Repeat episode of late-onset psychosis associated with efavirenz

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Dear Editor,

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor; it is one of the most widely prescribed HIV drugs as its efficiency is well established and its once-a-day dosing regimen makes it easy to take. In more than 50% of cases[1], it leads to mild psychiatric symptoms in the early stages of treatment, which may persist[2]. Further, some patients treated with EFV have reported experiencing severe psychiatric symptoms such as mania, depression, suicidal thoughts, psychosis, and hallucinations[3].

We have not found any description in the literature of late-onset psychiatric symptoms like those observed the case we present here. We describe a case that is unusual in terms of the late onset and the severity of the psychotic symptoms, as well as the fact that the patient experienced them on two different occasions after the same amount of time on EFV. Further, we discuss pathophysiological factors that might underlie these findings.

Case report

A 52-year-old patient was admitted to an acute psychiatric unit due to a brief psychotic episode. Notably, his personal medical and surgical history included HIV infection diagnosed at age 23. After the diagnosis the patient remained asymptomatic for 10 years, with undetectable viral load and without medical treatment. He didn't have a brain MRI scan then, neither he showed psychiatric symptoms. In addition, he had chronic liver disease caused by hepatitis C virus and was a former heroin addict, and though abstinent for many years, was on methadone at a maintenance dose of 15 mg/day. At the admission he continued on methadone and had been treated for 4 years with EFV (400 mg/day).

The patient had no family history of psychiatric illness. His personal psychiatric history included a first maniac episode at 47 years of age, with psychotic symptoms and persecutory delusion which also required psychiatric hospitalisation. At that time, he had been on EFV for exactly 4 years, the treatment was discontinued due to the aforementioned psychiatric episode and the symptoms resolved. At that moment he was only on antiretroviral treatment and the usual treatment with methadone. One year later, the treatment with EFV was resumed, at the request of the patient, and again after 4 years on EFV, the patient had the psychotic episode described in this case report.

The patient had a clinical picture consisting of ideas and delusions of reference and persecutory delusion, threatening auditory hallucinations and persistent insomnia. In this context, and despite being in a euthymic state, he reported suicidal ideation, feeling suicide was the only option in his situation.

We conducted an internal medicine evaluation, which ruled out an acute organic process that would explain the psychiatric symptoms. We also performed a neuroradiological study with computed tomography and MRI, this revealing mild cortical and subcortical atrophy, glial cell damage and microangiopathy in the supratentorial white matter.

On the advice of the infectious disease specialist, EFV was withdrawn and, given the severity of the symtoms, the patient was started on paliperidone 3 mg daily as an antipsychotic. The psychotic symptoms progressively lessened and after 3 weeks of hospitalisation, he was discharged. At this point, he was referred to the infectious disease specialist to discuss alternatives to treatment with EFV.

Discussion

Various factors, namely, that an acute organic process was ruled out in both episodes, the patient had no history of psychiatric illness, and the symptoms resolved after EFV withdrawal, suggest a toxic effect of the drug itself. It does not seem likely that the repeated late onset of symptoms is attributable to chance. In addition, using the adverse event probability scale developed by Naranjo et al, 1981[4], we calculated a score of 7/10, indicating a "probable" link between EFV and the psychotic symptoms.

The mechanisms by which EFV causes adverse effects at central nervous system level are unknown. Among those that have been proposed, some that might influence the apparent toxicity in our patient are presented in the table 1[5-10].

Studies of the relationship between plasma levels of EFV and toxicity have produced mixed results[5]. Additionally, our patient was on a 400 mg/day of EFV, associated with lower level of toxicity[11]. 90% of EFV is metabolised in the liver through cytochrome CYP2B6, which is also its inducer. There are functional polymorphisms of CYP2B6 that affect the metabolic rate and hence plasma levels of EFV. It could be that CYP2B6 activity was impaired due to the patient's chronic liver condition, although the adverse effects observed a second time do not seem compatible with this mechanism.

8-OH-EFV is the main metabolite of EFV, this metabolite being found in plasma and the brain. Nonetheless, 4 years seems to be an excessively long time for the induction of CYP2B6 to lead to toxic levels of 8-OH-EFV[7,8]. The other metabolites of EFV occur at very low concentrations and have not been associated with any adverse effects.

If the genetic polymorphisms that might influence plasma or brain levels of EFV[6] or 8-OH-EFV, were determinant of the adverse effects described, we believe that they would have been detected earlier .

Given the lack of biological diagnostic markers, we have been unable to rule out bipolar disorder with onset at a uncommon age. The psychotic symptoms resolved when EFV was stopped, although we also started antipsychotic treatment.

Our patient may have had multiple moderately severe risk factors which, combined, resulted in the toxic threshold being exceeded. The presence of one risk factor, while it would not lead to neuropsychiatric symptoms, might have increased the sensitivity of the patient to other risk factors. Various different mechanisms that are protective against EFV toxicity[8,9] include the genetic profile of redox enzymes,

Table 1 Possible mechanisms associated with toxicity of EFV to the central nervous system

Proposed toxic mechanism	Associated with	Factor involved in toxicity or protection	Reference
Elevated levels of plasma EFV	EFV is bound to plasma proteins	Plasma albumin levels may influence EFV concentration	5
	Inactivation of plasma EFV by glucuronidation	Genetic polymorphisms involved in conjugation	
	CYP2B6 metabolization of EFV in liver	Functional genetic polymorphisms of CYP2B6 gene	
	Plasma EFV crosses the blood-brain barrier	Elevated plasma EFV may produce toxic levels in the brain	6
Toxicity of EFV metabolite 8-OH-EFV	EFV is metabolised to 8-OH-EFV by CYP2B6 in the liver	8-OH-EFV is present in the brain and may be toxic	7
	Inactivation of 8-OH-EFV by glucuronidation	Genetic polymorphisms involved in conjugation	
	Induction of CYP2B6 by EFV	8-OH-EFV increases and EFV decreases over time	8
	Induction of CYP2B6 by EFV decreases over time in hippocampus	Protective mechanisms that might fail in our case	9
Toxicity of oxidation products of 8-OH-EFV	Generation of quinone-type structure, known to be neurotoxic	Genetic polymorphisms in redox system enzymes involved	10
Miscellaneous	Factors affecting EFV absorption or CYP2B6 activity	Fat and alcohol intake, smoking, medicinal herb use	

EFV: Efavirenz

the cytochrome and conjugation mechanisms, which in our patient might have failed on two occasions.

CLINICAL RECOMMENDATIONS

It is likely that monitoring the onset of adverse psychiatric effects is more complex than merely measuring plasma levels of EFV or genotyping cytochrome CYP2B6.

This monitoring should not be limited to the first few months of treatment, as very severe adverse effects may appear later on.

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CONFLICT OF INTERES

The authors declare that there is no conflict of interes.

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A case of severe hypothermia following three-month administration of paliperidone palmitate: a case report

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Dear Editor,

Antipsychotic drug use can induce hypothermia and hyperthermia. In clinical practice, much attention has been given to the elevation of neuroleptic-induced body temperature in the context of neuroleptic malignant syndrome. Despite its wide use, there are few cases of hypothermia reported in the literature[1–3] and the mechanisms by which these drugs alter thermoregulatory processes in the body are not yet fully known. Nonetheless, hypothermia, although it is presented as a low-incidence, probably underdiagnosed, adverse event (AE), is a serious phenomenon that can endanger the patient's life.

Case report

the case is a 49-year-old male patient, diagnosed with paranoid schizophrenia of years of evolution, without known drug allergies or another history of interest. The patient had been treated with paliperidone depot 150 mg/month since January 2016 (last dose administered 19th December 2018) and was clinically stable. Due to the difficulty experienced by the patient to attend the mental health unit monthly for treatment, a change was made to administer paliperidone depot 525 mg quarterly on 17th January 2019. Two days after administration, the family described that the patient manifested difficulty in walking and significant weakness, maintaining a good level of awareness. The situation continued to worsen, and on the fifth day after the administration of the antipsychotic depot, the patient was referred to the emergency department for a deteriorated the level of consciousness and generalised muscle stiffness. The initial physical examination revealed: 26ºC rectal temperature, 87/62 mmHg blood pressure, spontaneous ocular opening, lack of response to verbal and painful stimuli, stiffness of the four extremities and distal coldness. The electrocardiogram (ECG) recorded bradycardia (42 beats/minute) with Osborn Wave J (Figure 1). The analytical results showed slight platelet and leucocytosis (21.6 x 10^9/L) at the expense of neutrophilia (20.5 x 10^9/L). Toxicological screening of urine for drugs of abuse was negative.

Given this serious situation, the patient was transferred to the intensive care unit (ICU) with a main diagnosis of severe hypothermia, probably related to the administration of neuroleptics, that is the change from paliperidone monthly to quarterly. Possible alternative diagnoses were an endocrine disorder [prolactin 36.2 ng/mL (2.0–18.0), TSH 1.51 µUI/mL (0.34–5.5) and T4 1.2 ng/dL (0.75–1.86), moderate hypocalcaemia and mild hypokalaemia] and less likely, an infection. The initial therapeutic plan involved reheating the patient with a thermal blanket, hemodynamic and respiratory support, correction of electrolyte alterations (replacement of calcium, magnesium, phosphorus and potassium parenterally) and administration of biperidene. Figure 2 represents the evolution of the patient's central body temperature during the first 24 hours of admission to the ICU. During his stay in the ICU, he presented an adequate response to treatment and good hemodynamic control. Chlordiazepoxide and promptly propofol were administered for agitation control. After six days of admission, the patient was extubated, with adequate O_2 saturation, and gradually recovered consciousness. The psychiatry service monitored closely and recommended reducing the benzodiazepine pattern and introducing oral risperidone. Eight days after admission to the ICU, the patient was transferred to the internal medicine service and was again assessed by the psychiatry service, who optimised the psychopharmacological treatment, introducing olanzapine and risperidone suspension to achieve a more sedative profile of the medication, as well as gradual decrease of benzodiazepines. Sedation, ambulation and introduction of oral diet with good tolerance began.

The patient was discharged 16 days after admission to continue outpatient follow-up in his mental health unit of reference. The psychopharmacological treatment at dis-

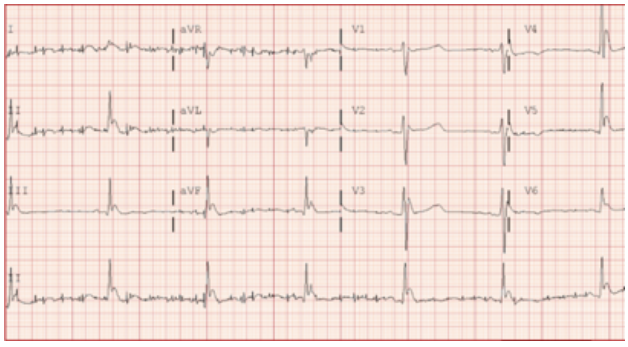

Figure 1 | *Osborn wave (J Wave)*

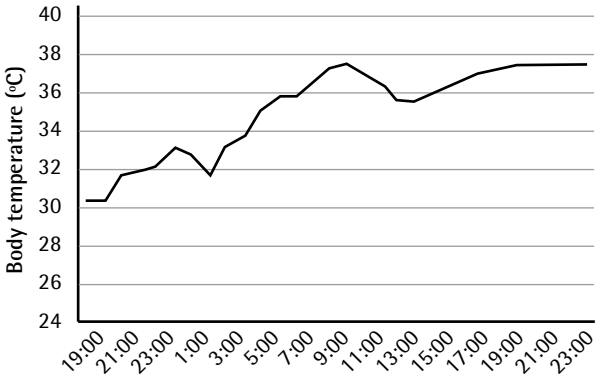

Figure 2 | *Evolution of the patient's central body temperature during the first 24 hours of admission to the ICU*

charge was: chlordiazepoxide (25 mg/day with descending regimen) and olanzapine (25 mg/day).

Discussion

hypothermia is defined as a decrease in the core body temperature below 35°C and classified depending on the severity: mild (33–35°C), moderate (28–33°C) and severe (<28°C)[4]. After an initial phase of activation, it causes a process of progressive depression of all organs. Episodes of severe hypothermia, as presented in this case, are characterised by bradycardia, ventricular arrhythmia, hypotension, pulmonary oedema, hypoventilation, dysflexia, oliguria, coma and occasionally, death[5]. Likewise, although it is not pathognomonic (cases have been described in subarachnoid haemorrhage, cranial trauma, hypercalcaemia, Brugada syndrome and acute cardiac ischaemia), up to 80% of cases of severe hypothermia occur with Osborn J wave. This deviation is inscribed in the ECG between the QRS complex and the beginning of the T segment, representing the alteration of the earliest phase of membrane repolarisation.

Hypothermia can be primary or secondary. The first type is due to exposure to extreme cold environmental conditions, while secondary hypothermia is due to an alteration in thermoregulation mechanisms (metabolic or neurological disorders, iatrogenesis, trauma)[6]. This case is an example of hypothermia secondary to an alteration of thermoregulation.

In 2014, the European Medicines Agency authorised a presentation of paliperidone injectable prolonged-release quarterly administration for the maintenance treatment of schizophrenia in clinically stable adult patients with paliperidone monthly injectable formulation. The paliperidone data sheets, both oral and parenteral presentations, describe hypothermia as a rare EA, that is, occurring in ≥1/10,000 to <1/1,000 patients. At present, no case has been published that relates the use of paliperidone with hypothermia symptoms. However, cases related to both first-generation antipsychotics [haloperidol[7,8] or chlorpromazine[9]] and atypical antipsychotics [risperidone[10,11], clozapine[12], olanzapine[13], aripiprazole[14] and ziprasidone[15]] have been reported. It is worth highlighting the case presented by the absence of previous publications and the severity of the EA, which caused a total of 16 days in hospital, half of them in ICU. According to the available literature, the risk of developing hypothermia related to the administration of antipsychotic drugs is higher in schizophrenic patients compared to non-schizophrenic patients (diagnosis of dementia, delirium, depression with psychotic symptoms) and appears to be increased at the start of treatment with these drugs or after dose increase[2,9], characteristics present in the case described. Likewise, the existence of somatic comorbidities (sepsis), endocrinological abnormalities (hypothyroidism), cerebral structural damage (mental retardation or epilepsy), concomitant medication (beta-blockers, benzodiazepines) and low ambient temperature[2] have been postulated as possible predisposing factors.

To determine the causality between this AE and the administration of paliperidone depot, the Naranjo algorithm[16] was applied, yielding a score of 5, suggestive of a probable adverse reaction to some drug.

This case study emphasises the importance of implementing pharmacovigilance programmes and of communicating adverse reactions to detected drugs, especially in those recently commercialised drugs, to establish specific safety programmes[17].

Conclusions

Despite the low frequency of hypothermia associated with antipsychotic drugs, healthcare professionals should be aware of this potential AE and monitor the temperature closely during the first 7–10 days in those patients who start or increase their drug dosage. Considering the case described, the patient should also be monitored and warned in the case of changing depot administration formulations, particularly.

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Schizophrenia-like psychosis induced by levetiracetam in a patient with epilepsy

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Dear Editor,

Epilepsy is one of the most common neurological disorders, frequently occurring with psychiatric comorbidity[1].

The risk of psychotic disorder in this population is calculated as eight times higher than in the general population[2].

The relationship between epilepsy and psychosis continues to be the subject of lively debate, with many explanatory theories developed over the years (Table 1)[3-7].

The authors present a case report of a patient with psychosis that was probably induced by levetiracetam, and their follow-up to the present date, over four years after the suspension of this antiepileptic.

Case report

A 45-year-old female patient, hospitalized in 2015, with auditory verbal and cenesthetic hallucinations, persecutory and mystic delusions and behavioural disturbance.

Past Personal and Familial Medical History

The patient was diagnosed with epilepsy secondary to bilateral parieto-occipital and perirolandic lesions of ulegyria at the age of five, presenting with several types of epileptic seizures: simple partial seizures of the left upper limb and complex partial seizures (with alteration of consciousness and masticatory automatisms and, since 2006, also complex automatisms) with some seizures with secondary generalization. The patient has been followed up by different neurologists since this diagnosis was made and has tried many antiepileptics (she cannot recall the names). In the Neurology outpatient department she is currently attending, in 2007 levetiracetam (1000 mg/day) was added to her long-term previous medication – carbamazepine 1200 mg/day and clobazam 20 mg/day. In 2009 levetiracetam was increased to 4000 mg/day, in 2010 clobazam was increased to 40 mg/day and in 2011 carbamazepine was increased to 1800 mg/day. In 2014 the patient reduced the dosage on her own initiative to 1200 mg/day) – Table 2.

Despite many therapeutic adjustments over the years the patient continued having seizures, mostly during catamenia (2-3 seizures/month).

At the time of this psychiatric hospitalization, her antiepileptic medication consisted of a combination of carbamazepine 1200 mg/day, levetiracetam 4000 mg/day, clobazam 40 mg/day and clonazepam 4 mg/day (Table 2).

Table 1 Possible explanatory factors of the association between epilepsy and psychosis[3,7]

Central nervous system disturbances common to epilepsy and psychosis:
Functional or structural disturbances of the central nervous system that cause epilepsy may also cause psychosis or confer susceptibility to the adverse effects of antiepileptic drugs.
Forced normalization:
Emergence of psychotic symptoms when seizure control is attained (alternating psychosis). These symptoms are associated with a relative normalization of EEG (compared with previous EEG) with a clinical alternation of seizures (when epilepsy is not controlled and there are alterations in EEG) and psychosis (when epilepsy is controlled, and the EEG is normalized).
The "release phenomenon" of antiepileptic drugs:
"Occult" psychosis due to frequent epileptic seizures dominating the clinical condition, that is only revealed when seizures are controlled.
Drug interactions:
Adverse effects are more frequent in polymedicated patients, including adverse psychiatric effects.

Table 2 Antiepileptic medication prescribed over the years up to the time of the second psychiatric hospitalization

Medicación basal	2007	2009	2010	2011	2012	2015
CBZ 1600mg/day	CBZ **1200 mg/day**	CBZ 1200 mg/day	CBZ 1200 mg/day	CBZ **1800 mg/day**	CBZ 1800 mg/day	CBZ 1200 mg/day
Clobazam 20mg/day	Clobazam 20 mg/day	Clobazam 20 mg/day	Clobazam **40 mg/day**	Clobazam 40 mg/day	Clobazam 40 mg/day	Clobazam 40 mg/day
	LVT 1000 mg/day	LVT **4000 mg/day**	LVT 4000 mg/day	LVT 4000 mg/day	LVT 4000 mg/day	LVT 4000 mg/day
					Clonazepam 4 mg/day	Clonazepam 4 mg/day

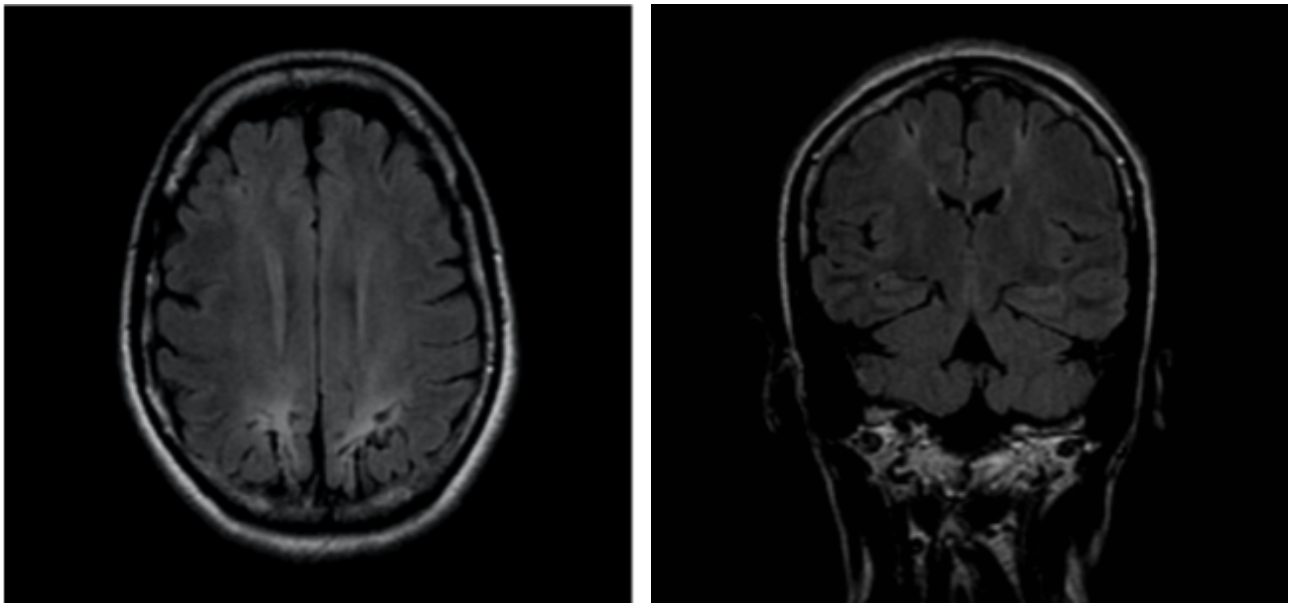
CBZ – Carbamazepine; LVT – Levetiracetam; **Bold** – indicates adjustments to the medication; ☐ Before the beginning of psychotic symptoms ▨ After the beginning of psychotic symptoms

Apart from the described epilepsy, there is no other medical history to refer.

There are no reports of psychiatric history in the family nor relevant medical history.

Developmental History

Concerning the patient's personal life story, she grew up with her parents and maternal grandmother until her parents divorced when she was 11. She considers her parents to be "*the best model of a good divorce*", because they managed the whole process without conflict and "*always kept parenting first*". She stayed with her grandmother, visiting her parents at the weekends. At school, although she always had learning difficulties, requiring her father's help to do her homework, she completed compulsory education (6th grade) without failing any grade. She has loved poetry since her childhood and used to write many poems that she has been trying unsuccessfully to get published until today. When she finished school she started working as a receptionist in her father's company and kept that job until 2013, when her father died, the company went out of business and she was awarded a disability pension for her psychiatric condition which is described below. She got married when she



Axial (top image) and coronal (bottom image) T2 Flair Images, demonstrating high-intensity signal at the perirolandic and parieto-occipital areas and atrophy with ulegyric pattern in the parieto-occipital area

Figure 1 | *Brain Magnetic Resonance Image Scans*

was 33 years old and had a child one year later. She describes her marriage as "*a relationship that never gave her the love she needed*". She divorced in 2017 and went back to her grandmother's house. Her son has been living with his father since then, spending the weekends with her. Interpersonally, she has a few friends from childhood and some friends she met in an association of people with epilepsy she attended during adolescence. Her mother describes her as "*stubborn, not easily moved away from what she decides*", "*very sweet, but too honest, when she does not like someone she says it in their faces*".

History of the Present Complaint

The patient had no psychiatric history until 2012.

In 2012, she had her first psychiatric hospitalization, as she was experiencing persecutory delusion. She was medicated with risperidone 6 mg/day and, after discharge, she was followed up at the outpatient department, being better overall, yet with considerable residual persecutory delusion. Electroencephalogram showed no alterations and Brain Magnetic Resonance Image Scans demonstrated high-intensity signal at the perirolandic and parieto-occipital areas and atrophy with ulegyric pattern in the parieto-occipital area (**Fig.1**). The Raven's Progressive Matrices test revealed a middle inferior level of intelligence (group IV, P.50), Addenbrooke's Cognitive Examination revealed memory compromise as the only cognitive function affected (16/26) and the Brief Symptom Inventory showed an above-average level of paranoid ideation. In 2013, due to functional disability, she was awarded a disability pension.

In 2015, her clinical condition became aggravated, with neglect of her daily routine; hetero-aggressivity; emotional lability; auditory verbal hallucinations ("*the Gods tell me what I have to do"; "I hear my neighbours talking everywhere*"); thought broadcasting ("*my neighbours know what I think"; "I always tell my doctor that I´m going to take the pills before I take them*") and thought echo ("*my neighbours repeat my thoughts*"); mystic and persecutory delusions ("*There are many Gods, there is the upside-down God. If I have my feet like this, it is one God, if I have them like that it is another*"; her husband reported that "*she almost beat my neighbour's son, believing he was chasing her*").

Despite many therapeutic adjustments, including starting long-acting injectable risperidone (37.5 mg/mL intramuscular, fortnightly) on suspicion of non-adherence to oral therapy, the patient did not improve, and was hospitalized.

By the time of her inpatient admission, physical examination and analytical tests showed no relevant alterations.

Long-acting injectable risperidone was increased to 50 mg/mL, without success. Zotepine was added, up to 300 mg/day, also without improvement. Disabling extrapyramidal symptoms motivated suspension of risperidone and decrease of zotepine. Meanwhile, the patient simulated taking the medication and had an epileptic seizure. She was observed by the Neurology department and it was hypothesized that she was suffering from levetiracetam-induced psychosis. This was tested by means of a gradual switch from levetiracetam to lamotrigine and suspension of antipsychotics. A week later no delusional or hallucinatory activity was found and three weeks later the patient recovered the functioning she had prior to 2012. She was discharged medicated with carbamazepine 400 mg 1+0+0+1, lamotrigine 100 mg 1/2+0+1+0, clobazam 20mg 0+0+1+0 and clonazepam 2 mg 1/4+1/4+0+1.

The patient is still being followed-up in the Psychiatry outpatient department. At the moment (over four years after discharge) the patient continues to be free of any psychotic symptoms, with her usual pattern of epileptic seizures (2-3 seizures per catamenium), medicated with the antiepileptic drug schema mentioned above, with the addition of a posterior titration of lamotrigine of 200 mg/day.

Discussion

Levetiracetam is a generally well-tolerated drug without serious adverse effects[8].

Although infrequent, there are some reported cases of levetiracetam-induced psychosis (0.7%)[5,9-11]. However, the emergence of psychotic symptoms usually occurs a few days after starting the drug or after increasing its dosage, and mostly in patients with a previous personal/family history of psychosis[4-12]. In this case, levetiracetam was started in 2007 (1000 mg/day) and increased in 2009 to 4000 mg/day. The only subsequent changes were to the dosage of clobazam in 2010 (increased to 40 mg/day) and carbamazepine in 2011 (increased to 1800 mg/day; in 2014 the patient reduced this on her own initiative to 1200 mg/day) – **Table 2**. The psychotic symptoms only appeared in 2012, at the time she was first hospitalized, and were interpreted as constituting an organic psychosis in the context of epilepsy. Despite the high dose of risperidone, there was never a full remission of the symptoms. Only after suspension of levetiracetam did the patient show total remission of psychotic symptoms, with a full recovery of her previous functioning, and without any change in her usual pattern of epileptic seizures. Although there is no temporal relation between the beginning of the symptoms and the starting of levetiracetam or the increase to its dosage, the fact that remission has continued for over four years after the suspension of this drug, without the administration of any antipsychotic drugs, reinforces the probability of this association (total score of 8 on the Adverse Drug Reaction Probability Scale, meaning that it is probable that the symptoms were caused by this drug)[13].

This alerts us to the possibility of adverse psychiatric effects occurring several years after starting antiepileptics or as a consequence of unknown drug interactions. Future research is necessary to enable a better understanding of the physiopathological mechanisms involved and to establish definite causality.

This case also reminds us that we must be careful about the accuracy of the first rank symptoms of schizophrenia: as our patient presented most of them, if we had limited our diagnosis to their presence we would not have hypothesized other possibilities, nor provided suitable treatment. Every psychiatric disorder, particularly psychosis, should only be diagnosed after a careful work up to exclude medical/neurological causes, which implies better communication between specialties and detailed knowledge of clinical practice in Neurology, an imperative already expressed by psychiatric trainees in Portugal[14,15].

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CONFLICT OF INTERESTS

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