistent hypomanic state characterized by over-valued ideas, extravagant shopping and insomnia. For at least 8 months, he continued to be hypomanic but not associated with alcohol and cocaine use, although he started using again in the Spring of 2007. During 2007, several drugs were successively associated with the stabilizing treatment but with no clinical improvement: clotiapine (up to 40 mg/day), haloperidol (15 mg/day), pimozide (4 mg/day), and aripiprazole (30 mg/day). The pattern of his illness was similar throughout 2008. During that year, he rejected anti-psychotic drugs but satisfactorily completed a psycho-educational programme while at the same time, consuming excessive amounts of alcohol and caffeine.

In 2009, he was treated for the first time with pregabalin (150 mg/day) for a painful shoulder, anxiety and insomnia, with the results of weight loss, significant reduction in alcohol and caffeine consumption and improvement in irritability and insomnia. By mid 2009, he stopped taking the pharmacological treatment on his own initiative. After several months of non-adherence to treatment, he had to be committed to a psychiatric hospital against his will owing to a manic episode with psychotic symptoms (delusional self-expansive and erotomanic ideas, delusions of persecution and harm). Pharmacological treatment with an association of VPA (1500 mg/day), clonazepam (2 mg/day), haloperidol (15 mg/day), and pregabalin (225 mg/day) for two weeks led to disappearance of the psychotic symptoms, normal mood recovery, and illness awareness. Ten months later, he is adhering to his drug treatment, with no mood-state oscillations, complete abstinence from alcohol and caffeine, spending control, he is critically

aware of his illness and giving attention to social, economic and family concerns. The patient has remained euthymic, with the exception of one isolated episode of slight signs of self-expansion (patient turned arrogant, with insomnia and irritability) that was resolved by increasing the dose of pregabalin to 300 mg/day. To date, he has remained euthymic on VPA (1500 mg/day), pregabalin (300 mg/day), and clonazepam (1 mg/day).

Our patient meets the DSM-IV criteria for a type I BD with substance abuse which started with a major depressive episode and has since been followed by numerous hypomanic episodes and two frank manic episode, one with psychotic symptoms. The disorder has remained stable for a long time. A substance-induced mood disorder was ruled out given that the substance use was always during the elated phase of illness, the acute manic symptoms persisted during 8 weeks of hospital admission and the patient suffered hypomanic symptoms over a substantial period (8 months) in the absence of alcohol and caffeine use. Moreover, his last period of affective problems occurred when he had not been using any toxic substances. With the exception of the periods he has spent in hospital, the patient has continued to work and be active. Since April 2010, he has been euthymic, his cognitive performance has been completely normal and he does not meet the criteria for any personality disorder.

VPA has traditionally been used in the treatment of BD. Although its mechanism of action is not fully understood, it is known to increase the action of gamma-aminobutyric acid (GABA) [2]. PGB is a GABA analogue that is indicated for the treatment of neuropathic pain, anxiety disorders, and fibromyalgia. It is not indicated for the treatment of BD.

Pae Chi-Un [3] is distrustful of the potential antimanic effect of PGB described by Oulis et al. [1] and considers that, without a placebo-controlled trial, their result has to be attributed to a combination of the anxiolytic effect of PGB with the antimanic effect of Quetiapine. The case we have described casts some doubts on these assumptions. The first issue raised by our case is that PGB works through a reduction in the appetite for alcohol and stimulants (coffee and cocaine) [4,5], potential factors maintaining the hypomanic fluctuations chronically suffered by this patient. In fact, when he first took PGB to help his painful shoulder, his levels of anxiety and irritability and his insomnia all improved in combination with lower consumption of coffee and alcohol. This observation partly vindicates Pae Chi-Un, [3] but suggests added effects that are not just the result of a reduction in anxiety; the reduction in craving for and consumption of alcohol and stimulants might explain another part of the treatment's effectiveness. PGB has been shown to reduce daily consumption of and diminish the appetite for alcohol [4,5]. Nonetheless, we feel that the therapeutic potential of PGB might not be limited to reducing anxiety or appetite for and consumption of substances such as those indicated. While monitoring this patient over recent months, the increase in his PGB dose was enough to halt his symptomatic affective peak, which was not associated with any prior consumption of toxic substances. In addition, for the first time in many years, the patient has acquired an awareness of his illness, which had been absent even after taking part in a psychoeducational programme in which this problem was dealt with intensively. For all of the above reasons, and with the evident limitations implied by a single case, we feel it is of interest to consider a more controlled analysis of the effects of PGB as an antimanic drug, as a complementary stabilizer in bipolar patients with manic predominance or as a complement to therapy in cases of dual pathology with a type I or II BD associated with the consumption of toxic substances.

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