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Successful bilateral electroconvulsive therapy in a patient with a seizure disorder taking levetiracetam, lorazepam, and zonisamide: A case report

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Abstract
Electroconvulsive therapy (ECT) may be considered for treatment of severe, treatment-resistant, and emergent depression associated with MDD or bipolar disorder. Patients with epilepsy usually take medications that raise the seizure threshold, which poses challenges during ECT. We report a 66-year-old male with epilepsy taking levetiracetam extended-release (XR), lorazepam, and zonisamide requiring ECT for severe MDD. After literature review, the XR form of levetiracetam was changed to higher doses of the immediate-release (IR) formulation, and zonisamide was discontinued 2 days prior to ECT in the hospital and was resumed when the patient underwent outpatient continuation ECT. The patient was treated to remission after receiving 8 acute bilateral ECT treatments before being transitioned to continuation ECT. We provide a brief review of medication management of antiepileptic drugs and other medications that increase the seizure threshold during ECT. To our knowledge, this is the first reported case describing the management of levetiracetam, lorazepam, and zonisamide concomitantly during ECT. Our case suggests that utilizing the IR formulation of levetiracetam, administering the evening dose early the day prior to the procedure, and temporarily discontinuing zonisamide prior to bilateral ECT is effective for the treatment of severe MDD while maintaining seizure prophylaxis.

Keywords: seizure disorder, epilepsy, major depressive disorder, electroconvulsive therapy, zonisamide, levetiracetam, anticonvulsant, benzodiazepine

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Background
Most treatment guidelines support the use of electroconvulsive therapy (ECT) in severe, treatment-resistant, or emergent cases of MDD. The neuronal mechanism of ECT seen in MDD is unclear with the main theory being that seizures induce changes in neurotransmitters, neuroplasticity, and brain tissue connectivity. Patients with epilepsy requiring ECT likely receive seizure threshold-raising medications, such as benzodiazepines (BZDs) or antiepileptic drugs (AEDs). The goal of medication management in such cases is to achieve adequate seizure (eg, 30 to 90 seconds) during ECT without causing spontaneous seizures. ECT is often delivered using brief pulse width and electrical intensity and titrated based on minimum intensity to exceed the seizure threshold.
Because BZDs and AEDs may diminish ECT response, considerations can be made to alter the anesthetic regimen prior to ECT, use flumazenil prior to ECT in patients using BZDs, and decrease or withhold the evening and/or morning doses of seizure threshold-increasing medications prior to ECT.3 Contradictory to this, studies have shown unilateral, bifrontal, or bitemporal ECT to be effective in patients with primarily nonepileptic mood disorders taking AEDs,5,6 and BZDs may not negatively affect ECT outcomes in patients with depression.3 In patients with seizure disorders undergoing ECT, it has been suggested to continue AEDs with neurology consultation and, in the event of medication alterations, return AEDs to previously prescribed doses after ECT is concluded.4 To our knowledge, we report the first patient with MDD and a seizure disorder managed with bilateral ECT who was taking levetiracetam, lorazepam, and zonisamide.

**Case Report**

Our patient is a 66-year-old male with MDD with psychotic features, unspecified anxiety disorder, and generalized tonic-clonic seizures admitted to the psychiatric hospital with suicidal thoughts. He presented with profound psychomotor retardation, cognitive latency, thought blocking, anorexia with weight loss, and difficulty with sleep maintenance. The patient also had nihilistic-type delusions that he was already dead or imminently dying. The patient had been seizure-free with no AED changes for at least 1 year. Medications at admission included fluoxetine 20 mg daily, levetiracetam 750 mg extended-release (XR) nightly, lorazepam 1 mg every morning and 2 mg every evening, and zonisamide 300 mg nightly. He initiated fluoxetine and lorazepam within the preceding month. Previous trials of escitalopram and quetiapine were not effective; mirtazapine was briefly effective. Fluoxetine and lorazepam were discontinued on the day of admission due to ineffectiveness and the possibility of worsening cognitive dysfunction, respectively. Oral venlafaxine 75 mg daily and mirtazapine 15 mg nightly were initiated on admission with considerations to start ECT if ineffective. Two days later, he began to refuse all medications and required assistance eating. On the third evening, he had an approximate 60-second seizure, which required transfer to the emergency department and treatment with IV levetiracetam and lorazepam and oral zonisamide. Lorazepam was continued IV at 0.5 mg 4 times daily on day 4, which improved his ability to take medications and make decisions. It was determined that ECT would be appropriate, but the patient was not ready to consent. Nonetheless, pharmacotherapy was modified in order to prepare for ECT. After literature review and discussion with neurology, levetiracetam was switched to 1000 mg immediate-release (IR) twice daily with the evening dose to be given at 2 pm the night prior to ECT while holding the morning dose on the day of ECT. Lorazepam was reduced to 0.25 mg 4 times daily on the seventh day of hospitalization and discontinued on the ninth day. Zonisamide was tapered and discontinued 2 days prior to the first ECT session and withheld during the remainder of hospitalization. The patient was observed to have a limited-duration seizure 2 days prior to initial ECT that may have been related to downward taper of AEDs. After deliberation, the patient agreed to ECT, and the acute series was initiated on day 12 for a total of 8 sessions (Table). ECT was administered with the Thymatron System IV (Somatics, LLC, Venice, FL) with a pulse width of 0.5 ms, 30 Hz, 40 joules, and duration of 7.5 seconds. Methohexital was the anesthesia-inducing agent used. Adequate seizure activity was seen (Table). He restarted oral lorazepam 0.5 mg twice daily after the first ECT for continued neurovegetative symptoms while holding the nightly dose prior to ECT. After the second ECT, improvements were robust across all domains of prior dysfunction; the patient was engaging socially, smiling, eating, and sleeping; mood was much improved, and delusions resolved. Following the fourth ECT, lorazepam was no longer indicated and discontinued. The patient discharged home after the fifth ECT, completed 8 acute treatments, and received continuation ECT following this. Following the acute ECT series, the patient resumed zonisamide and levetiracetam XR at previously prescribed doses. The patient held these AEDs 4 days prior to each continuation ECT and utilized twice daily levetiracetam 1000 mg IR monotherapy with the last dose at least 24 hours before ECT. Nights following continuation ECT, zonisamide and levetiracetam XR were
resumed. After the 10th treatment, the patient sustained resolution of depressive symptoms, denying insomnia, anhedonia, and suicidal thoughts.

**Discussion**

It is not clearly understood how AEDs affect ECT response, and there is no consensus on AED management. Although several studies report successful ECT with AEDs, no reports are available for the management of levetiracetam combined with zonisamide during ECT. We implemented a careful administration schedule for our patient’s AEDs based on their pharmacokinetic properties, balancing the goals of seizure prevention with ECT response. It was of high importance to obtain rapid depression improvement, and given our patient’s seizure-free duration prior to admission, antiepileptic medications were reduced with input from neurology. Our patient had adequate seizures during ECT with no restimulations required and no breakthrough seizures once ECT was initiated.

Zonisamide was discontinued 2 days prior to ECT initiation and resumed after acute ECT series completion. Zonisamide achieves peak concentrations 2 to 6 hours after administration and reaches concentration steady-state in approximately 2 weeks. In an effort to reduce seizure occurrence when not being administered ECT and also allow for quicker AED elimination on nights prior to ECT, levetiracetam was switched from the XR formulation to a higher dose of the IR formulation. Levetiracetam XR peak plasma concentrations occurs after 4 hours with peak time being 3 hours longer than the IR formulation. The elimination half-life of levetiracetam is 9 hours in the elderly with comparable bioavailability between the XR and IR formulations. Given its elimination half-life, zonisamide would likely have had detectable serum concentrations during this patient’s course of treatment, yet it did not prevent adequate seizure duration during ECT. Similarly, we did not see adverse impacts on treatment response or occurrence of breakthrough seizure from the increased levetiracetam IR dose prescribed.

There is debate regarding the optimal anesthetic agent to be used during ECT. Although etomidate monotherapy or adding ramifentanyl to lower doses of methohexital for anesthesia induction if inadequate seizures occur during ECT can be considered, we continued our current practice of using the barbituric acid derivative, methohexitol, as an inducing agent and altered the AEDs as described previously. One randomized, double-blind, crossover trial compared etomidate, methohexital, and propofol as inducing agents for ECT in 10 patients with MDD; however, none of these patients had seizure disorders or took AEDs. Briefly, EEG seizures were longest after etomidate induction and shortest with propofol, and the clinical meaningfulness of this effect was not assessed. Etomidate had no dose-related differences in EEG seizure duration although higher weight-based doses of methohexital and propofol reduced seizure duration. Cognitive recovery was longer in patients with longer seizure duration, and discharge time from recovery room was 5 to 7 minutes longer with etomidate compared with other agents. A meta-analysis, including open-label trials and case series, found etomidate EEG seizure duration to be 2.23 seconds (95% CI = –3.62, 8.01; \( P = .456 \)) longer than methohexital. Based on this data, etomidate as an inducing agent does not clearly offer an advantage in patients with epilepsy taking AEDs but could be considered.

Our use of low-dose lorazepam with brief washout periods the night prior to ECT procedures also appeared to have little impact on bitemporal ECT effectiveness. Data suggest BZDs decrease the efficacy of unilateral ECT but perhaps not during bilateral ECT. Retrospective data suggest patients receiving BZDs had higher depression remission rates than those not receiving BZDs (81.8% vs 52%, \( P = .017 \)) during primarily bilateral ECT. Another retrospective study found patients with monopolar depression who received an average of 17.95 mg (SD 20.3) diazepam equivalents had a response rate of 98.9% and a remission rate of 90% with bitemporal ECT.

Our case demonstrates that bilateral ECT effectiveness was not compromised with the use of low-dose lorazepam, levetiracetam, and lack of complete zonisamide elimination prior to the procedure. Limitations to our case include that it represents a single patient, AED and BZD serum concentrations were not monitored, and no standardized depression rating scales were utilized. Although our management of this case appears promising for successfully continuing lorazepam, levetiracetam, and zonisamide during ECT, more research and case reports are necessary to recommend safe and effective utilization of AEDs and BZDs during ECT.

**Conclusion**

Management of AEDs and BZDs during ECT poses challenges, especially in patients with seizure disorders. Valproate, carbamazepine, and lamotrigine have been successfully continued during ECT in patients without epilepsy, and a large case series supports AED continuation in most patients with epilepsy receiving ECT. BZDs do not usually impact ECT effectiveness when the dose is held the morning prior to bilateral ECT procedures. Our case suggests that utilizing the IR formulation of levetiracetam, administering the evening dose early the day prior to the procedure, and temporarily discontinuing zonisamide dosing prior to bilateral ECT is
effective for the treatment of severe MDD while maintaining seizure prophylaxis.

References


