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Olanzapine-related repetitive focal seizures with lingual dystonia

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ABSTRACT – Olanzapine-related seizures have rarely been reported despite associated proconvulsant risk factors described in the literature: myoclonic status, increased frequency of seizures, tonic-clonic seizures, as well as fatal status epilepticus. We present a psychiatric patient who developed repetitive focal motor seizures and lingual dystonia when olanzapine was added for psychomotor agitation and aggressiveness. Olanzapine was immediately suspended and the seizures progressively disappeared. A control EEG showed no paroxysmal discharges. Olanzapine shares some pharmacological similarities with clozapine, a neuroleptic with a high risk of dose-dependent seizures. This adverse effect should be taken into account, and olanzapine should be used with caution if concomitant circumstances decrease the seizure threshold. [*Published with video sequence online*]

Key words: olanzapine, side effect, seizure, focal motor seizure, lingual dystonia, EEG

Atypical antipsychotics are known to be associated with EEG abnormalities (Centorrino *et al*., 2002). Olanzapine is an atypical antipsychotic medication with fewer reported side effects than the traditional antipsychotic agents. This drug has considerable affinity for dopamine, serotonin, histamine, and adrenergic and muscarinic receptors (Fulton and Goa, 1997). Structurally, it is a thienobenzodiazepine derivative, with pharmacological profile similar to that of clozapine, the first atypical agent developed. Despite their similarities, clozapine has been noted to induce dose-dependent seizures in about 5-6% of patients (Grover *et al*., 2015; Williams and Park, 2015), whereas olanzapine has infrequently been associated with relevant epileptogenic risk although it can lower seizure threshold (Woolley and Smith, 2001). Earlier reports of the epileptogenic risk associated with olanzapine might have been potentially confounded by the presence of other medical disorders, pre-existing seizure disorders, or drug withdrawal. We report the first documented case of repetitive focal motor seizures with lingual dystonia induced by olanzapine in a patient with epilepsy and psychiatric disorder.

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Case study

A 47-year-old man was brought to the emergency department for psychotic episodes consisting of delusions, agitation and mood changes. Patient medical history revealed a diagnosis of paranoid subtype schizophrenia and post-traumatic seizure disorder since 16 years old; he fell off a bike with ictal episodes characterized by nocturnal hypermotor seizures. He regularly took topiramate at 300 mg/day and phenobarbital at 150 mg/day. He was first hospitalised in a non-neurological department where he was treated with olanzapine, 10 mg daily. After five days, he abruptly developed persistent dysartria with intermittent eyelid myoclonia. As the cerebral tomography (CT), as well as the interictal EEG, did not show any significant abnormality, these episodes were at first interpreted as pseudoseizures and the patient was treated with olanzapine, 15 mg daily. After two days, the patient was admitted to our neurological department due to sudden appearance of lingual dystonia, with repetitive episodes of right mouth deviation, eyelid myoclonia, and aphasia. These episodes were briefly followed by oral and left hand gestural automatisms. Neurological examination was normal, with the exception of dysartria and mild extrapyramidal signs. Several investigations were performed (full blood count, erythrocyte sedimentation rate, liver function tests, serum creatinine, prothrombin time, partial thromboplastin time, thyroxine and antithyroid antibodies, folic acid, and vitamin B12) and were normal. The ictal video-EEG revealed a clear correlation of symptoms with focal spikes and polyspike discharges (*figure 1*). The EEG recording showed a left fronto-temporal focus with recruiting polyspikes, followed by generalized spike-wave complexes at 4-5 Hz with phase opposition on T3 and T4. A generalized frequency reduction of about 7-8 Hz was then recorded, and finally a focal epileptic activity derived from the left fronto-temporal region was recorded. Clinically, we observed a right deviation of the mouth and eyelid myoclonia for about one minute, followed by gestural automatism of the left

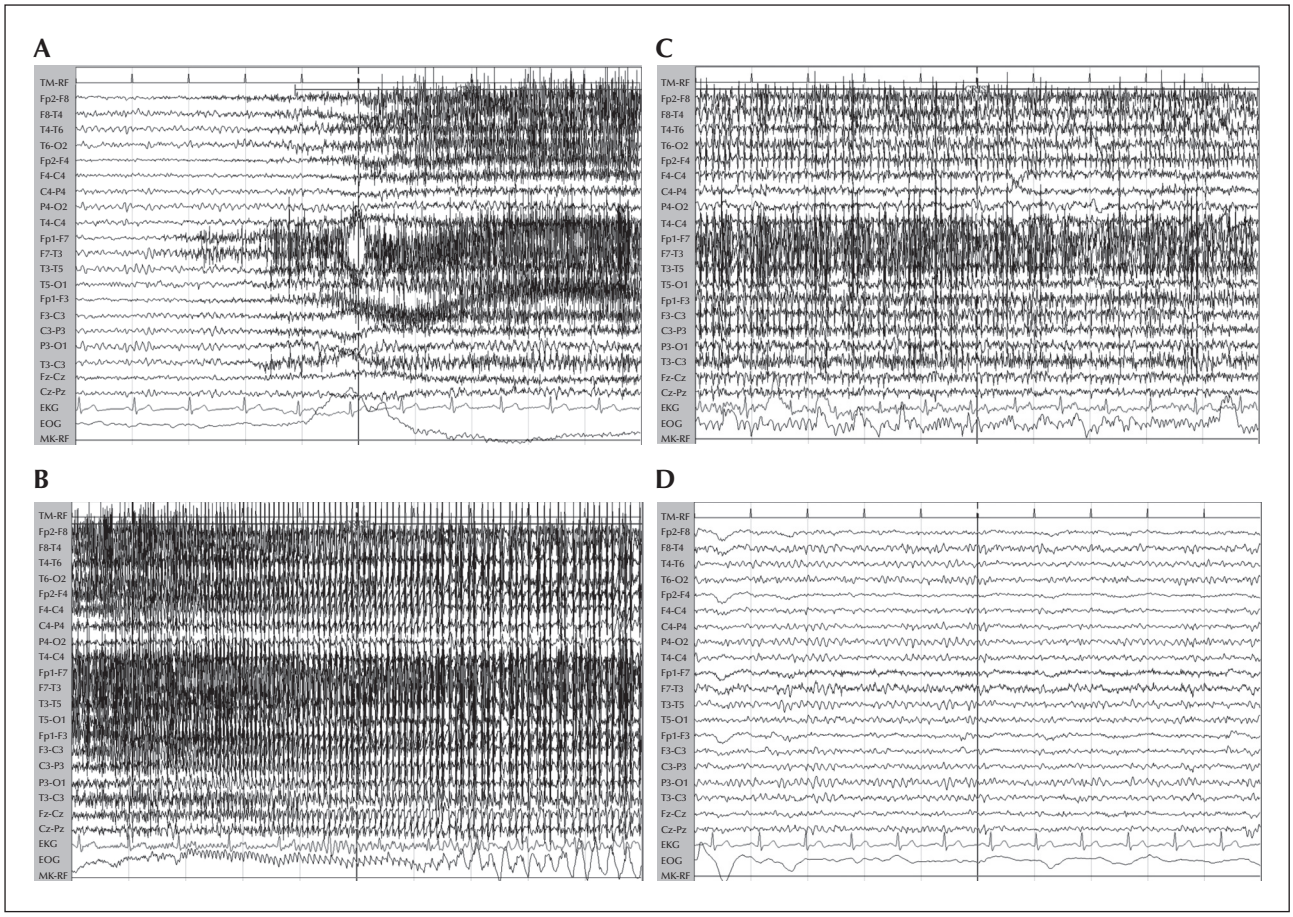

Figure 1. EEG recording showed a left fronto-temporal focus with recruiting polyspikes (A), followed by generalized spike-wave complexes at 4-5 Hz with phase opposition on T3 and T4 (B, C); finally a focal theta epileptic activity derived from the left fronto-temporal region was recorded (D).

hand (*video sequence*). No loss of consciousness was developed; during the seizure episode, the patient was able to understand simple commands even if he was unable to talk. He was also able to remember the ictal and interictal events after seizure cessation. Although his medical history documented the appearance of seizures after a head trauma, cranial MRI was normal. Due to the close temporal relationship between seizures and olanzapine administration, this medication was immediately interrupted and seizures were managed with diazepam at 1 mg three times daily. The patient was started on quetiapine at 50 mg/day, and the other medications were continued. Within the next 36 hours, the seizures subsided and a control EEG confirmed the absence of epileptic discharge, and psychotic symptoms progressively improved. At discharge, the patient's behavioural symptoms were well controlled and he was seizure-free.

Discussion

Seizures have been associated with both typical and atypical antipsychotic medications. Olanzapine is a very effective antipsychotic with the advantage of fewer side effects than typical neuroleptics, especially with regard to extrapyramidal symptoms. The main adverse reactions are somnolence, weight gain, glucose intolerance, and asymptomatic transaminase elevation (Beasley *et al*., 1997). Like other antipsychotic agents, it may lower the seizure threshold, provoking epileptic activity. According to Lilly Research Laboratories, olanzapine showed a 0.9% (22/2,500) seizure incidence in premarketing testing. Olanzapine is a thiobenzodiazepine derivative and shares pharmacological properties with clozapine (Schuld *et al*., 2000). Moreover, clozapine has been associated with seizure development in a dose-dependent manner (Kinon *et al*., 2004), and olanzapine is similarly reported to be associated with a risk of EEG alterations in a dose-dependant manner (Amann *et al*., 2003). A recent analysis of data arising from psychopharmacological clinical trials showed that olanzapine and clozapine, among other antipsychotics, accounted for increased seizure incidence when compared with that based on the general population (Alper *et al*., 2007). However, the association of olanzapine with seizures in clinical practice is relatively uncommon and reports are usually confounded by the presence of pre-existing seizure disorder, comorbid medical disorder, and drug interactions (Lee *et al*., 1999; Wyderski *et al*., 1999; Woolley and Smith, 2001); it is more difficult to establish the main precipitating factor because patients were simultaneously receiving olanzapine and other potentially proconvulsant drugs when seizures appeared (Lee *et al*., 1999; Deshauer *et al*., 2000; Hedges and Jeppson, 2002). During the last few years, two retrospective studies have been conducted which compared EEG effects of typical and atypical neuroleptics in the psychiatric population (Centorrino *et al*., 2002; Amann *et al*., 2003). Although clozapine showed the greatest impact on EEG, both groups found that EEG epileptiform abnormality was unusually high with olanzapine (35-38.5%), moderate with typical antipsychotics, and low with quetiapine. Olanzapine has been described to be associated with seizures and status epilepticus; generalized and myoclonic seizures have been described with olanzapine in two patients with neuropsychiatric disorders, namely, Huntington disease and Alzheimer disease (Bonelli, 2003; Camacho *et al*., 2005). A few reports associate olanzapine with myoclonus; Camacho *et al*. (2005) described a case of myoclonic status induced by olanzapine. This patient developed spontaneous and action-induced myoclonus in the trunk and extremities within 48 hours of starting the drug. The jerks subsided within 36 hours after olanzapine was suspended. Deshauer *et al*. (2000) described a case of combined olanzapine/clomipramine treatment resulting in myoclonic jerks in their patients on two occasions which progressed to generalized motor seizures on one of these two occasions. Woolley and Smith (2001) described an epileptic woman with paranoid psychosis whose seizure frequency increased when switched from zuclopenthixol to olanzapine. Even though one report describes a dramatic case ending in fatal status epilepticus (Wyderski *et al*., 1999), the remaining literature reports cases where seizure activity could be controlled either by olanzapine discontinuation or by concurrent antiepileptic drugs. Although there were confounding factors in some of these cases which may have contributed to the occurrence of seizures, it has been recommended that olanzapine be used cautiously in patients with a history of seizures or with conditions that may lower the seizure threshold (Koch-Stoecker, 2002). Our report is the first description of repetitive motor seizures involving the face and concomitant lingual dystonia induced by olanzapine. The type of seizure is the most striking feature of the case. Olanzapine was judged to be responsible for the described epileptic episodes because seizures appeared within 48 hours after administration, stopped with discontinuation, and the patient also remained seizure-free when diazepam was suspended. Although the ultimate pathophysiological mechanism is unclear, seizures are probably related to olanzapine-specific receptor profiles. In fact, seizures did not reappear when the patient received quetiapine. Nevertheless, other potentially contributing factors should be considered. Our patient had a neuropsychiatric syndrome and presented seizures amid the clinical features associated with his

neuropsychiatric syndrome; he was already taking topiramate, 150 mg twice day, and phenobarbital, 150 mg/day. □

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

Disclosures.
None of the authors have any conflict of interest to disclose.

Legend for video sequence

A focal motor seizure characterized by a right deviation of the mouth and eyelid myoclonia for about one minute, followed by gestural automatism of the left hand. During the episode, the patient understood simple commands but he was unable to talk. He remembered the event.

Keywords for the video research on www.epilepticdisorders.com

Syndrome: neuropsychiatric disease
Aetiology: olanzapine-induced seizures
Phenomenology: motor seizures with automatisms
Localization: left fronto-temporal focus

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TEST YOURSELF

(1) What are the main adverse reactions related to olanzapine?

(2) How do atypical antipsychotics impact EEG recording?

(3) What type of seizures are induced by antipsychotic drugs?

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".