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Case report

Clinical stabilisation with lacosamide of mood disorder comorbid with PTSD and fronto-temporal epilepsy

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Summary. *Background and aim of the work:* Mood disorders are often complicated by comorbidity with epilepsy. Anxiety and personality disorders may worsen prognosis and treatment outcome. Lacosamide has been recently introduced as adjunctive treatment for partial epilepsy. Its mechanism consists of selective slow inactivation of voltage-gated sodium channels, thus promoting an extended stabilisation of cell membranes. Antiepileptic drugs have been largely used since the 1950s in psychiatry as mood stabilisers due to their membrane stabilising and anti-kindling effects. Like lithium, antiepileptic drugs are first choice treatment for Bipolar and Cyclothymic Disorders. *Methods:* We tested the efficacy of the most recent antiepileptic medication, lacosamide, in a patient with simultaneously occurring cyclothymic disorder, severe post-traumatic stress disorder, and fronto-temporal epilepsy. Lacosamide was titrated up to 200 mg/day, added to ongoing 750 mg/day lithium, 15 mg/day oral aripiprazole then switched to 400 mg/month long-acting aripiprazole, and 2 mg/day *N*-desmethyldiazepam. *Results:* We observed EEG normalisation one month later, along with reduced anxiety and an additive effect to lithium-induced stabilisation of mood fluctuations since the second week of lacosamide addition. *Conclusions:* Further studies with this drug in the bipolar spectrum are warranted. (www.actabiomedica.it)

Key words: cyclothymic disorder, bipolar spectrum disorders, post-traumatic stress disorder, fronto-temporal epilepsy, lacosamide

Background

According to the DSM-5, cyclothymic disorder is classified among bipolar spectrum disorders (BPSD) and is characterised by the recurrence of mild-to-moderate hypomanic and depressive symptoms over a two-year period without meeting diagnostic criteria for bipolar I, bipolar II, or depressive disorder (1). The debate is still open among clinicians as to whether cyclothymia represents an exaggeration of cyclothymic temperament with a complex pattern of mood instability and interpersonal hypersensitivity, evolving into a borderline-like bipolarity (2) or as a definite precursor of bipolar disorder (3) with 15%-50% of individuals with cyclothymia developing bipolar I or II disorder lifetime (1), and 35% within 3 years (3). The lifetime prevalence of Cyclothymic Disorder is 0.4% to 1% and the typical onset is during adolescence or early adulthood (1). The relevance of the comorbidity of BPSD with anxiety disorders in cyclothymia is witnessed by the "anxious-distress" specifier in the DSM-5.

Comorbid anxiety can be debilitating in itself; its prevalence within BPSD is high. Lifetime comorbidity is estimated to be between 24% (4) and 74.9% (5). Around one third of BP-I and II patients meet criteria for an anxiety disorder. Lifetime and current

comorbidity, respectively, are 22.0% and 12.7% for social anxiety, 17.3% and 8.0% for panic disorder with or without agoraphobia, 9.9% and 5.7% for obsessive-compulsive disorder (OCD), 17.2% and 5.1% for post-traumatic stress disorder (PTSD), 8.5% and 4.4% for agoraphobia without panic, and 18.4% and 2.3% for generalised anxiety disorder (GAD) (6-7 and 8 for a detailed review). Comorbid anxiety has been linked to measures of poor outcome, such as illness severity (9), suicide attempts (10), poorer quality of life (11), and physical ill-health (12 and 13-14 for reviews). Anxiety is supported to be a "clinically meaningful correlate of poor outcome in the acute treatment of bipolar I disorder" (15).

Another interesting comorbidity still under investigation is between epilepsy and psychiatric disorders; 20-40% of epileptic patients are at risk for psychiatric comorbidity, and this rises to 70% in patients with refractory seizures (16). Comorbid mood disorders have a 24.4% lifetime prevalence for any type of mood disorder *vs*. 13.2% among the general population; temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) were those that were most commonly found in mood disorders (17). About 17% of patients with epilepsy show symptoms of bipolar disorder (18). The kindling model for epilepsy postulated by Goddard et al. in the late 1960s (19) and extended by Post in the 1980s to bipolar disorder (20), may help understanding the existence of similar underlying patterns of brain sensitisation in both disorders triggering seizures or mood episodes. Furthermore, similar precipitating factors (stress, sleep deprivation, antidepressant medication and the effect of seasons) have been recognised both in mania and partial seizures, suggesting common pathways, which may mediate the occurrence of epileptic and manic episodes (21). The use of the same antiepileptic drugs for both epilepsy and mood disorders is another tangible clue of some overlap between neurological and psychiatric disorders. Mood stabilisers (lithium, anticonvulsants and antipsychotics) are the recommended medication for acute and long term treatment of BPSD (22).

We describe here the case of a patient with comorbid cyclothymic disorder, PTSD, and fronto-temporal epilepsy who responded to 200 mg/day lacosamide added to an aripiprazole, lithium and benzodiazepine combination. We support the notion that lacosamide was crucial in obtaining improvement because the same treatment carried out repeatedly in the past without lacosamide had proven to be ineffective in the past and was inefficacious during the last hospitalisation.

Case

A 35-years-old Pakistani woman first came to our observation in a secondary psychiatric inpatient unit in December 2014. She had been transferred after her discharge from an acute psychiatric care service, where she had been hospitalised for ten days. Volunteers working at a refugee shelter based in a suburb of Rome had suggested psychiatric hospitalisation due to her complex symptomatology, involving depression, unjustified guilt for the death of her parents in a recent car accident, hopelessness, panic attacks, dissociative symptoms, flashbacks of traumatic remembrances, auditory and tactile hallucinations, and insomnia. A psychologist at the shelter told us she had been repeatedly verbally and physically abused while in Pakistan by her own family members, due to cultural and religious incompatibility with her partner. For this reason the couple fled from Pakistan to start a new life in Germany. However, they were hosted by other Pakistanis, including her brother, who again disapproved her choice and abused her physically. One of the violence episodes resulted in her being hospitalised at the orthopedics department. After this episode they decided to move to Modena, Italy, where the patient made her first contact with a psychiatrist. She complained for the recent onset of fatigue, headache, limb paraesthesia, anxiety, sadness, depersonalisation, flashbacks of traumatic events, and insomnia. She was hospitalised and prescribed sertraline, mirtazapine, amisulpride, and benzodiazepines (at unspecified doses), which she willingly discontinued after discharge without medical consultation. She was subsequently transferred together with her husband to a refugee shelter based near Rome, where she experienced worsening of the previous symptomatology and was first hospitalised and then referred to our observation with a diagnosis of PTSD, which was compatible with her psychopathological picture.

Her initial confusion, time disorientation, perplexity, and emotional fatuousness prevented us from collecting an adequate history. She and her husband were unable to remember any health issue in the patient's infancy and adolescence or medical issues in the patient's family members. Her ECG and blood chemistry were unremarkable, except for hyperprolactinemia (5094 ng/ml) that we attributed to 4 mg/day risperidone that the patient was prescribed during her last hospitalisation. During the patient's stay in our department we prescribed her clomipramine for depressive symptoms and thought rumination and cabergoline to reduce hyperprolactinaemia, while we switched gradually from risperidone to 20 mg/day aripiprazole and a benzodiazepine, 2 mg/day *N*-desmethyldiazepam (delorazepam). Anxiety subsided while the frequency of hallucinations gradually diminished across four weeks and changed in quality; residual hypnagogic hallucinations were disrupting the sleep-waking rhythm. Flashbacks disappeared within six weeks. Mood switched suddenly within three weeks of treatment from depression to euphoric peaks, together with increased sexual interest and lack of insight, which coexisted with guilt and worrying about her future. We extended the hospitalisation to another month over the standard discharge schedule to obtain mood stabilisation and sleep-wake cycle regulation. We titrated lithium carbonate up to 600 mg/day. During the extended period, hopelessness and guilt finally disappeared, while some residual dissociative symptom still persisted. The patient was discharged and referred to her public health outpatient care service. Four weeks after discharge she relapsed and had to be rehospitalised. She had voluntarily discontinued treatment, because she worried about side effects. At this second hospitalisation she showed dysphoric mood with psychomotor agitation, aggressive and self-harming behaviours, more severe dissociative symptoms with time disorientation and the recurrence of guilt and hypnagogic auditory and tactile hallucinations. We reestablished treatment with lithium carbonate (750 mg/day), aripiprazole (15 mg/day, switched after 2 weeks to 400 mg/month intramuscular long-acting aripiprazole monohydrate) and delorazepam (2 mg/day) and subjected the patient to electroencephalogram (EEG). We diagnosed right fronto-temporal epilepsy and promptly instituted treatment with lacosamide, a slow inactivator of voltage-gated sodium channels, at a dosage of 100 mg q 12 h (200 mg/day). We endorsed lacosamide because of its favourable side effect profile and its effectiveness as add-on in epilepsy.

One week after beginning the new treatment, an improvement of anxious symptoms allowed us to reduce benzodiazepines. The patient achieved mood stability, disappearance of hypnagogic hallucinations and sleep-wake cycle normalisation within two weeks.

Four weeks after beginning lacosamide the patient was euthymic, with no dissociative symptoms, guilt or self-harming ideation, reduced flashback episodes, but was unsure about her future. We confirmed her treatment schedule and sent her back to outpatient care for follow up and psychotherapy.

Eight weeks after discharge the patient was adherent to the therapeutic project. Her psychopathology was stable. She no more developed seizures or had any thought or perceptual disturbances.

Discussion

We observed a consistent effect on the core symptoms of this patient after the introduction of lacosamide as add-on to her ongoing mood stabilising treatment. Lacosamide has not been tested in the BPSDs, so this article is the first to report an effect in the bipolar spectrum, namely, in a patient with cyclothymic disorder. The reason we adopted this drug was that it showed efficacy in partial-onset seizures (23) and has an acceptable safety profile (23, 24). Lacosamide has still to be tested in BPSD and there is no evidence it could be effective in PTSD. It is currently evaluated for its cognitive-behavioural effects expecting that it will not be associated with cognitive impairment (ClinicalTrials.gov Identifier: NCT01175954), given that the FDA granted lacosamide the indication for partial seizures as monotherapy.

In spite of the dearth of data on the possible utility of lacosamide in psychiatric disorders, it is possible that this drug could prevent the mood elevation induced by substances, and possibly, life events. Lacosamide was shown to reduce the mood-elevating effects of cocaine in an animal model (25). We should recall

that in treating bipolar disorder, the main goal should be to control mania, since preventing mania avoids that the patient subsequently plunges into depression (26, 27). In the self-stimulation animal model of mania (25), lacosamide significantly reduced cocaine-induced intracranial self-stimulation in rats even at the low doses, whereas sodium valproate and lamotrigine did so only at the highest dose; furthermore, at the highest dose, lacosamide elevated the self-stimulation threshold even in the absence of cocaine. This animal study opens to the possibility to use lacosamide as add-on in BPSD and probably, also in substance use disorders, either comorbid with BPSD or not.

At any rate, lacosamide showed some efficacy in patients with epilepsy and anxious/depressive symptoms (28-29). In more detail, a first Spanish study (28) found lacosamide to abolish seizures in about 55% of 31 patients with epilepsy and detected a reduction at the 3- and the 6-month follow-up of anxiety/depressive symptoms, as assessed with the Hospital Anxiety and Depression Scale, a validated self-rated questionnaire (30). The second study has been conducted in Ohio, USA; the study evaluated 91 patients with epilepsy with the Neurological Disorders Depression Inventory for Epilepsy scale (NDDI-E) (31), which detects major depression in patients with epilepsy with a positive predictive value of 0.62, which is fair, but not extraordinary and does not render the scale fit for evaluating psychiatric patients without seizures. The study found no significant change after 6 months (29). However, those 25 patients with elevated scores on the NDDI-E (>15) obtained a significant reduction in depression. Anxiety, measured with a 7-item instrument in only 20 patients, was not significantly affected by lacosamide treatment.

The most common side effects of lacosamide include dizziness, headache, confusion, diplopia, nausea, nasopharyngitis, and vomiting, but a case of psychosis has recently been described (32). A reversible, short-lasting increase in suicidal ideation has been reported, which subsided after discontinuation and switch to another antiepileptic drug (32). Reduced sexual activity has also been reported (33). In our patient we observed no side effect after lacosamide addition.

Our results with this patient should encourage clinicians to try lacosamide in patients with mood disorders, with or without epilepsy. Future studies could be open, pilot studies at an initial stage, and double-blind, randomised controlled trials at a later stage. Regarding PTSD and other trauma-related disorders, we cannot conclude from what we observed in this patient that lacosamide holds promise, also because the core symptoms of PTSD took longer to respond and responded only partially.

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