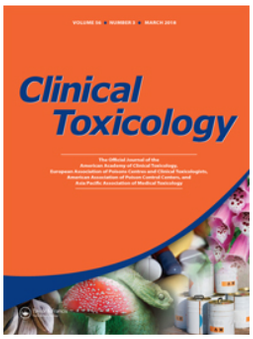

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CLINICAL RESEARCH

Levetiracetam in toxic seizures

Ted Lee[a], Brandon J. Warrick[a,b], Preeyaporn Sarangarm[a], Robert L. Alunday[c], Silas Bussmann[a], Susan C. Smolinske[b,d] and Steven A. Seifert[b]

[a]Department of Emergency Medicine, University of New Mexico Hospital, Albuquerque, NM, USA; [b]New Mexico Poison and Drug Information Center, Albuquerque, NM, USA; [c]Department of Neurosurgery, University of New Mexico Hospital, Albuquerque, NM, USA; [d]College of Pharmacy, University of New Mexico, Albuquerque, NM, USA

ABSTRACT

Background/Objectives: The use of levetiracetam (LEV) in the management of drug-induced seizures has not been systematically investigated. Repetitive and continuous seizures that do not respond to benzodiazepines require second line therapy. Levetiracetam has a unique receptor binding site, rapid absorption, no known cardiac effects at therapeutic doses, and is theoretically a good candidate for use in drug-induced seizures. We evaluate the safety of LEV and its association with seizure cessation in this retrospective chart review of patients who received LEV as a control agent in drug-induced seizures.

Methods: We identified the medical records of patients presenting to an urban, level 1 trauma center between 1 January 2010 and 31 May 2015 by ICD-9 codes based on the following: (1) a poisoning diagnosis, (2) a seizure diagnosis, and (3) administration of LEV. We included patients with a drug-induced seizure based on history, electroencephalogram results, blood alcohol concentrations, urine drug screens, and adequate documentation. We excluded patients with alcohol withdrawal, anoxic brain injury, subtherapeutic concentrations of other antiepileptics, hypoglycemia, and pseudoseizures. Primary outcomes of interest included cessation of active seizures or the prevention of seizure recurrence. We assessed safety by the presence or absence of adverse drug effects (ADE) attributed to the administration of LEV.

Results: Thirty-four patients met inclusion and exclusion criteria. Half of the study cohort (17) presented with generalized tonic-clonic seizures (TCS); half (17) presented in generalized convulsive status epilepticus (GCSE). Six patients in GCSE received LEV during their seizures; 2 also received fosphenytoin. One improved immediately following LEV administration, and the remaining 5 had seizure control. Eleven GCSE patients (65%) remained seizure free after LEV therapy. The patients with TCS (17) received LEV after seizure(s) control. Sixteen (94%) were seizure-free during their hospital course. We found no adverse drug effects. In total, 27 of 34 patients (79%) had a return to baseline neurological and physical health. Six had long-term sequelae; none of which are known LEV side-effects. We identified 46 toxic substances and 22 known seizurogenic agents (48%). The median length of stay was 3.7 days (0.4–96), and the median duration of in-hospital LEV therapy was 1.6 days (0–49).

Conclusions: Levetiracetam used as a second-line agent was associated with control of drug-induced seizures and prevention of seizure recurrence without obvious adverse effects. A prospective study is needed to confirm these results.

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Levetiracetam; drug-induced seizure; toxic seizure

Background

Drug toxicity causes two to ten percent of status epilepticus cases [1–5]. Clinicians must recognize and terminate drug-induced status epilepticus early to prevent mortality and poor functional outcomes [6–9]. Because there are no validated guidelines for managing toxic seizures, further guidance – especially for seizures refractory to benzodiazepines – is necessary [10–16].

The choice of second line agents is not clear in this setting. Phenytoin, valproic acid, and carbamazepine have relative contraindications due to ion channel blocking effects and paradoxical seizures in high doses. Phenobarbital and propofol are two recommended second line agents for drug-induced seizures; however, there are no prospective trials for their use in this setting.

Levetiracetam has a unique binding site with a different mechanism of action than that of benzodiazepines, propofol, and barbiturates. Levetiracetam is rapidly absorbed, renally excreted, does not modulate sodium, potassium, or calcium channels, and has no reported cardiotoxic effects at therapeutic doses [17–19]. Because of levetiracetam's favorable pharmacologic profile and minimal drug interactions, it may be preferred for use in this setting.

Clinicians at our institution utilize levetiracetam for benzodiazepine-resistant seizure cessation and seizure suppression,

CONTACT Steven A. Seifert sseifert@salud.unm.edu Department of Emergency Medicine, University of New Mexico Hospital, New Mexico Poison and Drug Information Center, MSC07 4390, 1 University of New Mexico, Albuquerque, NM 87104, USA

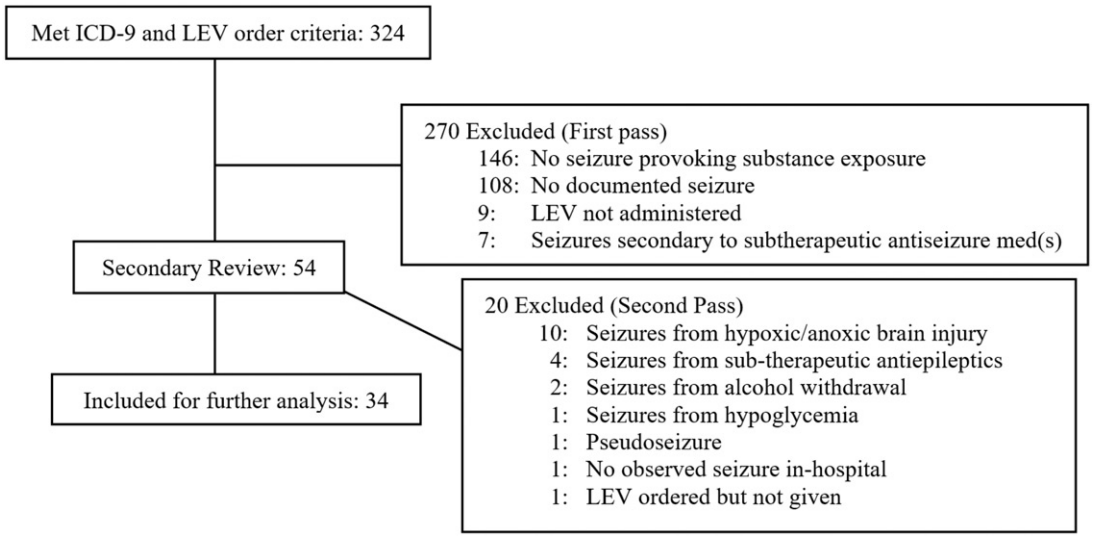

Figure 1. Included and excluded patients in primary and secondary screening.

including toxic seizures. However, data concerning the use of levetiracetam in drug-induced seizures are lacking. We aimed to describe whether levetiracetam controls drug-induced seizures. Our secondary aim was to describe adverse effects associated with levetiracetam when used for toxic seizures.

Methods

We performed a chart review of patients treated at the University of New Mexico Hospital, between 1 January 2010 and 31 May 2015 with ICD-9 codes for (1) a poisoning diagnosis, and (2) a seizure diagnosis, and (3) administration of levetiracetam intravenously. Of the 324 charts identified by ICD-9 screening, we reviewed cases for those with a documented history of toxic overdose, seizure(s), and levetiracetam administration for seizure termination and/or ongoing seizure control. We excluded cases with no documentation of seizure (e.g. known history of seizure disorder but no seizure on presentation), levetiracetam administration, or if there was a clear non-toxicological etiology for seizure (e.g. alcohol withdrawal, intracranial hemorrhage, hypoglycemia, pseudoseizures, etc.). Of the 54 remaining cases, all six clinical investigators reviewed case summaries, and we obtained a unanimous consensus for inclusion or exclusion (second-pass). Figure 1 illustrates the included and excluded patients. The authors involved in screening included two board certified medical toxicologists, a neuro-intensivist, a clinical toxicologist, a pharmacist and an emergency medicine resident. One toxicologist and the neuro-intensivist are also board certified in emergency medicine.

We reviewed medical records of the 54 included cases for provider notes, laboratory and other testing, medication administration indications, timing and response to treatment. We further divided patients into two groups: (1) those presenting in generalized convulsive status epilepticus (GCSE); and (2) those with generalized tonic-clonic seizures (TCS). We defined generalized convulsive status epilepticus based on two standardized criteria: (1) a seizure lasting greater than five minutes OR (2) more than one seizure occurring within five minutes without return to baseline neurologic function [20,21].

Primary outcomes were: (1) Therapeutic response to levetiracetam, determined by cessation of active seizures in a time-frame consistent with its pharmacologic properties or the absence of seizure recurrence and (2) Safety of levetiracetam in toxic seizures, determined by the presence or absence of adverse drug effects attributed to the administration of levetiracetam, based on known side effects of levetiracetam. Because respiratory depression is not a known side-effect of levetiracetam, we did not include intubation or respiratory depression as an adverse event.

Ethical approval

The University of New Mexico School of Medicine Institutional Review Board reviewed and approved the study.

Results

Thirty-four patient encounters met inclusion and exclusion criteria (Figure 1). Patient demographics included 11 women and 23 men. The median age was 39 [IQR 24.3–48.3]. Forty-four percent had history of seizures and 56% did not. Further demographic information is listed in Table 1.

We identified 46 substances and 22 known seizure-provoking agents (48%) by history and, where available, by laboratory testing (Table 2). Toxins most frequently involved in our study were cocaine (6) and amitriptyline (5). We identified more than one seizure provoking substance in 17 patients; the median number of substances was 1.5 [IQR 1–3]. Twenty-nine patients (85%) had serum ethanol measurements, among which four patients tested positive for ethanol. A different subset of 29 patients (85%) underwent immunoassay urine drug screens for drugs of abuse (Table 3); we used urine drug screens to confirm history of cocaine and amphetamine use. Seventeen patients (50%) presented with generalized TCS and 17 (50%) presented

Table 1. Demographic characteristics of patients treated for toxic seizures.

Demographic characteristics of patients treated for toxic seizures			
	Male	Female	Total
Sex: *N* (%)	23 (68)	11 (32)	34 (100)
Age: Median (IQR)	39 (23–45)	39 (32–55)	39 (24–48)
No. of substances of exposure: Median (IQR)	1 (1–2)	3 (1–4.5)	1.5 (1–3)
Prior seizure history: *N* (% within sex)	10 (43)	5 (45)	15 (44)
History of prior LEV use: *N* (%)	5 (22)	3 (27)	8 (24)

Table 2. Substances identified by history, urine, and/or blood.

Substance	Count	Substance	Count	Substance	Count	Substance	Count
Cocaine	6	Quetiapine	2	Ibuprofen	1	Lamotrigine	1
Amitriptyline	5	Trazodone	2	Tiotropium	1	Levetiracetam	1
Ethanol	5	Venlafaxine	2	Levothyroxine	1	Metoclopramide	1
Methamphetamine	4	Oxycodone	2	Tramadol	1	Zolpidem	1
Gabapentin	4	Metoprolol	2	Baclofen	1	Methocarbamol	1
Methadone	3	Cannabis	1	Oxybutynin	1	Diazepam	1
Carbamazepine	3	Ethylene glycol	1	Energy drink	1	Difluoroethane	1
Heroin	3	Propylene glycol	1	Nortriptyline	1	Fluoxetine	1
Bupropion	3	MDMA	1	Boric Acid	1	Hydromorphone	1
Acetaminophen	3	Alprazolam	1	Ciprofloxacin	1	Bath Salts	1
Synthetic cannabinoid	3	Phenytoin	1	Diphenhydramine	1	Buspirone	1
Mirtazapine	3	Clonazepam	1				

Table 3. Demographic characteristics of patients treated for toxic seizures.

Adverse events with long term sequelae:	Other in-hospital adverse events:
Cerebrovascular accident and acute kidney injury	Rhabdomyolysis
Brain injury with persistent neurologic sequelae	Acute kidney injury requiring hemodialysis
Death from sepsis and aspiration pneumonia	Acute kidney injury (2)
Persistent vegetative state	Aspiration pneumonia
Acute kidney injury and non-ST segment elevation myocardial infarction	Continued suicidal ideation
Heart failure with reduced ejection fraction	Tibia & fibula fracture
	Change in affect

in GCSE. For a complete list of study patients' presentations and hospital course please refer to Table 4.

Seizure termination

Among the 17 patients with GCSE, 15 had seizures that did not terminate with benzodiazepines alone. Six patients received levetiracetam during their seizures. The remaining 11 patients received levetiracetam after control of GCSE with other agents. Among the six patients who received levetiracetam during their seizures, one had termination of generalized convulsive status epilepticus immediately following levetiracetam administration; four had seizure control at an unspecified time after administration. One patient received endotracheal intubation, sedation with propofol, and was seizing at the time of levetiracetam administration. An EEG performed two days later was inconclusive.

All the 17 patients with TCS obtained initial seizure cessation spontaneously, either with benzodiazepines, or with other antiseizure medications. Therefore, all the patients with TCS received levetiracetam for seizure suppression, rather than seizure termination.

Seizure suppression

Among the study cohort, 27 of 34 (79%) of the patients with drug-induced seizures remained seizure free after levetiracetam administration. Sixteen of 17 TCS patients remained seizure-free during their hospital course.

All the patients with GCSE received midazolam or lorazepam prior to receiving levetiracetam, with the exception of one patient who only received naloxone. Two patients with GCSE received benzodiazepines and fosphenytoin before levetiracetam. One patient received olanzapine, diazepam, and propofol. Eleven with GCSE remained seizure-free after levetiracetam administration and six had a seizure recurrence. Of the six with seizure recurrence following levetiracetam: (1) Two patients had seizure suppression after titration of levetiracetam dose from 500 to 750 twice daily in one patient and 1000 to 1500 twice daily in the other; (2) One patient who received levetiracetam for clinically apparent seizure (reflected in contemporaneous physician and nursing notes) later had an electroencephalogram (EEG) which showed myoclonic jerking without epileptiform activity. We included this patient based upon the empirical use of levetiracetam for apparent seizure; (3) Three patients had a seizure after discontinuing levetiracetam during their hospital stay; their seizures occurred 1 day, 3 days, and 7 days, respectively, after in-hospital levetiracetam termination.

Of the 15 patients with a seizure history, levetiracetam achieved seizure control in seven of eight prior levetiracetam users and four of seven with no prior levetiracetam use.

The median length of stay was 3.7 days (range of 0.4–96 days), and the median duration of in-hospital levetiracetam

Table 4. Complete list of patients.

Type of seizure	Sex	Age (Years)	Toxic substances	Number of seizures after LEV	Patient outcome	Length of stay (Days)	Summary of events
GCSE	F	22	Methamphetamine	0	Recovered	3.7	Prehospital seizure, intubated, EEG showing persistent seizure, received lorazepam (LOR) and levetiracetam (LEV). Documentation reports seizure "improved after keppra and ativan."
GCSE	F	32	Ethylene glycol, propylene glycol	3	Cerebrovascular accident, acute kidney injury	15.8	Prehospital seizure, intubated, received midazolam (MID) & LEV. Patient unresponsive on ground three days into admission, thought to be unwitnessed seizure. Complained of "aura," which ceased after LEV dosage increase.
GCSE	F	18	Acetaminophen, boric acid, ciprofloxacin	3	Takotsubo cardiomyopathy, persistent myoclonus	18.8	Altered, intubated, received propofol, 15 min seizure in ED after propofol infusion decreased, given LOR. Second seizure 2 h later, lasting two minutes after propofol stopped. Received LEV 2 h later. Patient had myoclonus the following day, confirmed on EEG, but documented as seizures, given LOR
GCSE	F	55	Methamphetamine, synthetic cannabinoid, synthetic cathinone, cocaine	0	Recovered, tibia & fibula fracture	20.3	Prehospital seizure, persistent altered mental status with initial response to naloxone. EEG confirmed persistent seizure for greater than 24 h. Received LEV, EEG showed possible seizure termination two days later.
GCSE	F	88	Venlafaxine, buspirone, gabapentin, mirtazapine, trazodone, levothyroxine, metoprolol	0	Death, sepsis, aspiration pneumonia	9.3	Prehospital seizure of 30 min, received LOR, MID, MID infusion, intubated, LEV 8 h later.
GCSE	M	36	Amitriptyline	0	Recovered, rhabdomyolysis	2.7	Prehospital seizure, received MID and LOR. Obtunded and agitated in ED, given LEV after seizure control.
GCSE	M	23	Heroin	0	Persistent vegetative state	96.1	Prehospital seizure, second seizure at outside facility, received LOR, MID, LEV, intubated, and transferred.
GCSE	M	16	Synthetic cannabinoid	0	Stabilized and transferred to an outside facility	0.2	Prehospital seizure, three seizures en route, given MID. Two seizures upon arrival, received fosphenytoin and LEV. Transferred to an outside hospital due to insurance issues.
GCSE	M	23	Difluoroethane	2	Acute kidney injury	12.8	Persistent seizure in ED, given LOR, MID, LEV, phenytoin, intubated.
GCSE	M	50	Cocaine	1	Recovered	16.5	Two prehospital seizures, received MID en route, started LEV thirty-four minutes later. LEV stopped the following day. Patient had a second seizure three days later, given LOR, LEV, phenytoin.
GCSE	M	16	Methadone, MDMA	0	Anoxic brain injury with neurologic sequelae	55.6	Prehospital seizure, received fosphenytoin & placed on LOR infusion. LOR stopped because of respiratory failure. LEV started 5 days later. Patient noted to be "posturing" 16 days later, EEG reported non-epileptiform activity.
GCSE	M	55	Alprazolam, heroin	0	Recovered	1.5	Prehospital seizure, received naloxone, LOR, MID, intubated. Persistent seizure-like motions, with reported EEG of "potentially epileptogenic cerebral dysfunction." Received LEV 0-4 hours after termination.
GCSE	M	41	Heroin, methamphetamine	0	Recovered	2.1	Prehospital seizure of 20 min, received naloxone, MID. Second, 24 min seizure five hours later in hospital, received MID, LOR, olanzapine. Received LEV two hours after second seizure.

(*continued*)

Table 4. Continued

Type of seizure	Sex	Age (Years)	Toxic substances	Number of seizures after LEV	Patient outcome	Length of stay (Days)	Summary of events
GCSE	M	28	Clonazepam, methadone	1	Recovered	1.6	Prehospital seizure, followed by 25 min seizure in outside hospital, received LOR, diazepam, went into respiratory failure, intubated, received LEV, with immediate seizure termination. Had another seizure the next day, given fosphenytoin.
GCSE	M	22	Amitriptyline, diazepam	3	Recovered	10.6	Patient presented altered, intubated. Seized after receiving LOR, propofol; received LEV 1+ hours later. Patient had three more seizures 4 h later, received LOR, and LEV dosage increased.
GCSE	M	44	Nortriptyline, bupropion, gabapentin	0	Persistent suicidal ideation	7.8	*Seizure in ED, placed on MID infusion. Second seizure later in the day, MID infusion increased and given LEV.
GCSE	M	64	Methadone, oxycodone, quetiapine, metoprolol, ibuprofen, tiotropium	0	Recovered	2.5	Prehospital seizure, received MID and LOR, LEV started 1+ day after admission for seizure prophylaxis.
TCS	F	39	Cocaine, etoh	0	Recovered	0.4	Unwitnessed prehospital seizure, missed morning LEV dose, restarted on LEV 5 h after presentation.
TCS	F	32	Methamphetamine	0	Recovered	0.4	Missed two doses of LEV, prehospital seizure, received LEV 4 h after admission.
TCS	F	45	Carbamazepine	0	Recovered	1.1	Prehospital seizure. LEV restarted 8 h after presentation.
TCS	F	32	Quetiapine, trazodone, venlafaxine, mirtazapine	0	Acute kidney injury with need for hemodialysis	16.2	Prehospital seizure, received MID, intubated. Had 2-3 seizures same day, received LEV 3-4 h after seizure control.
TCS	F	57	Baclofen, bupropion, mirtazapine, hydromorphone, gabapentin	0	Recovered	3.1	Prehospital seizure, received LEV 5 h after admission.
TCS	F	54	Diphenhydramine, lamotrigine, levetiracetam, gabapentin, metoclopramide, oxycodone, zolpidem, acetaminophen, methocarbamol, marijuana	1	Change in affect	3.7	History of epilepsy on LEV, presented with three prehospital seizures. Had one seizure in hospital the day after admission, received LEV 30 min later. Had another seizure 1 h later. LEV initially withheld due to concerns of toxicity.
TCS	M	44	Carbamazepine	0	Recovered	2.6	Seized in ED, administered LOR with no further seizure activity. History of LEV and carbamazepine use, restarted on LEV.
TCS	M	46	Phenytoin	0	Recovered	24.0	Several witnessed seizures pre-hospital in the past week, received LEV on hospital day 2.
TCS	M	18	Synthetic cannabinoid	0	Acute kidney injury	5.7	Prehospital seizure, received LEV 11 h after presentation.
TCS	M	39	Cocaine	0	Recovered	6.1	Two prehospital seizures, received "benzodiazepine" from EMS, unknown agents given at outside facility, seized en route. Received LEV 0–9 h after arrival.
TCS	M	22	Tramadol	0	Recovered	0.6	Prehospital seizure with subarachnoid hemorrhage injury, received LEV 5 h later.
TCS	M	34	Energy drink	0	Recovered	1.5	Prehospital seizure, with second seizure in ED, received LOR, ondansetron, promethazine, LEV.
TCS	M	67	Cocaine	0	Acute kidney injury, NSTEMI	1.4	Unwitnessed prehospital seizure. Received LEV 22 h after admission.
TCS	M	32	Cocaine	0	Recovered	0.6	"Rather quick" seizure while in ED, received LOR and LEV.

(*continued*)

Table 4. Continued

Type of seizure	Sex	Age (Years)	Toxic substances	Number of seizures after LEV	Patient outcome	Length of stay (Days)	Summary of events
TCS	M	49	Oxybutynin, amitriptyline	0	Departed against medical advice	11.2	Prehospital seizure, received MID, LOR, intubated admitted to MICU. Two seizures 37 and 40 h after admission, received LOR, documented LEV administration not confirmed by nursing. Patient went into ventricular tachycardia, became pulseless, 30 min code. LEV charted to have been given 4 hours after onset of code.
TCS	M	40	Amitriptyline, bupropion, acetaminophen	0	Recovered	9.6	Altered mental status on arrival, three witnessed seizures three hours of admission. Received LEV 44 min after final seizure.
TCS	M	39	Carbamazepine, amitriptyline, fluoxetine	0	Recovered	2.4	Unwitnessed prehospital seizure, received LEV 11 h after presentation.

therapy was 1.6 days (range of 0–49 days). Twenty-seven of 34 patients (79%) had a return to baseline neurological and physical health.

Adverse events associated with levetiracetam

Table 3 lists all recorded in-hospital adverse events. The discharge summary for one patient mentioned change of affect. However, confounding factors may include the patient's hospitalization of 3.7 days and substance abuse. The only death occurred in an 88-year-old woman who succumbed to sepsis from aspiration pneumonia nine days after achieving seizure control with levetiracetam. No contemporaneous record attributed any adverse event to LEV. On secondary review, the investigators did not attribute any adverse event to levetiracetam.

Discussion

Many commonly used second line treatments lack efficacy data in drug-induced seizure or have adverse effects. Propofol is effective but may cause respiratory depression [22,23], and phenobarbital may be associated with respiratory depression and paradoxical seizures [11,24,25,26]. Phenytoin, a sodium channel blocker, may increase the risk of adverse cardiac events in amitriptyline poisoning and causes paradoxical seizures in high doses [16,27,28,29]. Valproic acid, in addition to blocking sodium channels, also blocks calcium channels [30,31,32]. Carbamazepine, like phenytoin, causes paradoxical seizures in supratherapeutic doses and may induce cardiac arrhythmias [33,34].

Levetiracetam is an effective first and second-line control agent for the management of generalized convulsive status epilepticus [35,36,37]. Whether this translates to efficacy in drug-induced seizures is unknown. Interestingly, the overall rate of seizure suppression in our study approximates levetiracetam's efficacy in non-drug induced seizures (44–94%) [35,36].

Levetiracetam has a distinct binding site at the synaptic vesicle protein 2A (SV2A) by which it may inhibit neurotransmitter release [38]. This unique mechanism of action may modulate seizure suppression by targeting a site different from the primary insult in drug-induced seizures. Furthermore, it may suppress seizures resistant to GABA-agonists.

We identified no evidence of levetiracetam-related adverse effects. Common levetiracetam side effects include somnolence, dizziness, irritation, hostility, nervousness, and aggression; these behavior changes are primarily documented during chronic use [39]. Given the severity of illness in our study sample, clinical documentation may not record minor adverse effects. For instance, treating physicians may have attributed symptoms such as somnolence of dizziness to post-ictal condition or to co-administered medications.

Limitations

This is a retrospective case series and subject to all of the limitations inherent in that study design. We relied upon clinical records of contemporaneous care. Laboratory investigations and management of seizures occurred at the discretion of the treating physicians without regard to research. Seizure control may have resulted from levetiracetam, other agents, or the combination. Seizures may have terminated on their own. Contemporaneous records may not systematically describe response to treatment or capture all adverse drug effects. Some patients' seizures may have resulted from withdrawal of anti-epileptic medication, alcohol, or other medications. Since this is a retrospective chart review without a control or comparison group, we cannot determine efficacy of levetiracetam, and we are likely underestimating adverse effects.

Conclusions

Levetiracetam used as a second-line agent was associated with control of drug-induced seizures and prevention of seizure recurrence without obvious adverse effects. We propose

a prospective clinical trial to more completely assess efficacy and safety.

Disclosure statement

The authors have no conflicts of interest to report.

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