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CASE

The case of a geriatric female experiencing frequent falls and epileptic seizures during long-term low-dose clozapine and extended-release bupropion treatment

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Abstract

There are few reports describing the incidence of seizures in patients prescribed a combination of clozapine and bupropion for the treatment of psychiatric disorders, despite the known drug-drug interaction associated with concomitant use. We report the case of a 67-year-old geriatric woman who experienced multiple falls and seizures while receiving a low daily dose of clozapine 200 mg and bupropion extended-release (XL) 150 mg. There was no recurrence of seizure activity after discontinuation of bupropion and initiation of an antiepileptic drug, divalproex. This case report suggests that bupropion in combination with low-dose clozapine may increase the risk of seizures in elderly patients.

Keywords: Epilepsy, drug-induced seizures, adverse drug reaction, bupropion, clozapine, geriatric, falls, falls risk

Introduction

Although the occurrence of a single seizure does not constitute a diagnosis of epilepsy, seizure episodes can have serious consequences and should therefore be a constant consideration when prescribing, and when risky combinations are clinically necessary, this pharmacologic monitoring should include reducing the additive risk whenever possible. One such risk-reduction strategy is the addition of an antiepileptic drug such as divalproex (Depakote), which has mood-stabilizing benefits in addition to reducing seizure risk [1]. Other risk factors in the elderly include infection, head trauma/injury (which can occur as a result of falls), and electrolyte imbalances [2]. Some of these factors are more prevalent in the geriatric population. In addition, several medications have been associated with the potential to cause seizures, including medications used to treat psychiatric disorders, such as antipsychotics and antidepressants [2, 3].

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Two medications commonly associated with seizure risk are the dopamine-modulating antidepressant bupropion (Wellbutrin) and the second-generation antipsychotic clozapine (Clozaril) [4, 5]. Concomitant use of both has been reported to increase this risk. However, there is little information on the absolute risk or rate of seizures associated with the combination of low-dose clozapine and bupropion, and there is no clear indication of whether these medications, when used together, provide a synergistic effect that results in improved psychiatric outcomes where the benefit of the combination exceeds the risk of seizures [6].

Clozapine is indicated for patients with treatment-resistant schizophrenia or for patients with suicidal ideation in schizophrenia and is associated with serious side effects, including seizures [4, 7]. There are conflicting results in the literature regarding the rate of seizures with clozapine use. One report concluded that the incidence of seizures was 6%, with the risk increasing with increasing daily dose, with a risk of 3% in those receiving less than 300 mg, 8% in those receiving 325 mg to 500 mg, and 38% in those receiving more than 500 mg daily [7]. Clozapine may be continued in patients with seizures if their epilepsy is controlled, whereas bupropion is contraindicated in patients with a seizure disorder [4, 7]. Bupropion is indicated for patients with major depressive disorder and has been shown to be safe and effective in elderly patients [7]. As with clozapine, evidence suggests that the risk of sei-

zures with bupropion use is dose-dependent, with higher doses associated with greater risk.

Although epileptic seizures in adults are most common in later life, with 25% of new seizures occurring in the elderly, seizures are difficult to identify in this population [8]. For this and likely other reasons, seizure-related falls are underestimated and not well documented in older adults. While generalized tonic-clonic seizures can lead to a fall while standing, several types of seizures can lead to falls, including focal parietal or frontal seizures and generalized myoclonic seizures [8]. However, other types of seizures may also lead to falls and cannot be excluded. It must be considered that our patient may have had undiagnosed seizures that were attributed to falls [8].

This case report discusses an elderly patient who experienced sixteen falls over a five-month period. Some of the falls were documented as seizures or seizure-like activity. However, due to the nature of seizures, which are difficult to diagnose in this population, and because several falls were unwitnessed, the patient may have experienced more seizures than were documented. The patient had been receiving a combination of bupropion XL 150 mg daily and clozapine 200 mg daily for several years to treat her depression and schizophrenia. While neither medication was dosed at its maximum, there is little information to reflect the potential synergistic effects these medications may have on the seizure threshold. Their use together should be approached with extreme caution. Because clozapine is used in treatment-resistant schizophrenia, bupropion should be substituted with another medication when appropriate, especially in geriatric patients who are prone to falls.

Case report

A 67-year-old Hispanic woman was admitted to an inpatient psychiatric facility with a diagnosis of schizophrenia, treated with 200 mg oral clozapine and 5 mg oral fluphenazine daily, and depression, treated with 150 mg oral bupropion XL daily. Her medical diagnoses included osteopenia treated with alendronate and calcium carbonate; constipation treated with docusate, polyethylene glycol, magnesium hydroxide, and phosphate enema; vitamin D deficiency treated with ergocalciferol; and hypothyroidism treated with levothyroxine. The patient had no history of seizures before and during her treatment with clozapine and bupropion, which began in 2015 and 2017, respectively, and continued through 2019. In addition, her mother had a history of epileptic disorder, but no additional information was available.

Beginning in March 2019, the patient experienced frequent falls, resulting in the initiation of hip pads and a helmet (Table 1). Her falls were attributed to behavioral and environmental factors. The patient received nonpharmacologic interventions, including a haircut to ensure that her bangs were out of her face, decluttering of her bedroom, and education on the importance of standing and walking slowly and safely. On June 24, 2019, staff reported that she fell to the floor and appeared to be having a seizure. She experienced upper and lower extremity twitching, an inability to follow commands or concentrate, and a scalp laceration. She was also noted to have an increase in impaired neurological function and subsequent increase in falls according to her psychologist's reports. Following the fall, she was transported to an acute care medical facility for further evaluation and returned to the inpatient psychiatric facility the following day. Her pharmacotherapy was continued without change.

On July 4, 2019, the patient experienced a fall that was described as myoclonic jerking with repetitive hand movements and limited response to verbal cues. On August 11, 2019, she experienced another seizure. This seizure was longer, lasting three minutes. The seizure was described as having started while the patient was walking. The patient was transported to an acute care facility for follow-up, where she was diagnosed with acute post-ictal encephalopathy. Bupropion was withheld due to its potential contribution to seizure activity, and divalproex was added as an antiepileptic agent. Although clozapine has a side effect of seizures, it was continued because of the risk of withdrawal symptoms with abrupt discontinuation. A head CT without IV contrast on August 16 showed mild age-related brain changes and chronic small vessel ischemic disease. There was no evidence of acute abnormality, intracranial mass, hemorrhage, fracture, or significant interval change. The patient's psychiatrist was uncertain whether the seizure was due to a recent fall in which the patient hit her right forehead.

Upon return to our inpatient facility five days later, bupropion was not reinitiated and divalproex was titrated and

Table 1. History of frequent falls.

Fall date (2019)	Additional details
March 18	Tripped on the way to lunch
April 7	Patient found on floor, required stitches
May 9	Unwitnessed, laceration to right forehead
May 14	Reopened previous wound with two new lacerations requiring Steri-Strips
June 10	Occurred while walking, skin tear to forehead
June 16	Contusion to forehead
June 24	Seizure with head laceration requiring sutures
June 26	Occurred while walking and resulted in no injuries
July 4	Myoclonic jerks, repetitive hand motion, and limited response to verbal cues
July 11	Tripped over feet
July 12	Unwitnessed, found lying in hall
July 20	Lost balance running down hallway
July 23	Walking fast, bruised knees and palm
July 28	Tripped over her feet standing from chair
August 9	Found sitting on floor in hallway
August 11	3-minute seizure with convulsions, mouth frothing and unconsciousness
July 23	Walking fast, bruised knees and palm
July 28	Tripped over her feet standing from chair
August 9	Found sitting on floor in hallway
August 11	3-minute seizure with convulsions, mouth frothing and unconsciousness

switched to valproic acid. Lithium was also discontinued. On August 22, the patient's valproic acid level was within the therapeutic range for the treatment of epilepsy at 61 µg/mL. Sertraline was started on September 14 and titrated to 100 mg daily. The patient did not have another fall or seizure during the remainder of her treatment at our institution. She was discharged in January 2020.

Discussion

Medications, alcohol withdrawal, metabolic disorders, stroke, and traumatic brain injury are some causes of seizures [9]. Medications considered to have a moderate risk of seizures include chlorpromazine, meperidine, clozapine, and bupropion. Of the medications prescribed to this patient, bupropion and clozapine are two medications that may have precipitated the two seizure events as an adverse drug reaction (ADR). A drug safety committee reviewing this event as a potential ADR accepted the prescriber's suggestion that other factors were responsible for these events because the patient had been taking the two medications concurrently for an extended period of time without seizures.

Bupropion has a long history of known seizure risk and was removed from the market by the FDA in 1985 due to the high incidence of seizures and was implicated in 23 percent of drug-induced seizures reported to the California Poison Control System in 2003, nearly three times the rate of any other drug, according to a retrospective review [10, 11]. However, the risk of seizures with bupropion XL has not been formally reviewed [11]. With bupropion in particular, older adults may be at greater risk of accumulation with chronic dosing [6]. As our patient was over 65 years of age, serum bupropion levels may have been useful in determining the cause of her seizures, but these levels were never obtained.

Antipsychotics share a class-related risk of lowering the seizure threshold. The antipsychotic most commonly associated with seizures is clozapine, the most effective antipsychotic for treatment-resistant schizophrenia [3, 6]. Clozapine lowers the seizure threshold in both epileptic and non-epileptic patients, and a seizure can occur at any stage of treatment [12]. The estimated cumulative risk of seizure is 10 percent in patients treated with clozapine for 3.8 years [6]. Seizures may be avoided or the risk minimized if the daily dose does not exceed 450 mg, as was the case in our patient who was on a daily dose of 200 mg [3].

Interestingly, an evidence-based review found that there is little convincing evidence to support a strict relationship between clozapine serum levels and seizure risk [13]. Seizures can occur at doses as low as 37.5 mg daily. Plasma clozapine levels as low as 144 nmol/L have been associated with seizure activity. Therefore, serum clozapine concentrations may be used as a guide but are not a definitive predictor of therapeutic efficacy or seizures [12]. A seizure is not an adverse reaction that generally warrants discontinuation of clozapine, and its onset usually occurs between two and four weeks after initiation, but may occur at any stage of treatment. If discontinuation of clozapine is not appropriate, as was the case in our patient, an antiepileptic drug such as divalproex can be started and the patient monitored for adverse effects [3].

Seizure risk may be increased in patients with a history of seizures, head trauma, anorexia/bulimia, CNS tumor, severe liver cirrhosis, abrupt discontinuation of a sedative hypnotic or alcohol, and medications that lower seizure threshold [14]. In our patient's case, she had a history of one seizure in June 2019, experienced head trauma from her many frequent falls, some of which required stitches and hospitalization, and was prescribed clozapine and bupropion. Another factor to consider is the patient's age, which at the time was 67 years old. Older patients differ from younger patients in their response to pharmacologic treatment, which can be unpredictable and variable. In comparison, the average therapeutic dose of clozapine for non-geriatric adults is 300-600 mg/day.

Both clozapine and bupropion are recognized as medications with a tendency to lower seizure thresholds individually, but there is currently little information on the risk of using these two medications in combination. It is unclear whether these agents have an additive seizure risk or possible synergistic effects when used in combination. However, bupropion should be used with caution in patients treated with clozapine. Agents that do not lower the seizure threshold should be used as a safer option when possible [6]. In the case of two patients without a history of seizures who experienced epileptic events while treated with clozapine and bupropion, the seizures resolved after bupropion was discontinued and divalproex was initiated for seizure prophylaxis, as was observed in our patient [6].

The patient had two seizures within two months of each other. The factors that caused the falls cannot be definitively determined. In two cases of elderly patients with falls secondary to seizures, the falls were not recognized as seizures because of the many other comorbidities [8]. Clozapine and bupropion have a long history of lowering the seizure threshold. The risk of seizures increases with dose escalations of each of these medications, but the risk of seizures when these two medications are used together is unknown. The patient also had a history of frequent falls that may have resulted in neurologic injury, a factor that was considered by her care team. The patient's history of tolerating the combination of low-dose clozapine and bupropion is known. Her psychiatrist ensured that the patient was on the lowest effective dose of each medication. However, with age, some medications can become less well tolerated. In addition, the patient's recent history of falls leading to neurological changes and possible brain injury are exactly the conditions that could have led to seizures.

The patient's history of multiple falls, many of which resulted in injury even while wearing protective equipment, placed her at even greater risk for seizures. The patient's care team quickly changed her therapy to remove bupropion and continue an antiepileptic drug, divalproex, added by the acute care facility where she was being treated. Clozapine was continued, as it is typically used for treatment-resistant schizophrenia, and the patient has remained

stable on this therapy. Seizures are not a contraindication to clozapine therapy; however, seizure disorders are a contraindication to bupropion therapy. Therefore, the decision to discontinue bupropion rather than clozapine to reduce the risk of seizures is the most appropriate option from a patient care perspective. The patient was also ordered a geriatric chair to reduce her risk of falls. With these changes, the patient had no further epileptic events. Bupropion and clozapine likely contributed to an adverse drug reaction of seizures in this patient, and for this reason, bupropion should be used cautiously in patients treated with clozapine, especially those with a history of head trauma, including those with a history of frequent falls.

In addition, this case provokes consideration of how a prescriber's perception or definition of an ADR can influence and alter the course of both clinical and academic investigation of the actual event [15]. There are numerous definitions of adverse drug reactions; however, most in the medication safety community would agree that a previously reported adverse effect of a known drug-drug interaction, regardless of the timeline in which it occurred, is an undesirable but preventable adverse drug reaction. The benefit and value of identifying, investigating, and reporting ADRs not only to the institution's clinical leadership, but also to the FDA through MedWatch, is that these rates can be more realistically measured and new, previously unrecognized ADRs can be evaluated for possible inclusion in updated package labeling information [16].

Declarations

Authors' contributions: Dzierba C, Lee C, and Demler TL contributed equally to the preparation of this case report. All listed authors concur in the submission and are responsible for its content; they have consented to its publication and have authorized the corresponding author to act on their behalf in all matters relating to publication.

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