Clinical commentary

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Antiepileptic effect of olanzapine in epilepsy patients with atypical depressive comorbidity

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ABSTRACT – Depression is relatively common among patients with epilepsy, but often with predominant atypical symptoms. Some antiepileptic drugs show positive psychotropic effects, but these are not always sufficient to stabilize mood in epilepsy patients. Antidepressants are recommended to treat atypical depression but are not always effective and present a certain risk of seizure provocation. Thus, new treatment options are welcome. Here, we describe three cases of refractory epilepsy with atypical depression in which olanzapine, contrary to its earlier reported proconvulsant effect, showed excellent antidepressant action and resulted in seizure control. Possible mechanisms of this action are discussed.

Key words: epilepsy, depression, bipolar disorder, interictal dysphoric disorder, olanzapine

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About an eighth of adult patients with epilepsy (PWE) are resistant to antiepileptic drug (AED) therapy (Picot *et al*., 2008), thus new treatment options are welcome. Depression, which refractory patients frequently suffer from, is one of the most common co-morbidities with a prevalence ranging from 13% to almost 36% (Fiest *et al*., 2013). Yet, using DSM diagnostic criteria, almost 50% of depressive patients with epilepsy actually present atypical depression (Mendez *et al*., 1986). In patients primarily diagnosed with major depressive disorder according to DSM criteria, irritability with or without outbursts of fury, anxiety, headaches, insomnia, and, less often, euphoria are considered as indicators of atypical depression (Mula, 2013a).

Regarding treatment, some AEDs such as carbamazepine (CBZ) and oxcarbazepine (OXC), lamotrigine (LTG), and valproic acid (VPA) have positive psychotropic effects (Mula, 2013b). A case report showed

that as monotherapy, LTG provides both seizure control and satisfactory mood stabilization (Sepic-Grahovac *et al.*, 2011). In more severe cases, add-on treatment with antidepressants is required (Kanner, 2016), and these should be chosen carefully to avoid seizure-inducing effects. The ideal would be an antidepressant with anti-seizure properties. The latter have been reported for citalopram (CTP), a selective serotonin reuptake inhibitor (SSRI), based on an animal model (Vermoesen *et al.*, 2012) and older open-label studies (Favale *et al.*, 2003; Specchio *et al.*, 2004). However, confirmation based on more recent and controlled investigations is missing. According to Stahl (2013), antipsychotics exert antidepressant actions either alone or in combination with antidepressants.

Olanzapine (OLZ) is an atypical neuroleptic used for psychosis and bipolar disorder (Sharma *et al.*, 2006). Several authors have reported seizure precipitation in patients both with and without pre-existing epilepsy (Wyderski *et al.*, 1999; Hedges and Jeppson, 2002; Camacho *et al.*, 2005; Behere *et al.*, 2009; Spyridi *et al.*, 2009; Rosen *et al.*, 2012; Anzellotti *et al.*, 2016). However, based on a comparative cross-over study with 16 psychotic patients with epilepsy (Thomas *et al.*, 2003), an increase of seizure frequency did not occur with OLZ. To our knowledge, an anticonvulsive effect in PWE has not been described. Here, we report three cases with drug-resistant epilepsy and atypical depressive symptoms in which co-medication with CTP produced no measurable improvement, whereas addition of OLZ led to impressive antidepressant as well as anti-seizure effects, resulting in mood stabilization and complete seizure control in all three.

Informed consent was obtained from all the three individual participants.

Case studies

Case 1

A 28-year-old woman with right amygdalar epilepsy had, since age five, seizures consisting of sudden, intense fear, without any apparent cause, lasting for several seconds. At first, she became seizure-free with CBZ treatment but at age 23 had a relapse during a stressful period, and the seizures are presently not pharmacologically controlled. Video-EEG monitoring revealed interictal persistent right temporal slow waves and frequent irregular spikes and slow waves, as well as ictal right temporal epileptiform activity. Magnetic resonance imaging (MRI) was reported to show "enlarged right para-sellar soft tissues" (the original images were not available). Seizures occurred daily, sometimes in clusters, and surgical treatment was proposed and performed. The anterior right temporal lobe, including the amygdala, was resected. Postoperative outcome was Engel Class 1a, as no seizures or isolated auras occurred in the first three postoperative years. However, seizures relapsed in the fourth year and increased to an average of about five per day with a peak frequency of more than 10 per day during a menstrual period. Fear was still the presenting seizure symptom, and an ictal EEG during 24-hour video-EEG recording showed a rhythmic seizure pattern of right temporal onset (*figure 1*). OXC at 1,200 mg/d + levetiracetam (LEV) at 2,000 mg/d did not control the seizures. A change of the AED regimen to OXC + topiramate (TPM) resulted in no improvement. CTP at 20 mg was added because of depression (the HAMD [Hamilton Depression Rating Scale] assessment revealed a score of 24, with item 3 [suicide evaluation] indicating suicidal ideation, and the HAMA [Hamilton Anxiety Rating Scale] revealed a score of 12, indicating unremarkable anxiety), only to find no improvement. It was noted that her condition presented features such as dysphoria, aggressive behaviour, and distractability, which indicated atypical depression. OLZ at 2.5 mg/d was added and surprisingly, not only her depression improved markedly but the patient also became seizure-free. Her present medication is OXC at 1,200 mg/d, TPM at 100 mg/d, and OLZ at 2.5 mg/d. The follow-up period is 18 months. A control test after two months showed a HAMD score of 13 (*versus* 24).

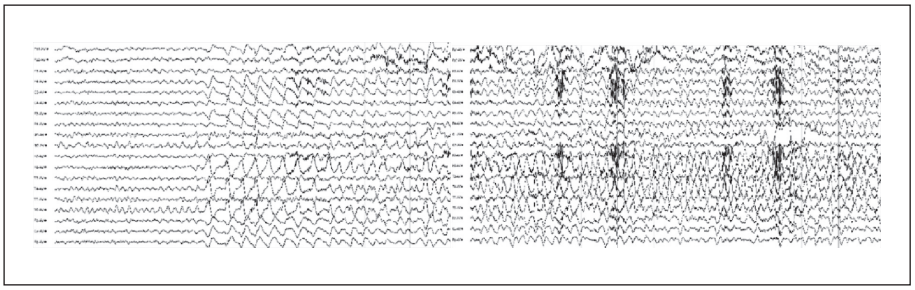

Figure 1. Ictal EEG shows rhythmic seizure activity with frequency that increases from 3 to 5 Hz, mainly at F8, T4, and T6. During this activity, the patient experiences fear which is absent before and after.

Case 2

A 27-year-old woman with cryptogenic focal epilepsy had brief (up to 40 seconds) bilateral tonic-clonic seizures starting with asymmetric bilateral tonic posturing (*figure 2A*). The seizures first occurred at age 16. She had no MRI abnormalities, and her video-EEG was reported to show multiple spikes. She was experiencing one seizure per month and became seizure-free with VPA at 1,000 mg/d. When she became pregnant at age 22, she stopped taking drugs without consultation and had a relapse with weekly and later daily seizures. After delivery, she was retreated with VPA, but without sufficient effect. Twenty-four-hour video-EEG was performed to rule out non-epileptic attacks, and ictal EEG apart from ample muscle artefacts revealed initial left rhythmic activity with a maximum at P3 and rapid bilateral spread (*figure 2B*). She continued to have seizures also with VPA at 1,000 mg/d + LEV at 1,000 mg/d. Psychiatric evaluation revealed an abnormal mood state (a mainly depressed mood and infrequent pressure of speech). Bipolar disorder with major depressive episodes was diagnosed and CTP at 20 mg/d was added to the AEDs to deal with her severe depression. This neither changed her mood nor her seizure frequency. Subsequent addition of OLZ at 2.5 mg/d resulted in substantial improvement of her mood (HAMD score decreased from 22 to 14) and complete seizure control which has now lasted >18 months.

Case 3

A 24-year-old female with cryptogenic left frontal lobe epilepsy had two generalized tonic-clonic seizures, both during sleep, at age 18. She was treated with lamotrigine (LTG) at 50 mg/d and remained seizure-free for two years. At age 20, she relapsed with focal seizures starting with a compulsory urge to look for written characters in her surroundings or on her cellular phone. She would then become unresponsive and stare for several seconds without further symptoms. We considered this a variant of the rare seizure symptom of forced thinking which raised suspicion of a frontal lobe focus (Mendez *et al*., 1996), although no MRI abnormalities were found. Ictal EEG presented left frontal rhythmic delta activity (*figure 3*). Her seizures occurred in series of more than five/day, with a peak of more than 10/day. LTG at 200 mg/d plus TPM at 100 mg/d or OXC at 600 mg/d did not control the seizures. VPA at 1,000 mg/d caused intolerable hand tremor. LEV at 1,000 mg/d was added and slightly decreased seizure frequency to an average of 2-3/day. Depressed mood was observed, yet CTP seemed to have no effect on either mood or seizure frequency. OLZ at 2.5 mg/d was introduced because of irritable mood and flight of ideas. Seizure frequency decreased dramatically after introduction of OLZ, and control tests for HAMD and HAMA provided scores of 5 (*versus* 21) and 4 (*versus* 20), respectively. The follow-up period is 18 months. Present medication is LTG at 200 mg/d, LEV at 1,000 mg/d, and OLZ at 2.5 mg/d. At present, the state of the patient's mood is good and she is seizure-free.

Discussion

The three patients reported here have pharmacoresistant focal epilepsies. One of the patients had become seizure-free after epilepsy surgery, but had a relapse. All developed similar psychiatric comorbidity of atypical depression with a strong component of dysphoria. The symptoms are reminiscent of a bipolar disorder but also strongly resemble the condition described as "interictal dysphoric disorder" (IDD) (Blumer *et al*., 2004). Administration of a modest dose of OLZ following unsuccessful treatment with CTP surprisingly had a positive effect on both mood and seizures. Comorbid mood disorders in epilepsy often present as subclinical or subsyndromic forms of depression or with atypical features reminiscent of bipolar disorders with dysphoria as a predominant feature (Blumer, 2000; Mula, 2013a). In 1986, based on DSM-III-R, Mendez *et al*. categorised 50% of depressive disorders as atypical depression (Mendez *et al*, 1986). In 2000, Blumer introduced the concept of IDD, comprising eight key symptoms to classify the more than 50% epileptic patients not satisfying the standard DSM or ICD criteria of depression (Blumer, 2000). IDD was once viewed as an epilepsy-specific variant of depression, but was later found also in migraine patients (Mula *et al*., 2008). The eight key symptoms of IDD were categorized into three groups: labile depressive symptoms, labile affective symptoms, and specific symptoms (irritability and euphoric moods). It is the specific symptoms that make IDD reminiscent of bipolar disorders. Combination therapy using AEDs and antidepressant drugs was commonly used for bipolar depression and also observed to be effective in IDD patients, moreover, small doses of neuroleptics can enhance the action of antidepressants (Blumer *et al*., 2004). In the cases presented here, the mood symptoms did not improve with the use of CTP. We hypothesize that the positive antiepileptic effect of OLZ is related to the atypical features of the mood disorder. Previous research has also established that in patients with acute dysphoric mania (*i.e*. mania with baseline depressive symptoms), the addition of OLZ to mood stabilizers (*e.g*. VPA) improves depressive symptoms, mania, and suicidality ratings (Baker *et al*., 2004).

Previous cases and reports have indicated a propensity of APD (atypical antipsychotic drug) to lower the seizure threshold. The association between usage of

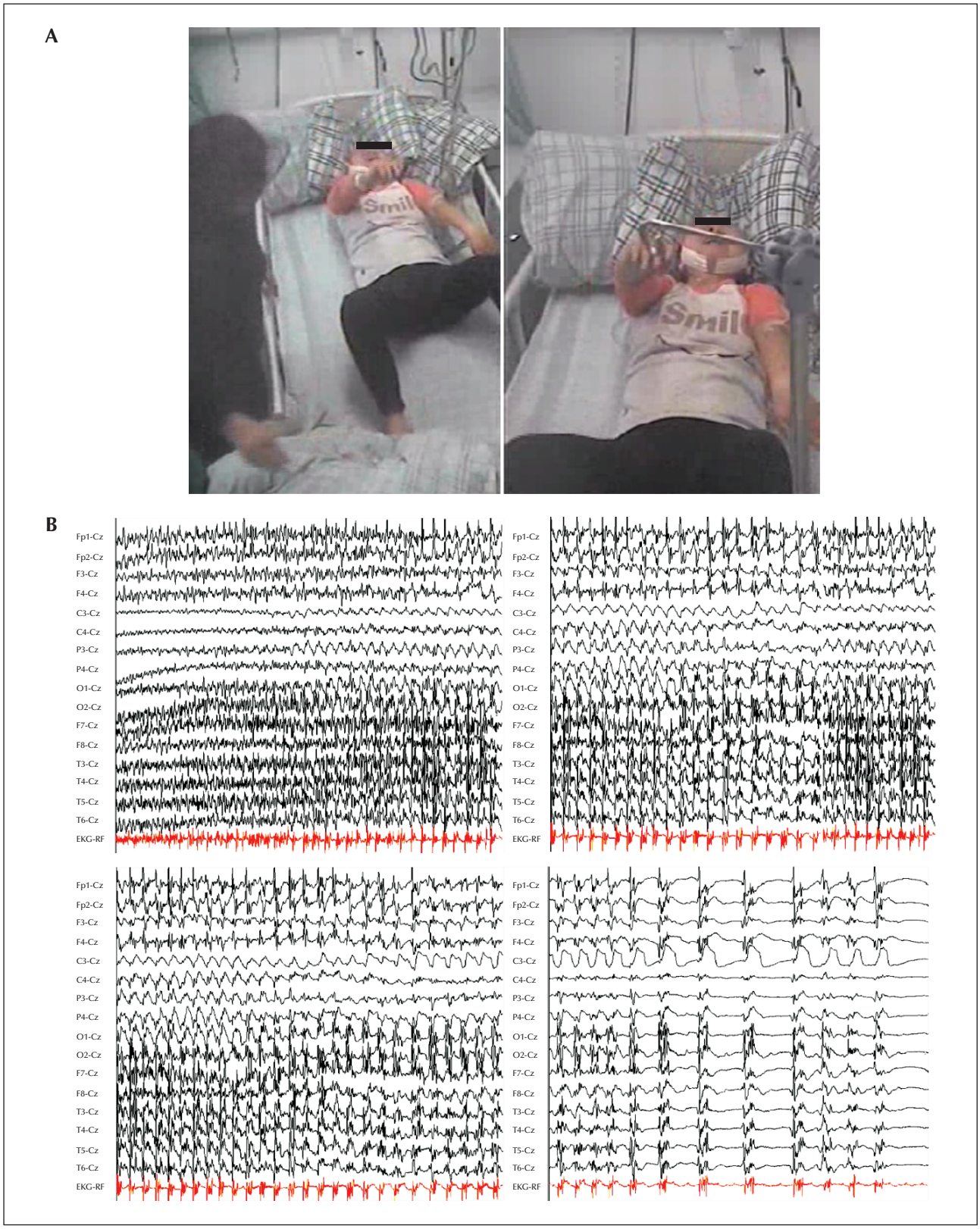

Figure 2. (A) Onset of a tonic seizure in Patient 2. (B) Ictal EEG of Patient 2 showing ample muscle artefacts and seizure onset with rhythmic activity that starts with a maximum at P3.

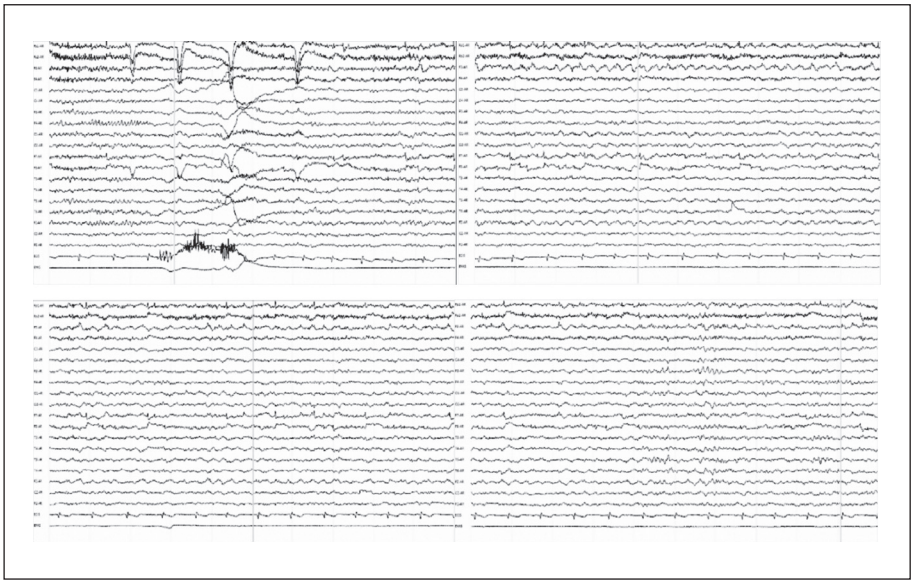

Figure 3. Ictal EEG of Patient 3 showing rhythmic slow-wave activity at F3/Fz > Fp1 (10 s/page; 7 μV/mm; low-pass: 50 Hz); the patient demonstrates her habitual ictal urge to look for written characters and then stares for around 25 seconds.

APDs and risk of first-time seizure was analysed in a case-control study, revealing a 2.5-fold increased risk of seizures in patients with affective disorders (Bloechliger *et al*., 2015). These considerations could challenge the use of APDs for the management of psychiatric disorders in epilepsy. However, following critical review of previous reports, we propose more careful consideration of these relationships, taking into account the OLZ dose. In two reports of seizures related to OLZ in patients with epilepsy (Woolley and Smith, 2001; Anzellotti *et al*., 2016), the daily dose was 10 mg. In another patient with epilepsy, 5 mg/d of OLZ did not induce seizures (Bockow-Kaplan *et al*., 2012). With respect to psychiatric patients, myocloni were reported with doses lower than 10 mg per day in two cases (Camacho *et al*., 2005; Rosen *et al*., 2012), who were diagnosed with Alzheimer's disease, a condition with frequently decreased seizure threshold. The myocloni of another case (Spyridi *et al*., 2009) were not necessarily epileptic, whereas the patient reported by Hedges and Jeppson (2002) exhibited EEG findings strongly suggestive of pre-existing untreated epilepsy. All these cases do not unequivocally support that low-dose OLZ, as such, can provoke seizures in psychiatric patients and PWE. Based on a cross-over study, Thomas *et al*. (2003) observed no increase in seizures with OLZ, whereas the same patients presented seizure increase with haloperidol. Likewise, studies showing EEG abnormalities in psychiatric patients treated with OLZ (Centorrino *et al*., 2002) indicated a dose-dependent effect with the lowest dose, resulting in EEG abnormalities above 5 mg/d (Amann *et al*., 2003). The reported cases thus appear to indicate that OLZ, at daily doses of less than 5 mg, does not have proconvulsant properties. There is also supportive evidence that APDs are relatively safe (Gross *et al*., 2000) and may improve seizure outcome (Ojemann *et al*., 1987) in PWE. Furthermore, based on a comparative study among PWE on APDs, it was also concluded that use of APDs was associated with better seizure outcome in patients with focal epilepsies throughout a one-year follow-up period, regardless of the type of APD and psychiatric conditions (Okazaki *et al*., 2014).

According to Stahl (Stahl, 2013), APDs probably exhibit the most complicated pattern of binding to neurotransmitter receptors of any drug class in psychopharmacology. Regarding mechanisms, OLZ probably exerts its actions through binding to receptor systems with different affinity. It has a strong potency as an antagonist for 5-HT_{2A} and H_1 receptor. In addition, OLZ blocks 5-HT_{2C} receptor, which enhances dopamine and norepinephrine release in the prefrontal cortex, contributing to efficacy as treatment for cognitive and affective symptoms (Stahl, 2013). Regarding the impact of OLZ on seizures and epilepsy, some animal studies appear to imply proconvulsant properties (Citraro *et al*., 2015). 5-HT receptor agonists were shown to have anticonvulsant properties in seizure models (Bagdy *et al*., 2007; Gholipour *et al*., 2010), and OLZ is an antagonist of many kinds of 5-HT receptors (Bymaster *et al*., 2001). However, to our knowledge, dose effects have not yet been investigated. The protective properties of OLZ against seizures are likely to be due to allopregnenolone, a potent gamma-aminobutyric acid type A ($GABA_A$)

receptor. Studies from bipolar disorders have indicated that OLZ increases levels of allopregnenolone in the hippocampus, cerebral cortex, and serum of rats (Marx *et al*., 2000, 2003). Allopregnanolone increases the influx of chloride ions by binding to sites of $GABA_A$ receptors which enhances both the frequency and duration of the opening of the ion channel (Kelley *et al*., 2007), leading to hyperpolarization of the membrane. In clinical trials, ganaxolone, an analogue of allopregnanolone, demonstrates positive effects on refractory partial-onset seizures (Nohria and Giller, 2007). Increased neurogenesis and proliferation, which may affect neuroplasticity, might also be mechanisms for neuroactive steroids, pregnenolone (Mayo *et al*., 2005) and allopregnanolone (Wang *et al*., 2005), to protect against seizures.

Conclusions

Our cases indicate a possible therapeutic effect of OLZ in patients with epilepsy, not only for affective symptoms but also for seizures. In prior studies, it is reported that OLZ may lower the seizure threshold, leading to limited use of OLZ in epileptic patients. However, our cases, in accordance with some earlier publications, demonstrate that low-dose OLZ may not only be safe but may sometimes even exhibit an anti-seizure effect. Atypical depressive symptoms, reminiscent of interictal dysphoric disorder, appear to be an indication for adding low-dose OLZ to AEDs. However, future studies are required to establish the mechanisms of action of OLZ on seizures and affective symptoms, with special attention to doses. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Do atypical antipsychotic drugs (APDs) always increase seizure risk in epilepsy patients?

(2) Among epilepsy patients, for which conditions does olanzapine show antiepileptic effects?

(3) What is the most probable focus localization for ictal forced thinking?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".