Epilepsy & Behavior Case Reports 10 (2018) 102–105

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

A case of interictal dysphoric disorder comorbid with interictal psychosis: Part of the same spectrum or separate entities?☆

Susumu Morita [a], Go Taniguchi [a,*], Hidetaka Tamune [a,b], Yousuke Kumakura [a,c], Shinsuke Kondo [a], Kiyoto Kasai [a]

[a] Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[b] Department of Cellular Neurobiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[c] Department of Mental Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:
Received 6 April 2018
Received in revised form 9 July 2018
Accepted 10 July 2018
Available online 3 August 2018

Keywords:
Temporal lobe epilepsy
Interictal depression
Interictal dysphoric disorder
Interictal psychosis
Sertraline
Aripiprazole

ABSTRACT

Depressive disorders in epilepsy often present characteristic clinical manifestations atypical in primary, endogenous depression. Here, we report a case of a 64-year-old woman with right mesial temporal lobe epilepsy, who complained of bizarre, antipsychotic-refractory cenesthetic hallucinations in her interictal phase, and was hospitalized after a suicide attempt. Detailed clinical observations revealed mood symptoms, which led to the diagnosis of interictal dysphoric disorder comorbid with interictal psychosis. Sertraline with low-dose aripiprazole markedly alleviated both depressive and psychotic symptoms. This case suggested that the two diagnostic entities may overlap and that depressive symptoms tend to be concurrent when concurring with psychosis, which hampers the appropriate choice of a treatment option.

1. Introduction

Patients with epilepsy have a higher incidence of psychiatric comorbidities than does the general population [1]. Psychiatric disorders associated with epilepsy are classified into those with a temporal relationship to seizures (periictal) and those without (interictal). Periictal psychiatric disorders can further be classified into those occurring during (ictal), preceding (preictal), and following (postictal) seizures. A large-scale study involving the general population revealed that depression was comorbid in 18% of adults with epilepsy, and psychosis in 9% [1]. Additionally, a meta-analysis that included studies of four populations found the prevalence of lifetime depression in patients with epilepsy to be 13.0% (95% CI: 5.1–33.1) [2]. A community-based study comprising patients with epilepsy identified a higher incidence of depression in patients with recurrent seizures than in those in remission [3].

The clinical association between epilepsy and depression had been recognized as early as 400 BC, when Hippocrates highlighted their comorbidity (reviewed in [4]). Kraepelin noted that interictal mood disorders in epilepsy often present atypical manifestations, such as irritability intermixed with euphoric moods, fear, anxiety, anergia, pain, and insomnia (reviewed in [4,5]). These patients often fail to meet conventional criteria such as the International Classification of Diseases or Diagnostic and Statistical Manual of Mental Disorders [6]. Blumer coined the term interictal dysphoric disorder to re-define this atypical mood disorder, stressing eight symptoms in three categories for operational diagnosis [5]. In recent years, the importance of diagnosing and treating mood disorders in epilepsy has been recognized, following the discovery that depression, and not seizure frequency, is the major predictor of quality of life in treatment-refractory epilepsy [7]. Even milder depressive episodes increase the risk of suicide, cause an adverse effect on the quality of life and seizure control, and increase the healthcare cost, irrespective of seizure severity or duration [8]. For this reason, self-report inventories, such as the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) for the screening of depression in epilepsy [9] and Interictal Dysphoric Disorder Inventory (IDDI) for standardized diagnosis of IDD [10], were developed.

Controversy exists on the reliability of the IDDI as a diagnostic tool. Additionally, whether IDD can be considered an independent, epilepsy-specific diagnostic entity is debated [11]. In fact, IDD is highly comorbid with major depression and is as prevalent in migraine as it is in epilepsy [10]. This suggests that characteristic symptoms of IDD are shared among different types of depression with different etiologies.

In addition to the effect of psychosocial disadvantage, underlying common etiologies have been suggested for epilepsy and mood disorders

Abbreviations: EEG, Electroencephalogram; MRI, Magnetic resonance imaging; ECD-SPECT, 99mTc-ethyl cysteinate dimer brain single photon emission computed tomography; IDD, Interictal dysphoric disorder; IIP, Interictal psychosis.

☆ **Disclosures:** None of the authors has any conflict of interest to disclose.

* Corresponding author at: 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: taniguchi-jes@umin.ac.jp (G. Taniguchi).

https://doi.org/10.1016/j.ebcr.2018.07.007

such as changes in cortical and subcortical anatomical structures, neurotransmitter activities (reviewed in [12,13]), and sclerosis in the limbic system [14],although much remains to be understood. For example, the effects of lateralization of epileptic foci on depression severity are still unclear (reviewed in [14]).

Psychosis in epilepsy has been known since the times of ancient Greece. However, it was not until the mid-20th century that "schizophrenia-like psychosis" was formally reported with characteristics such as the absence of cognitive deterioration [15]. The current definition of IIP was formalized as psychosis in clear consciousness in patients who have been diagnosed with epilepsy, where the psychosis occurs not exclusively during or immediately following a seizure (reviewed in [16,17]). The diagnosis of IIP relies on psychiatric assessment by clinicians, and although IIP is relatively infrequent compared with mood disorders, the symptoms of IIP markedly affect the daily lives of patients and families. There are other forms of psychosis in epilepsy that can be distinguished from IIP based on their temporal relationship with seizures. Ictal psychosis is not common, and is usually brief, stereotyped, and often associated with subtle automatisms [18]. In contrast, postictal psychosis typically occurs within the 72 h following a seizure and is characterized by a "lucid interval" between seizure cessation and psychosis onset [19].

Similar to depression in epilepsy, the pathophysiological basis of psychosis in epilepsy is largely unknown. Candidate mechanisms include aberrant neurotransmitter systems, hippocampal circuits, and autoimmune etiologies including those related to *N*-methyl-D-aspartate (NMDA) receptors (reviewed in [13]).

Here, we present a case of IDD with comorbid IIP, which was refractory to perospirone and risperidone, and responded well to sertraline with low-dose aripiprazole. Further, we discuss diagnostic, nosological, and therapeutic issues.

2. Case presentation

We report the case of a 64-year-old, right-handed Japanese woman with right mesial temporal lobe epilepsy (mTLE), who was admitted to the psychiatric department of our hospital after a suicide attempt. Her family history was negative for psychiatric disorders or epilepsy. She had experienced epileptic seizures since her early teens, for which anti-seizure medications were prescribed. This treatment reduced her seizure frequency to one time over several months. The habitual seizure started with malaise in the head, followed by loss of consciousness, ictal speech, oral automatism, and tonic posturing of the upper limbs. She recovered consciousness after several minutes, followed by a severe headache and nausea. At the age of 55 years, she quit her job and stopped enjoying her hobbies of stage play and sewing. At the age of 60 years, she began to feel a burden on her shoulders and upper limbs and stopped performing housekeeping. When she was 64 years old, she visited the psychiatric department of our hospital. Detailed examination, including electroencephalography (EEG), magnetic resonance imaging (Fig. 1), and ethyl cysteinate dimer-single-photon emission computed tomography (ECD-SPECT) revealed right mTLE with right hippocampal sclerosis. Administration of lamotrigine 200 mg in addition to carbamazepine 600 mg, phenytoin 200 mg, and clonazepam 1 mg, reduced her seizure frequency and alleviated depression and anxiety. Four months prior to admission, she started to complain about sticky feelings on her skin and foul odor from rice caused by her touch. Treatment with perospirone 8 mg was started, which she discontinued the following month. She complained of "plaster-like" matter on her front teeth that a dentist found nonexistent, "slimy matter" throughout the insides of her house, hot feelings in the right half of her body, and a feeling of weakness. Treatment with risperidone 1 mg was started for her cenesthopathy, without any success. Six days prior to admission, she wrapped foods many times in cellophane films, complaining of a foul odor spreading to the neighborhood, and talked to herself crouched in the bathroom. Five days prior to admission, she called her family and discussed her suicidal ideation, went to a pond, and immersed herself to her knees; however, she was stopped by her family.

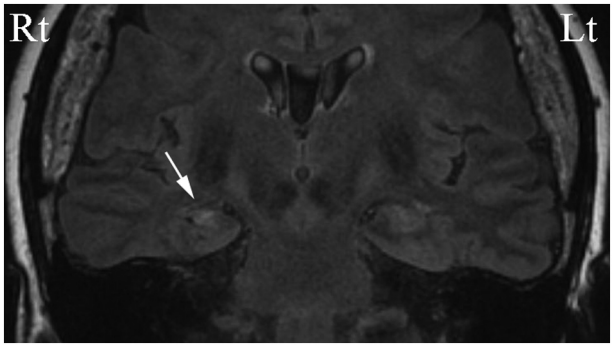

Fig. 1. MRI FLAIR coronal section. Right hippocampal sclerosis is indicated by an arrow.

During her mental status examination at admission, she was a well-dressed lady conforming to her stated age. Although she looked rather weak lying on the bed, she enthusiastically explained her cenesthopathy in detail as her "seizure." She was extremely sensitive to odor from food and sanitizing alcohol. Her affect was not interrupted with intermittent smiles, giving a neurotic impression. She complained of nausea induced by seeing text, which prevented her from completing a self-report inventory. Meanwhile, the risperidone dose was increased to 4 mg to suppress hallucinations, and then replaced by aripiprazole 3 mg; neither of the treatments showed success. During her hospitalization, we observed at least two depressive episodes; within several hours, she stopped talking and eating, was in a state of stupor, and scarcely blinked on pain, but showed fierce resistance towards nurses who helped her with her toilet duties. After several days, she recovered, again within several hours, followed by euphoria. The EEG that was performed during one of her depressive episodes revealed normal results, except for the presence of several sharp waves maximal at F8 and spreading to T4 and Fp2 (Fig. 2), which were similar to but less frequent compared to the previous recording. The observation led to the diagnosis of IDD, and sertraline 25 mg was started. When sertraline was adjusted to 100 mg, she started to walk and eat, and her complains regarding hallucinations reduced. One month after admission, her depressive mood, suicidal ideation, and cenesthetic hallucination had completely disappeared. At this point, the IDDI total score and total severeness were 6/8 and 27, respectively.

After her discharge, aripiprazole was suspended twice, each time leading to an apparent recurrence of the depressive symptoms, and aripiprazole was therefore resumed. Otherwise, however, she has now been living seizure-free, and without psychiatric symptoms except for intermittent mild psychotic symptoms that do not affect her daily life. Written informed consent was obtained from the patient for the publication of this case report.

3. Discussion

3.1. Diagnostic and nosological issues

After years of dysthymia and anergia, the patient developed prominent psychosis, which worsened over a few months, masked her depressive symptoms, and was refractory to treatment with antipsychotics. She was seizure-free for months before and during hospitalization, and her EEG during the dysphoric episode showed less frequent sharp waves than did the previous EEG, together reflecting that the mood and psychotic symptoms were interictal.

The patient was in frank psychosis and satisfied the relatively simple definition of IIP, and the absence of negative or cognitive symptoms was typical for the diagnosis [17]. However, the most prominent symptoms of her psychosis were not the well-reported auditory hallucinations or

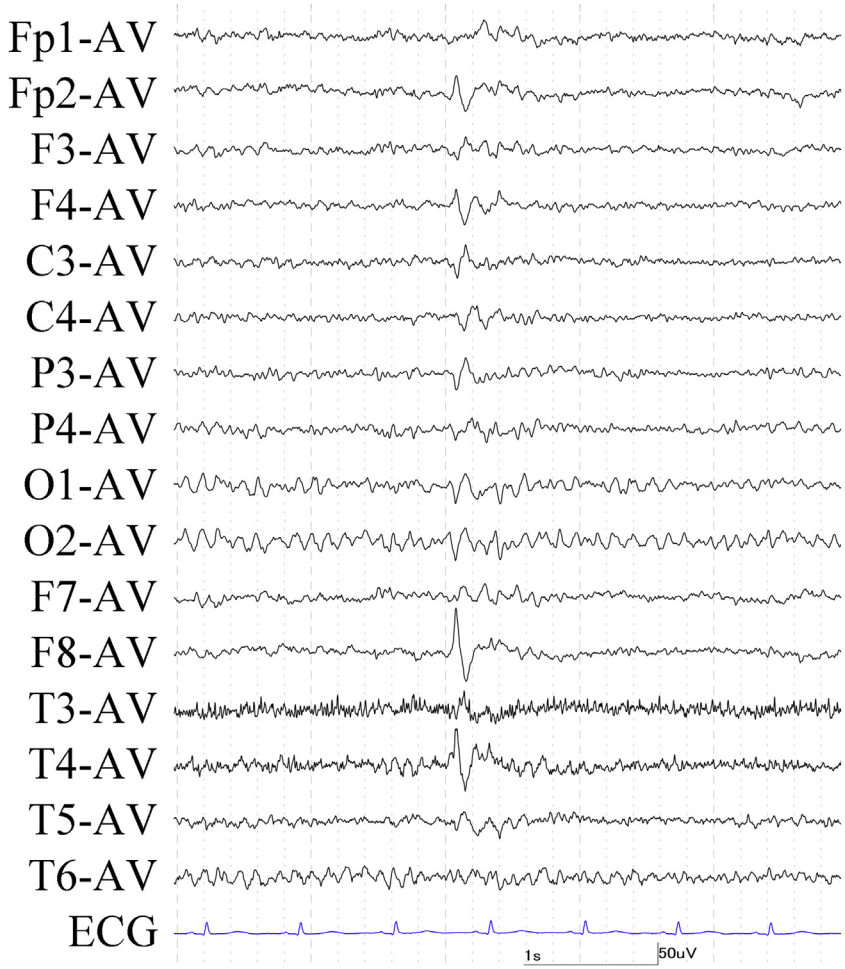

Fig. 2. Interictal EEG. A sharp wave peaking at F8 and spreading to T4 and Fp2 is shown (Time constant, 0.3 s; High-cut filter, 50 Hz; Average reference montage).

delusions, but cenesthetic hallucinations. Furthermore, the psychosis was refractory to treatment with antipsychotics, although IIP is generally more responsive to antipsychotics than is schizophrenia [16]. After close clinical observation, the case was found to satisfy almost all eight major symptoms of IDD, except for pain [5,10]. Other features of IDD not included in the eight symptoms, such as rapid onset and termination of dysphoric episodes in a uniform manner without an apparent external trigger, and response to selective serotonin reuptake inhibitors (SSRIs) [4,5], were also present.

In addition to the abovementioned assessment of IDD and IIP, formal diagnosis using Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) [20] was also performed by two experienced psychiatrists. The diagnosis was psychotic disorder due to a medical condition with hallucinations, and depressive disorder due to a medical condition with mixed features. Late-onset schizophrenia was a possible differential diagnosis, although this was less likely due to the evident presence and involvement of organic etiology.

Comorbidity of IDD and IIP is relatively poorly studied, and recent guidelines and reviews treat interictal psychotic disorders separately from interictal mood disorders [8]. However, Blumer's original concept of IDD incorporated IIP as a severe subtype of IDD [5,21], based on the notion that dysphoria precedes psychosis in most cases of IIP. Whether Blumer's description of IIP captures the majority or only limited cases of psychosis in epilepsy is unclear, but the present case well fits Blumer's description of IIP as IDD with psychotic features. Considering the treatment option discussed below, special attention should be paid not to dismiss mood symptoms in epilepsy, which are potentially masked by psychosis.

The most prominent psychotic symptom was mood-incongruent cenesthopathy with body dysmorphic features. Cenesthopathy was reported in 7 of 69 patients in Slater's schizophrenia-like psychosis of epilepsy [15].

3.2. Challenges in diagnosing IDD, limitations of using the IDDI, and importance of objective psychiatric assessments merits attention

Diagnosis of IDD is challenging in some patients due to the atypical and pleomorphic nature of the symptoms, and other manifestations related to seizures or side effects of the antiepileptic drug treatment [4]. In the present case, the diagnosis of IDD was possible only during hospitalization for several reasons; the prominent hallucination masked depressive symptoms, neither the patient nor the family could distinguish between epileptic seizures and severe dysphoric episodes, her mixed state caused an apparently neurotic presentation that the family did not take seriously, and the IDDI could not be completed because of nausea caused by reading text.

An assessment using self-report inventories is recommended for screening of depression in patients with epilepsy [8]. However, patients' subjective experiences of psychiatric symptoms often diverge from their objective severity, and self-report inventory results are compromised in this sense. In this patient, the IDDI could not be used in the acute state of dysphoria, and even after the remission of depression, the score was too low relative to our other objective observations and raised doubts on its reliability in this case. This suggested that the IDDI scores are considerably influenced by the mental status of the patient at the time it is administered. This could partly explain the poor

reproducibility of IDD diagnosis using the IDDI [11]. Objective measures to be used by clinicians or family members could be more suitable for the accurate diagnosis and treatment of IDD.

3.3. Pharmacological treatment

SSRIs are recommended as the first-line pharmacological treatment for interictal depressive disorders because of their favorable side effect profiles, and the proconvulsant effects reported to be associated with some tricyclic antidepressants can be avoided [8]. Sertraline [22,23], citalopram [24–26], reboxetine [26], mirtazapine [26], and fluoxetine [23] were all shown to be effective in open trials, although there is no randomized-controlled trial to date that shows the superiority of SSRIs over other types of antidepressants or antiepileptic drugs with psychotropic effects [27]. As such, the treatment of interictal depression is recommended to tentatively be similar to that of endogenous depression [27].

The pharmacological treatment of interictal psychosis also lack supporting evidence from controlled studies, and currently, following the guidelines for primary schizophrenia is recommended. Although second-generation antipsychotics are the first-line therapeutics [8,17], care should be taken due to their proconvulsant effects [28]. In contrast, according to Blumer's view of IIP as severe IDD, treatment with a tricyclic antidepressant and the addition of an SSRI or risperidone in treatment-refractory cases are instead recommended based on the remarkable response in his case series [21].

In the present case, neither perospirone 8 mg, risperidone 4 mg, nor aripiprazole 3 mg was effective for treating hallucinations; however, sertraline 100 mg with aripiprazole 3 mg was remarkably effective for both depression and hallucinations, and suspension of aripiprazole caused the recurrence of depression. The clinical course suggests that their combination and not monotherapy with either medication was effective in the present case. The ineffectiveness of antipsychotics monotherapy is compatible with Blumer's description of IIP as severe IDD [5,21]. Sertraline with adjunctive aripiprazole was shown to be superior to sertraline monotherapy for major depression in two randomized, double-blind, placebo-controlled trials [29,30]. The mechanism of efficacy of aripiprazole adjunction in humans is largely unknown, but in a study using animal models of depression comparing the efficacy of aripiprazole as an adjunct to various antidepressants, only desipramine, a selective norepinephrine reuptake inhibitor, was not augmented by aripiprazole, suggesting a complex regulation between dopamine D2 and serotonin 5-HT1A and 5-HT2A receptors [31]. Blumer recommended the addition of a second antidepressant in treatment-refractory cases of IIP, and we reproduced a similar remarkable efficacy with a modern, well-established augmentation therapy in endogenous major depression. Notably, IIP and severe IDD is symptomatically closer to schizophrenia or schizoaffective disorder than psychotic depression, whereas the treatment response profile resembles that of the latter. Sertraline with adjunctive low-dose aripiprazole should be considered in treatment-refractory IDD especially with psychotic features.

4. Conclusion

We reported a case of IDD comorbid with IIP with prominent cenesthetic hallucinations. Mood symptoms were difficult to detect; however, once detected, treatment with sertraline augmented with aripiprazole was remarkably effective for both the psychotic and mood symptoms.

The previously reported concept of IIP as severe IDD well fits this case. Therefore, the nosological relationship between IIP and IDD should be further clarified in the future. Considering that mood symptoms tend to be underrecognized, even if derived from self-report inventories, an objective psychiatric assessment delivered by qualified clinicians is essential for the accurate diagnosis of IDD.

Acknowledgments

None.

References

[1] Gaitatzis A, Carroll K, Majeed A, Sander J. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia 2004;45:1613–22.
[2] Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80:590–9.
[3] O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract 1999;49:211–4.
[4] Mula M. In: Trimble MR, Schmitz B, editors. The interictal dysphoric disorder. Camb Univ Press; 2011. p. 80–9.
[5] Blumer D. Dysphoric disorders and paroxysmal affects: recognition and treatment of epilepsy-related psychiatric disorders. Harv Rev Psychiatry 2000;8:8–17.
[6] Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE Commission on Psychobiology of Epilepsy. Epilepsy Behav 2007;10:349–53.
[7] Boylan Flint, Labovitz Jackson, Starner Devinsky. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 2004; 62:258–61.
[8] Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia 2011;52:2133–8.
[9] Gilliam F, Barry J, Hermann B, Meador K, Vahle V, Kanner A. Rapid detection of major depression in epilepsy: a multicentre study. Lancet Neurol 2006;5:399–405.
[10] Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, et al. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia 2008;49:650–6.
[11] Amiri M, Hansen C. The interictal dysphoric disorder in patients with epilepsy: a doubtful disorder lacking diagnostic tools. Seizure 2015;24:70–6.
[12] Kanner A. Depression and epilepsy: a new perspective on two closely related disorders. Epilepsy Curr 2006;6:141–6.
[13] Josephson CB, Jetté N. Psychiatric comorbidities in epilepsy. Int Rev Psychiatry 2012; 29:409–24.
[14] Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 2000;39:121–5.
[15] Slater E, Beard A. The schizophrenia-like psychoses of epilepsy. Br J Psychiatry 1963; 109:95–102.
[16] Kanner A. Psychosis of epilepsy: a neurologist's perspective. Epilepsy Behav 2000;1: 219–27.
[17] Adachi N, Kanemoto K, de Toffol B, Akanuma N, Oshima T, Mohan A, et al. Basic treatment principles for psychotic disorders in patients with epilepsy. Epilepsia 2013;54(Suppl. 1):19–33.
[18] Mula M. Epilepsy-induced behavioral changes during the ictal phase. Epilepsy Behav 2014;30:14–6.
[19] Kanner A, Stagno S, Kotagal P, Morris H. Postictal psychiatric events during prolonged video-electroencephalographic monitoring studies. Arch Neurol 1996; 53:258–63.
[20] American Psychiatric Association. Diagnostic and statistical manual of mental disorders5th ed. ; 2013.
[21] Blumer Wakhlu, Montouris Wyler. Treatment of the interictal psychoses. J Clin Psychiatry 2000;61:110–22.
[22] Kanner A, Kozak A, Frey M. The use of sertraline in patients with epilepsy: is it safe? Epilepsy Behav 2000;1:100–5.
[23] Thomé-Souza MS, Kuczynski E, Valente KD. Sertraline and fluoxetine: safe treatments for children and adolescents with epilepsy and depression. Epilepsy Behav 2007;10:417–25.
[24] Hovorka J, Herman E, Nemcová I. Treatment of interictal depression with citalopram in patients with epilepsy. Epilepsy Behav 2000;1:444–7.
[25] Specchio L, Iudice A, Specchio N. Citalopram as treatment of depression in patients with epilepsy. Clin Neuropharmacol 2004;27:133–6.
[26] Kühn K-U, Quednow BB, Thiel M, Falkai P, Maier W, Elger CE. Antidepressive treatment in patients with temporal lobe epilepsy and major depression: a prospective study with three different antidepressants. Epilepsy Behav 2003; 4:674–9.
[27] Mula M. The pharmacological management of psychiatric comorbidities in patients with epilepsy. Pharmacol Res 2016;107:147–53.
[28] Lertxundi U, Hernandez R, Medrano J, Domingo-Echaburu S, García M, Aguirre C. Antipsychotics and seizures: higher risk with atypicals? Seizure 2013;22:141–3.
[29] Lin C-H, Lin S-H, Jang F-L. Adjunctive low-dose aripiprazole with standard-dose sertraline in treating fresh major depressive disorder: a randomized, double-blind, controlled study. J Clin Psychopharmacol 2011;31:563–8.
[30] Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008;28:156–65.
[31] Bourin M, Chenu F, Prica C, Hascoët M. Augmentation effect of combination therapy of aripiprazole and antidepressants on forced swimming test in mice. Psychopharmacology 2009;206:97–107.