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Epileptic seizures, coma and EEG burst-suppression from suicidal bupropion intoxication

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ABSTRACT – Bupropion, an amphetamine-like dual mechanism drug, is approved and increasingly used for the treatment of major depression, and its use is associated with a dose-dependent risk of epileptic seizures. Suicide attempts are frequent in major depression and often an overdose of the drugs available is ingested. Therefore, it is important to be aware of the clinical course, including EEG and neurological symptoms, as well as treatment and prognosis of bupropion intoxication. We report on the clinical and EEG course of a women who ingested 27 g of bupropion in a suicide attempt. Myoclonic seizures were followed by generalized tonic-clonic seizures and coma associated with EEG burst-suppression and brief tonic seizures. Active carbon and neuro-intensive care treatment, including respiratory support, were given. Within three days, the patient returned to a stable clinical condition with a mildly encephalopathic EEG. In conclusion, bupropion intoxication requires acute intensive care treatment and usually has a good prognosis, however, misinterpretation of the clinical and EEG presentation may lead to errors in management.

Key words: seizure, coma, bupropion intoxication

Bupropion is a dual mechanism antidepressive drug, initially approved by the Food and Drug Administration for major depression (MD) in 1984. It was taken off the market from 1986 to 1989 for reasons, among others, related to dose-dependent proconvulsive properties, in particular for patients with bulimia, epilepsy, and a history of head trauma. Bupropion regained market access and an increasing market share after a sustained release formulation became available (Belson and Kelley, 2002; Shepherd *et al*., 2004; Starr *et al*., 2009). While the risk of epileptic seizures appears to be lower with in-label use of the slow-release formulation (seizure risk on

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bupropion: 0.1% at doses up to 300 mg, 0.4% at 300 to 450 mg a day), information on the clinical course of a suicidal intoxication and the appropriate medical management thereof is sparse.

In Germany, where slow-release bupropion (Elontril®) has been approved for the treatment of MD since 2007, bupropion use is significant and increasing; 184,000 packets (consisting of 150-mg [~60%] and 300-mg [~40%] tablets; IMS Pharmascope) were sold from November 2011 to October 2012 and 263,000 from November 2013 to October 2014.

In one study (Sokero *et al.,* 2003), almost 60% of depressed patients reported suicidal ideation and attempted suicide was reported in 15% of patients at baseline and 8% during an 18-month follow-up period. Therefore, suicide attempts are relatively common in the population treated with bupropion and there is a need to be informed about the clinical presentation and course of suicidal intoxication with this drug. In order to provide such information, we report such a case and review the pertinent literature.

Case study

A 51-year-old woman with suicidal intoxication was referred to our hospital. She had reportedly ingested 27 g bupropion. The suspected additional ingestion of benzodiazepines or alcohol was excluded by toxicological screening. Before admission to our A&E department the patient had already been treated with activated carbon (1 g/kg body weight).

Initially, she was somnolent, but fully orientated regarding person, partially orientated regarding time and place, and able to follow commands. On neurological examination, the pupils were dilated but reactive to light. She had myoclonic jerks and intermittent hyperkinetic movements, but no other neurological signs or symptoms. The initial ECG showed a normal corrected QT-interval (QTc).

Subsequently, she became increasingly agitated, her level of consciousness decreased, and she had a generalized tonic seizure. She received 4 mg of lorazepam to terminate the generalized tonic seizure and was subsequently intubated for airway protection. Neurological examination then showed dilated pupils unreactive to light and generalized myoclonic jerks. Because of hypotension, a treatment with low-dose norepinephrine became necessary.

A CT scan of the head was considered to show possible brain oedema, while MRI, 72 hours later, was unremarkable.

Approximately seven hours after intubation, the first EEG was performed, during which the patient received propofol (100 mg/h) and sufentanil (0.05 mg/h) as anaesthetics, but no other antiepileptic drugs.

The EEG showed severe encephalopathy with burst-suppression pattern consisting of groups of generalized polyspike-wave complexes, separated by electrodecrement (*figure 1A, B, C*). Associated with the polyspike-wave complexes, the patient showed repetitive tonic eye opening and upward gaze associated with tonic neck extension.

As the patient received only low-dose anaesthetics during the EEG, we suggested that the burst-suppression pattern was induced by the bupropion overdose.

The ECG then showed a prolonged QTc interval of up to 120%. Initially, neuron-specific enolase (NSE) level and blood chemistry were normal. Later, she developed a paralytic ileus with lactate acid elevated up to 3.9 mmol/dl and fever up to 38.5°C.

Although under anaesthetics with propofol (maximum dose: 1,000 mg/h) and sufentanil (maximum dose: 0.05 mg/h), intermittent myoclonic jerks continued and midazolam (maximum dose: 2 mg/h) was added, which terminated the myoclonic jerks.

On the third day after admission, the patient was extubated without complications. The patient was awake, able to communicate and follow commands, but suffered from amnesia and temporal disorientation. A second EEG performed four hours before extubation showed mild diffuse encephalopathy, no burst-suppression pattern, and no sign of epileptic activity (*figure 2A, B*). During the second EEG, she did not receive any anaesthetics or antiepileptic drugs. Later, she was transferred to a psychiatric ward for further treatment.

Discussion

Bupropion is a mild norepinephrine and dopamine reuptake inhibitor (NDRI) with no effect on the serotonergic system or any affinity for postsynaptic receptors. It is a racemic mixture and has three metabolites. It is primarily metabolized to hydroxybupropion by CYP2B6. After eight days, a steady state plasma concentration is reached. The mean elimination half-life during chronic use is 21 hours. Peak plasma levels are achieved within two hours after oral ingestion (Wellbutrin factsheet, 2014).

Several short-term and long-term studies have demonstrated the efficacy and tolerability of bupropion if used within the dose range which has now been approved (150-300 mg/d). It has antidepressive efficacy in patients with major depressive disorder when first-line therapy with selective serotonine reuptake inhibitors (SSRI) has failed, in patients with bipolar disorder, and also in patients with attention deficit hyperactivity disorder (Dunner *et al*., 1998; Weihs *et al.,* 2002; Stahl *et al*., 2004; Fava *et al*., 2005; Rush *et al*.,

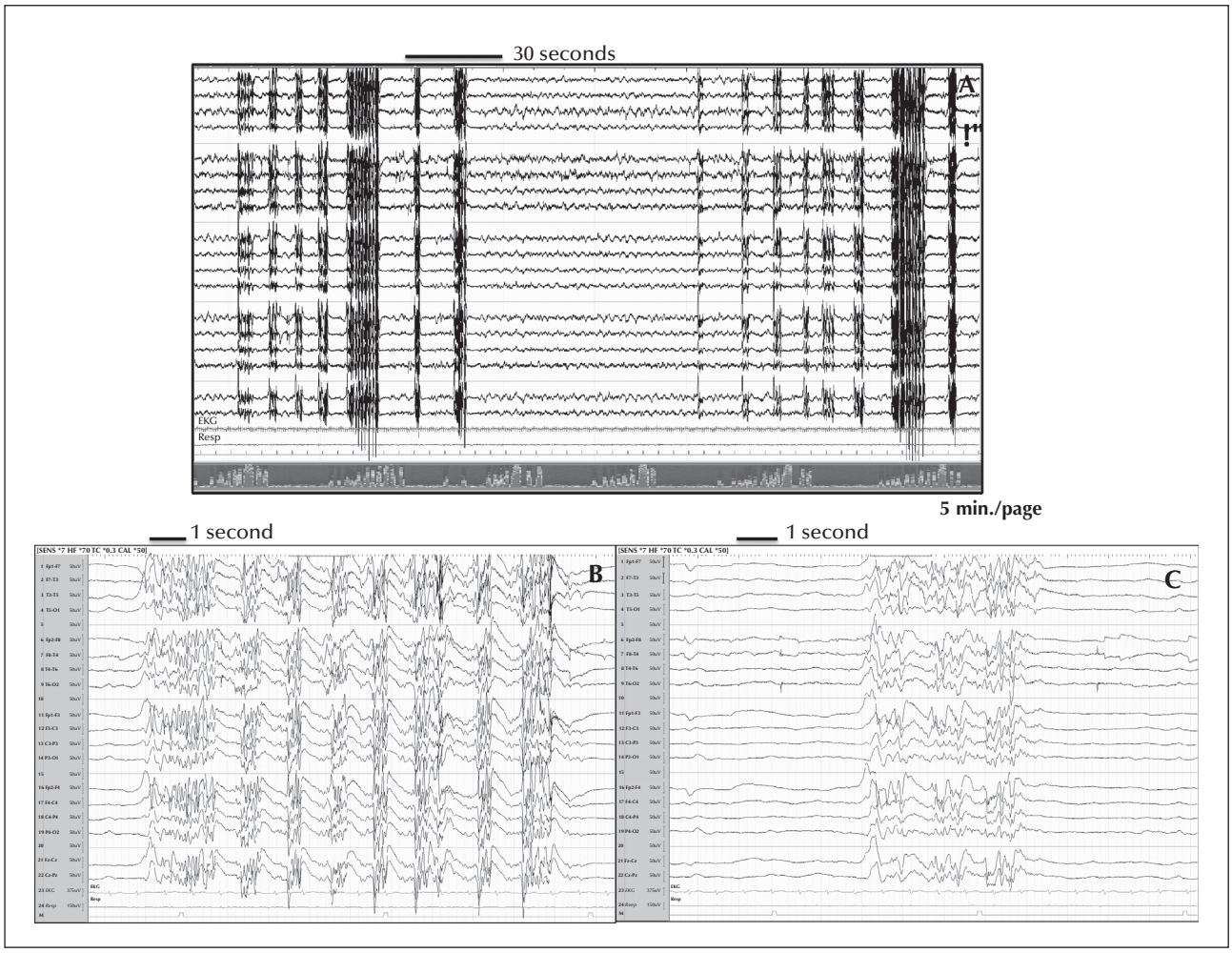

Figure 1. EEG during acute intoxication on a bipolar longitudinal montage on Day 1, when the patient was comatose and ventilated. (A) EEG with power spectrum showing a pattern of recurrent burst suppression at a scale of 5 minutes/page, at 50 μv. (B, C) EEG with a single group of generalized polyspike bursts with intermittent suppression at a scale of 15 seconds/page, at 50 μv, which were associated with periodic tonic upward gaze and neck extension.

2006; Cipriani *et al*., 2009; Hewett *et al*., 2009). While generally considered a relatively safe drug when taken as prescribed, there have been several case reports of patients with severe intoxication.

Data from 7,384 patients with bupropion-only exposure from the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) for the years 1998 and 1999 where reviewed by Belson and Kelley (2002). The majority of patients were female (56%) and 45% were children or teenagers (<6-19 years). Overdose occurred mainly unintentionally (61%). The majority of bupropion exposure involved Wellbutrin SR® (sustained release form). Of the patients, 31% developed symptoms after bupropion ingestion. Eighty percent developed minor symptoms such as tachycardia, agitation, drowsiness, and vomiting. Severe symptoms included seizures, coma, hypotension, and respiratory depression and occurred more often after intoxication with Wellbutrin®. Nineteen percent of all symptomatic patients (*n*=2247) developed seizures. Symptoms lasted for two hours in 13%, for two to eight hours in 32%, for eight to 24 hours in 40%, and over 24 hours in 12%. Of the patients with clinical symptoms, 60% had taken a bupropion overdose intentionally. Five people (<0.1%) who had probably taken bupropion with suicidal intention died; the amount they ingested remained unclear. Ten further patients died who had cointoxication with other drugs or alcohol (Belson and Kelley, 2002).

Another review on bupropion overdose with Wellbutrin XL® (extended release form) has described the onset of seizures to occur about 0.5-24 hours after intoxication with a quarter occurring more than eight hours after ingestion. Half of the patients experienced more than one seizure. There was no significant relationship between dosing and seizure

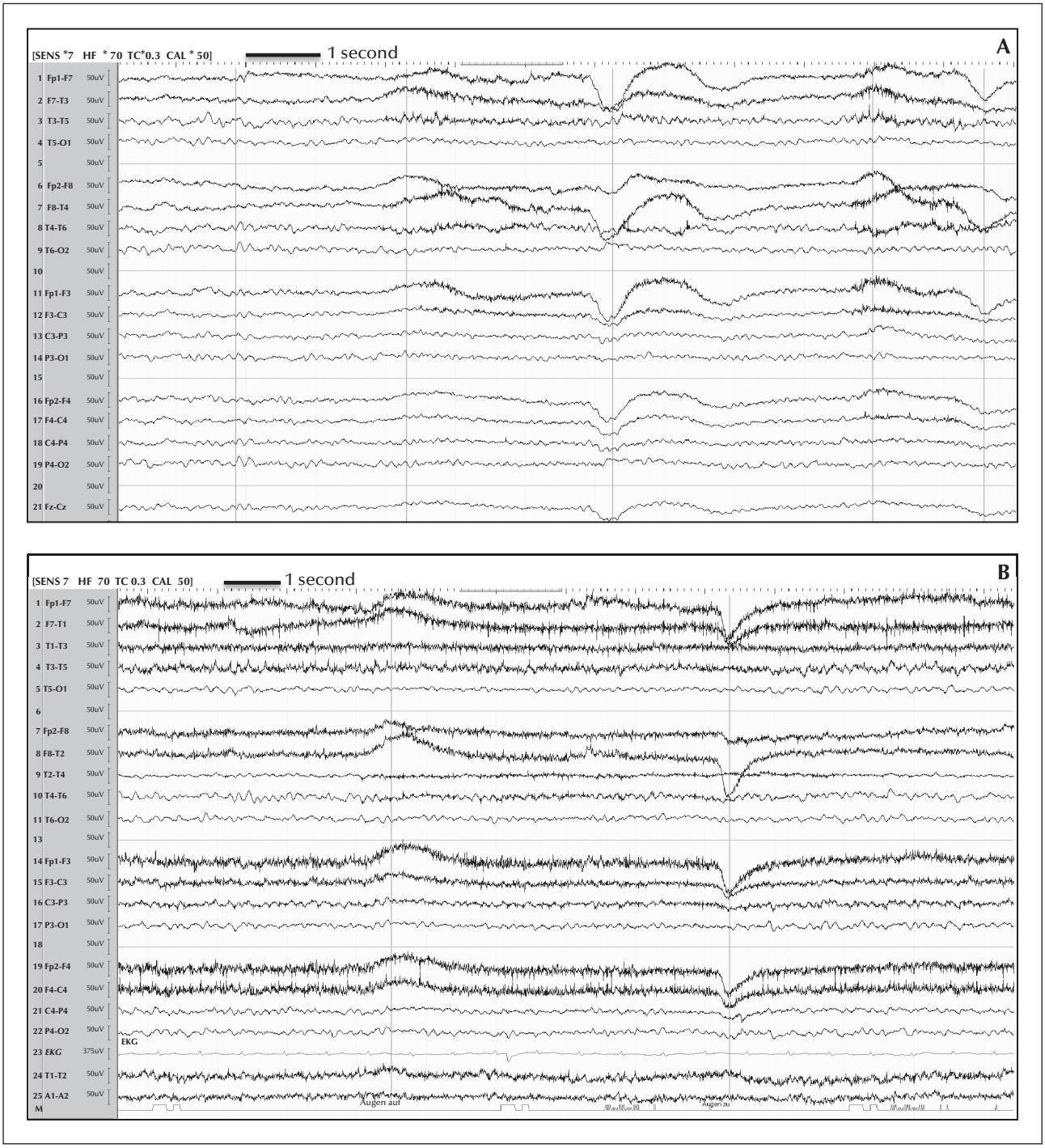

Figure 2. (A, B) EEG two days later following near-complete recovery. The EEG on bipolar longitudinal montage two days later after recovery of the patient. Background activity was 7-8 Hz, with no more burst suppression pattern or epileptic discharges (scale: 15 seconds/page; 50 μv).

onset. Agitation, tremor, and tachycardia occurred more frequently but not exclusively in patients with seizures (Starr *et al*., 2009).

In two case reports which included EEG findings, such as in our case, a burst-suppression pattern with complete remission after several days was reported. Furthermore, as observed by us, anticholinergic effects including mydriasis, hyperreflexia, and cardiac manifestation (tachycardia and prolongation of the QTc-interval) were described (Mundi *et al*., 2012).

Patients with bupropion overdose are reported to be mainly treated with active carbon. Other interventions include intravenous or orogastric dilution and bowel irrigation (Belson and Kelley, 2002; Shepherd *et al*., 2004; Starr *et al*., 2009). Unfortunately, until now, no antidote for bupropion is available (Wellbutrin factsheet, 2014).

Conclusion

As bupropion is increasingly used as an antidepressant in a population with a high risk for suicidal ideation and behaviour, it is crucial to be aware of the dramatic effects that can be caused by bupropion intoxication. In particular, bupropion-induced coma associated with a burst-suppression pattern and periodic tonic movements can be misinterpreted as indication of a poor prognosis. Knowledge of the clinical course may prevent errors in management. □

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

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References

Belson MG, Kelley TR. Bupropion exposures: clinical manifestations and medical outcome. *J Emerg Med* 2002; 23(3): 223-30.

Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; 373(9665): 746-58.

Dunner DL, Zisook S, Billow AA, *et al*. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 1998; 59(7): 366-73.

Fava M, Rush AJ, Thase ME, *et al*. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 2005; 7(3): 106-13.

Hewett K, Chrzanowski W, Schmitz M, *et al*. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol* 2009; 23(5): 531-8.

GlaxoSmithKline. Wellbutrin Factsheet. 2014.

Mundi JP, Betancourt J, Ezziddin O, *et al*. Dilated and unreactive pupils and burst-suppression on electroencephalography due to bupropion overdose. *J Intensive Care Med* 2012; 27(6): 384-8.

Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006; 354(12): 1231-42.

Sokero TP, Melartin TK, Rytsälä HJ, *et al*. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry* 2003; 64(9): 1094-100.

Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. *J Emerg Med* 2004; 27(2): 147-51.

Stahl SM, Pradko JF, Haight BR, *et al*. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry* 2004; 6(4): 159-66.

Starr P, Klein-Schwartz W, Spiller H, Kern P, Ekleberry SE, Kunkel S. Incidence and onset of delayed seizures after overdoses of extended-release bupropion. *Am J Emerg Med* 2009; 27(8): 911-5.

Weihs KL, Houser TL, Batey SR, *et al*. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. *Biol Psychiatry* 2002; 51(9): 753-61.

TEST YOURSELF

(1) What is the chemical mechanism of bupropion?

(2) What are the clinical signs of severe bupropion intoxication?

(3) What is the treatment for bupropion intoxication? Is there a specific antidote?

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".