Case Report

Title: 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 that describe incidence of seizures in patients prescribed a combination of clozapine and bupropion for the treatment of psychiatric disorders, despite the known drug-drug interaction involving concomitant use. We report a case of a geriatric 67-year-old female 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 upon discontinuation of bupropion and initiation of an antiepileptic medication, divalproex. This case report suggests that bupropion in combination with low dose clozapine has the potential to 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 the diagnosis of epilepsy, seizure episodes can result in serious consequences and therefore should be a constant consideration when prescribing, and when risky combinations are clinically necessary, that pharmacologic monitoring should also include decreasing additive risk whenever possible. One such risk reducing strategy is the addition of an antiepileptic agent such as divalproex (Depakote) that contributes mood stabilizing benefits in addition to reducing seizure risk [1]. Additional risk factors for the elderly include infection, head trauma/ injuries (which can occur secondary to falls), and electrolyte imbalances [2,3,4]. Some of these factors are more common in the geriatric population. Additionally, several medications have been associated with the potential to cause seizures, including medications used to treat psychiatric disorders, such as antipsychotics and antidepressants [2,5,6]. Two medications commonly associated with seizure risk include the dopamine-modulating antidepressant bupropion (Wellbutrin) and the second-generation antipsychotic clozapine (Clozaril) [7,9]. Concomitant use of both is reported to increase this risk even more. However, there is little information to reflect the absolute risk or rate of seizures associated with combination 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 seizure [6].

Clozapine is indicated for patients with treatment-resistant schizophrenia or in patients with suicidal ideation with schizophrenia and is associated with serious side effects, including seizures [7,9]. Literature has varying results on rates of seizures with clozapine use. One report concluded the incidence rate of seizures as 6%, with the risk increasing with daily dose increases, and 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 [9]. Clozapine can be continued in patients with seizures if their epilepsy is controlled, whereas bupropion is contraindicated in patients with a seizure disorder [7,9]. Bupropion is indicated for patients with major depressive disorder and has been shown to be safe and effective in elderly patients [9]. As is the case with clozapine, it is suggested that the risk of seizures with bupropion use is dose-dependent with higher risk associated with higher doses.

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 [10]. For this reason and likely others, falls due to seizures are underestimated and not well documented in older adults. While upon onset, generalized tonic-clonic seizures can result in a fall if standing, different types of seizures may also lead to falls, including focal parietal or frontal seizures and generalized myoclonic seizures [10]. However, other types of seizures may also lead to falls and cannot be ruled out. It must be taken into consideration that our patient may have experienced undiagnosed seizures that were attributed to falls [10].

This case report discusses an elderly patient who experienced sixteen falls in a five-month time frame. Some falls were documented as seizures or as having seizure-like activity. However, due to the nature of seizures being difficult to diagnose in this population, and as several falls were unwitnessed, the patient may have experienced more seizures than those documented. The patient received a combination of bupropion XL 150 mg daily and clozapine 200 mg daily to treat their depression and schizophrenia for several years. 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. As clozapine is used in treatment-resistant schizophrenia, bupropion should be substituted with another medication when appropriate, especially in geriatric patients who experience frequent falls.

**CASE REPORT**

A 67-year-old Hispanic woman was hospitalized at an inpatient psychiatric facility with a diagnosis of schizophrenia, treated with 200 mg of oral clozapine and 5 mg of oral fluphenazine daily, and depression, treated with 150 mg of oral bupropion XL daily. Her medical diagnoses include 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 did not have a history of seizures prior to and including during her treatment with clozapine and bupropion, beginning in 2015 and 2017 respectively, until 2019.

Beginning in March of 2019, the patient began experiencing frequent falls, which resulted in the initiation of hip pads and a helmet (Table 1). Her falls were attributed to behavioral and environmental features. The patient received nonpharmacologic interventions, which included a haircut to ensure her bangs were out of her face, her bedroom was decluttered, and she was educated on the importance of standing and walking slowly and safely. On June 24th, 2019, staff reported that she fell to the floor and appeared to have a seizure. She experienced twitching of the upper and lower extremities, inability to follow commands or focus, and a scalp laceration. She was also noted to have an increase in impaired neurologic functioning and subsequent increase in falls per reports submitted by her psychologist. Following the fall, she was transported to an acute medical facility for further evaluation and later returned to the inpatient psychiatric facility the following day. Her pharmacotherapeutic regimen was continued without change.

**Table 1. History of Frequent Falls**

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

On July 4th, 2019, the patient experienced a fall that was described as myoclonic jerks with repetitive hand motion and limited response to verbal cues. She experienced another seizure on August 11th, 2019. This epileptic event was lengthier, lasting three minutes. The seizure was described to have begun while the patient was walking. The patient was transported to an acute medical facility for follow-up where she was diagnosed with acute encephalopathy secondary to postictal state. Bupropion was held due to the possibility of its contribution to seizure activity, and divalproex was added as an antiepileptic agent. Although clozapine has a side effect of seizures, it was continued due to the risk of withdrawal symptoms upon abrupt discontinuation. A head CT without IV contrast on the 16th revealed mild aging brain changes and chronic small vessel ischemic disease. There was no evidence of an acute abnormality, intracranial mass, hemorrhage, fracture, or significant interval change. The patient’s psychiatrist was uncertain if the seizure was due to recent falls that resulted in the patient hitting the right forehead area.

Upon return to our inpatient facility five days later, bupropion was not reinitiated, and divalproex was titrated and changed to valproic acid. In addition, lithium was discontinued. On the 22nd, the patient’s valproic acid level was within therapeutic range for the treatment of epilepsy at 61µg/mL. Sertraline was initiated on September 14th, 2019 and titrated to 100 mg daily. The patient did not have another fall or seizure throughout her remaining treatment at our facility. She was discharged January 2020.

**DISCUSSION**

Medications, alcohol withdrawal, metabolic disorders, stroke, and traumatic brain injuries are some causes of seizures [11]). Medications considered to have a moderate seizure risk include chlorpromazine, meperidine, clozapine, and bupropion. Of the drugs prescribed for this patient bupropion and clozapine are two medications that could have influenced the two seizure events due to an adverse drug reaction. A medication safety committee that reviewed this event as a potential ADR accepted the suggestion by the prescribing physician that because the patient had been on the two medications concurrently for a significant period of time without any seizures, that other factors were responsible for these events.

Bupropion has a long history of known seizure risk and was removed from the market in 1985 by the FDA due to the high incidence of seizures and was considered the source of 23 percent of drug-induced seizures called into the California Poison Control System in 2003, almost three times more than any other drug, according to a retrospective review [12,13]. However, the risk of seizures in bupropion XL has not been officially reviewed [13]. Specifically, with bupropion, older adults may be at greater risk of accumulation during chronic dosing [14]. As our patient was over the age of 65, bupropion serum concentrations may have been beneficial in determining the cause of her seizures, however, these levels were never drawn.

Antipsychotic agents share a class-related risk of lowering the seizure threshold. The antipsychotic that is most often associated with seizures is clozapine, the most effective antipsychotic for treatment resistant schizophrenia [5,15]. Clozapine lowers the seizure threshold in both epileptic and non-epileptic patients, and a seizure can occur at any stage of treatment [16]. The estimated cumulative seizure risk is 10 percent in patients treated with clozapine for 3.8 years [15]. Seizures can be potentially avoided, or minimally, the risk mitigated if the daily dose does not exceed 450 mg, as was the case for our patient who was on a 200 mg daily dose [5].

Interestingly, an evidence-based review found there has been little convincing evidence to support a relationship strictly between clozapine serum levels and seizure risk [17]. Seizures can occur at dosages as low as 37.5 mg daily. A plasma level of clozapine as low as 144 nmol/L has been associated with seizure activity. Therefore, clozapine serum concentrations can be used as a guide but not as a definite predictor of therapeutic efficacy or seizures [16]. A seizure is not an adverse reaction that generally warrants discontinuation of clozapine, and its onset usually occurs between two to four weeks of initiation but may occur at all stages of treatment. If clozapine discontinuation is not appropriate, as was the case for our patient, an antiepileptic drug, such as divalproex, can be initiated and the patient monitored for adverse effects [5].

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

Both clozapine and bupropion are recognized as medications with propensity to lower the seizure threshold individually, however, there is currently little information on the risk of using these two medications in combination. It is unclear whether these agents, when used in combination, have additive seizure risk or possible synergistic effects. However, bupropion should be used cautiously in patients treated with clozapine. Agents that do not lower the seizure threshold should be utilized as a safer option when possible [15]. 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 the bupropion was stopped, and divalproex was initiated for seizure prophylaxis, as was observed with our patient [15].

The patient experienced two seizures within two months of one another. The factors that caused the falls cannot be definitively known. In two cases of elderly patients experiencing falls secondary to seizures, their falls were not recognized as seizures due to the many other co-morbidities [10]. Clozapine and bupropion have a long history of decreasing the seizure threshold. The risk of seizures increases with the dose of each of these medications, but the risk of seizures when using these two medications together is unknown. The patient was also experiencing frequent falls which may have led to neurologic injury, a factor considered by her treatment team. The patient’s history of tolerating the combination of low dose clozapine and bupropion is well known. Her psychiatrist ensured the patient was on the lowest effective dose of each medication. However, with age some medications can become less tolerable. In addition, the patient’s recent history of falls, leading to neurologic changes and possible brain injury, are precisely the conditions that could have led to seizures.

With the patient’s history of multiple falls, many of which resulted in injury even while wearing protective equipment, the patient was at an even greater risk of seizure. The patient’s treatment team quickly altered her therapy to remove bupropion and continued an antiepileptic, divalproex, that was added by the acute medical facility where she was treated. Clozapine was continued, as it is typically used for treatment resistant schizophrenia, and the patient has done well on this therapy. Seizures are not a contraindication to clozapine therapy; however, seizure disorders are contraindicated in bupropion therapy. That is why the decision to discontinue bupropion instead of clozapine to decrease the risk of seizures is the most appropriate option with patient care in mind. The patient was also ordered a geriatric chair to decrease her risk of falls. With the addition of these changes, the patient did not have any further epileptic events. Bupropion and clozapine likely contributed to an adverse drug reaction of seizures experienced by this patient, and for this reason, bupropion should be used cautiously in patients treated with clozapine, especially in those experiencing head trauma, including patients who experience frequent falls.

Additionally, this case provokes consideration for how a prescriber’s perception of adverse drug reactions, or the definition therein, can impact and alter the course of both clinical and academic exploration of the actual event (18). There are numerous definitions for adverse drug reactions; however, most in the medication safety community would agree that previously reported adverse consequences of a well-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 to not only the facility’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 potential inclusion in updated package label information (19).

**DECLARATIONS**

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Written informed consent for publication of their clinical details and/or clinical images was not obtained from the patient as the patient was not available for consent due to discharge.

**Authors’ Contributions**

Dzierba C, Lee C, Demler TL

Made equal contributions to the writing of this case report. All listed authors concur in the submission and are responsible for its content; they have agreed to its publication and have given the corresponding author the authority to act on their behalf in all matters pertaining to publication.

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Not applicable.

**Consent for Publication**

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