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The Effect of High and Low Antiepileptic Drug Dosage on Simulated Driving Performance in Person's with Seizures: A Pilot Study

Abstract

Background: Prior studies examining driving performance have not examined the effects of antiepileptic drugs (AED's) or their dosages in persons with epilepsy. AED's are the primary form of treatment to control seizures, but they are shown to affect cognition, attention, and vision, all which may impair driving. The purpose of this study was to describe the characteristics of high and low AED dosages on simulated driving performance in persons with seizures.

Method: Patients (N = 11; mean age 42.1 ± 6.3; 55% female; 100% Caucasian) were recruited from the Epilepsy Monitoring Unit and had their driving assessed on a simulator.

Results: No differences emerged in total or specific types of driving errors between high and low AED dosages. However, high AED drug dosage was significantly associated with errors of lane maintenance ($r = .67, p < .05$) and gap acceptance ($r = .66, p < .05$). The findings suggest that higher AED dosages may adversely affect driving performance, irrespective of having a diagnosis of epilepsy, conversion disorder, or other medical conditions.

Conclusion: Future studies with larger samples are required to examine whether AED dosage or seizure focus alone can impair driving performance in persons with and without seizures.

Keywords

seizures, epilepsy, driving performance, simulator, antiepileptic drugs

Cover Page Footnote

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Credentials Display

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When occupational therapists are determining an individual's fitness to drive, they do so primarily by conducting comprehensive driving evaluations, which typically consist of off- and on-road assessments. In many cases, drivers whose fitness to drive has been questioned are referred by physicians or are flagged by the regulatory licensing board. However, with some medical conditions, such as epilepsy, there is a paucity of literature concerning how the symptoms or side effects of antiepileptic drugs can impair driving performance. Current guidelines do not provide strong directions for occupational therapists, who, ultimately, are responsible for determining how the symptoms and medications related to epilepsy can impact an individual's driving ability (National Institute of Neurological Disorders and Stroke, n.d.).

Epilepsy, characterized by recurrent seizures resulting in altered neurological function (Tippin, Sparks, & Rizzo, 2009), can pose a risk to road safety (Classen, Crizzle, Winter, Silver, & Eisenschenk, 2012; Sheth, Krauss, Krumholz, & Li, 2004) due to impairments of motor, visual, and cognitive skills (Drazkowski, 2007). One way to control seizures is through the use of antiepileptic drugs (AEDs). While AEDs result in seizure remission in approximately two-thirds of people with epilepsy (World Health Organization, 2005), the side effects of some of these medications may impair multiple domains of cognition, such as memory and attention (Meador et al., 1995), and may cause blurred vision and/or fatigue (Drazkowski, 2007). For example, topiramate, a

commonly used AED, causes confusion, dizziness, fatigue, and decreased concentration in patients with seizures (Shorvon, 1996). Another AED, zonisamide, produces other cognitive deficits, such as impairment of communication skills and recall of visual-graphic task stimuli, and may cause sleepiness in patients with partial seizures (Berent et al., 1987). Because cognitive and visual processing skills are important to driving, AEDs may also adversely impact driving performance.

In a double-blind randomized crossover study in 27 healthy drivers without neurological conditions, simulated driving performance was compared at baseline (no meds) and after dosages of either carbamazepine (CBZ) or oxcarbamazepine (OXC) were administered and progressively increased (Kaussner et al., 2010). The participants made significantly more lane maintenance errors and more total driving errors when taking both AEDs. When comparing the two drugs, the participants taking CBZ made significantly more total driving errors than when taking OXC, indicating that CBZ may have more adverse side effects on driving (Kaussner et al., 2010). Comparatively, another study examined the effects of AED dosages on driving performance in healthy drivers without neurological conditions on a road test (Ramaekers et al., 2002). The participants were randomized into three groups (600 mg of CBZ vs. 600 mg of remacemide vs. a placebo), and it was found that CBZ resulted in worse driving performance based on deviations of standard lane positioning compared to remacemide and the

placebo. However, neither of these studies included persons with epilepsy or seizures. The underlying impairment of seizures may also cause cognitive, motor, or visual impairment potentially leading to difficulties with driving further exacerbated by AED therapy.

While the criterion measure for assessing driving performance is an on-road evaluation (Kay, Bundy, Clemson, & Jolly, 2008), the risk of seizures while driving places the driver, evaluator, passengers, and other road users at risk. Although questions still remain on the utility of simulators in clinical practice for determining fitness to drive, research studies can use simulators to test driving performance in a safe, objective, and accurate manner (de Winter et al., 2009). Research studies using simulators have found evidence of relative and absolute validity compared to on-road testing (Shechtman, Classen, Awadzi, & Mann, 2009).

Only one study has prospectively examined simulated driving performance in people with epilepsy and found associations between clinical tests and driving errors (i.e., visual scanning, adjustment to stimuli, lane maintenance, vehicle position, and total errors), but that study did not examine specific AEDs or their dosages on driving performance (Crizzle et al., 2012). Given that improving evidence-based practice is at the forefront of research agendas in occupational therapy, identifying features of medical conditions and associated medications that can impair driving is of paramount importance. Thus, the objective of the present study was to describe the simulated

driving performance (number and type of errors) in persons with seizures on their high vs. low AED dosages. The primary aim of this study was twofold: (a) to identify simulated driving errors (e.g., lane maintenance, adjustment to stimuli, speed regulation, gap acceptance, signaling, visual scanning, and vehicle position) made during high and low AED dosage in persons with seizures; and (b) to determine if correlations existed between high and low AED dosage with specific and total number of simulated driving errors in persons with seizures.

Method

Participants

The Institutional Review Board at the University of Florida (UF) granted ethics approval, and each participant provided informed consent prior to participation. Persons with epilepsy or seizures were referred to the UF in-patient Epilepsy Monitoring Unit (EMU) if they had refractory epilepsy, increased seizure frequency despite using AEDs, or had new variations of seizure activity (e.g., simple partial to complex partial) not exhibited previously. The participants, referred by fellowship-trained epileptologists from the EMU, were eligible if: (a) they were 18 years or older, (b) showed evidence of paroxysmal events with loss of consciousness, (c) had a valid driver's license or an intent to obtain one, (d) were community dwelling, and (e) had the physical and mental capacity to complete the study as determined by the epileptologist. Exclusion criteria consisted of: (a) severe psychiatric (e.g., psychosis) and physical conditions (e.g., missing limbs), (b) multiple

psychotropic medications that negatively affect physical and cognitive function, and (c) pregnant females. Two individuals were screened out due to meeting the exclusion criteria.

Design

This quasi-experimental study employed a single group design to determine the effects of AED dosages on driving performance using a simulator. Participants in a single group were compared on their simulated driving performance while taking low and high dosages of AEDs. As persons with epilepsy can have residual cognitive deficits from repeated seizures, a control group was not included as part of this study (as healthy adults are unlikely to have cognitive deficits).

Procedure

The participants were admitted to the EMU and monitored continuously (typically over 5 days) via electroencephalogram. To elicit seizures, AED dosages were reduced or withdrawn under medical supervision. The participants were tested on the simulator twice: first under their usual medication dosage (prescribed dosage) and then after having their AED's reduced or withdrawn to elicit seizure activity. To control for practice effects, six of the participants completed their first drive on their lowest AED dosage, followed by a second drive on their usual medications. Alternatively, five participants completed their first drive on their usual medications followed by a second drive on their lowest AED dosage. The participants' exact AED dosages were obtained from medical records provided by the epileptologist. Medications for all

of the participants during the low and high AED dosage drives are shown in Table 1. Low-dose AED was determined if the patient was taking \leq 50% of the original AED doses at more than three half-lives for the specific AED prior to testing. "No medications" was designated if AED(s) had been discontinued for more than three half-lives prior to testing. The participants completed questionnaires on demographics, driving habits, and history, followed by driving on a high-fidelity DriveSafety DS-250r™ simulator, which is fully maneuverable on the EMU.

Table 1
Medication Type and Dosage Taken During High vs. Low AED Drives

Participants	Medication at high dosage	Medication at low dosage
#1	Lacosamide 200 mg	Lacosamide 100mg
#2	Zonisamide 100mg; Lacosamide 50mg	No medications
#3	Lamotrigine 150mg; Levetiracetam 1000mg;	Lamotrigine 50mg
#4	Clonazepam 0.50mg Lamotrigine XR 100mg; Oxcarbazepine 750mg	Lamotrigine XR 50mg
#5	Zonisamide 50mg	No medications
#6	Phenytoin 400 mg; Topiramate 200mg	Topiramate 50mg
#7	Zonisamide 300mg	No medications
#8	Levetiracetam 1500mg	No medications
#9	Topiramate 50mg	No medications
#10	Levetiracetam 1000mg	No medications
#11	Valproate 1500mg	No medications

Driving Simulator and Scenarios

The simulator design is based on a one-fourth cab of an automatic transmission Ford Focus with a single adjustable seat and 5-point safety harness (see Figure 1). To optimize driving close to the real world experience, the simulator was equipped with vehicle components (e.g., brake and gas pedal, air conditioning, turn signals). The simulator has a high-resolution display (1024 x 748 pixels) and provides the participants with a 110-inch horizontal view across three screens (each screen is 19 inches). The participants were required to adjust the seat and fasten the safety belt, and to control the steering wheel and gas and brake pedals.



Figure 1. Portable DriveSafety DS-250 r™ simulator with a 5-point restraint

To optimize comfort and confidence in driving the simulator, the participants completed three acclimation scenarios (driving in the middle of the lane, driving around curves, and stopping)

lasting approximately 5 min each. After the participants felt comfortable driving on the simulator, they drove a 35-min scenario while on low and high AED dosages (or vice versa), usually a few days apart. A 35-min simulator drive has been employed in prior studies examining the influence of drugs (Brown, Milavetz, & Murry, 2013), epilepsy (Crizzle et al., 2012), and obstructive sleep apnea (Vakulin et al., 2011). The scenario was created to portray daylight and included ambient traffic but no turns. The drive started in a rural setting, progressed to a commercial area, a freeway, and then to a residential area, with speed limits appropriately varying from 25-65 miles per hour. The participants were instructed to identify all yellow road signs, exit signs, and billboards. A clinical researcher, trained by a certified driving rehabilitation specialist with 98% of inter-rater reliability in test administration, evaluated the participants' driving performance and recorded driving errors. The Simulator Sickness Questionnaire (SSQ) (Kennedy, Lane, Berbaum, & Lilienthal, 1993) was administered to screen for simulator sickness symptoms before and after the participants completed three acclimation scenarios (curvy roads, stopping, and lane control) and after the main drive.

The driving errors the researcher recorded were: visual scanning, lane maintenance, speed regulation, vehicle position, adjustment to stimuli, signaling, gap acceptance, and yielding (Shechtman et al., 2009). As detailed in a prior study (Crizzle et al., 2012), the drive also included three scripted

events that required the driver to avoid collisions: one at a train crossing and two where a car enters the driving lane from a parked position. All of the participants had equal opportunities to make these errors over the two simulated drives.

Data Analysis

All data was entered into SPSS (version 20.0) for analyses. The researchers used descriptive statistics (mean, standard deviation, and range) to analyze continuous variables (i.e., number of driving errors) and frequencies (percent) to analyze categorical variables. The researchers also used Spearman's rank correlations to examine the associations between low and high AED dosages with the numbers of driving errors (total and type). Statistical significance was considered for $\alpha \leq .05$ in a two-tailed test.

Results

Participants

Twenty-two participants enrolled in the study; however, only 11 were able to complete the entire protocol. Reasons for study incompleteness included fatigue over the course of the hospital stay (e.g., being busy with family visitations) and the development of simulator sickness. The sample (six women; five men) ranged from 32 to 51 years of age (mean age of 42.1 ± 6.3), had an average high school education ($12.6 \text{ years} \pm 3.0$), and was all Caucasian. Eighty-two percent ($n = 9$) lived with their spouse or partner while two lived alone. After

admission to the EMU, seven were diagnosed with epilepsy and four with conversion disorders (non-epileptic seizures). We did not segregate by epilepsy and convergent disorders as there were no differences in driving performance between the groups ($z = -.878$, $p = .38$) and the patients in both groups were taking AEDs.

Self-Reported Driving Habits and History

The participants reported driving 2.9 ± 3.4 days per week. Six of the 11 participants had quit driving prior to EMU admission. Two of the participants reported having been in a crash in the past three years, both current drivers. Four of the participants reported receiving citations in the past three years—three of which reported speeding infractions (two former and one current driver) and one an improper turning citation (current driver). Twenty-seven percent ($n = 3$) of the sample reportedly avoided driving in the rain, during rush hour, on the highway, or at nighttime.

Simulated Driving Performance

Descriptive statistics for type and total number of driving errors during high and low AED dosages are provided in Table 2. The most frequently committed driving errors in both low and high AED dosage drives included errors of speed regulation and lane maintenance. Generally, the participants made more total driving errors, as well as errors of visual scanning and speed regulations, while on their high compared to low AED dosage.

Table 2

Descriptive Statistics for Driving Errors between High and Low AED Drives

	High Dosage	Low Dosage
Driving Errors	<i>M</i> ± <i>SD</i> Range	<i>M</i> ± <i>SD</i> Range
Visual Scanning	3.8 ± 3.2 [0-10]	2.8 ± 3.3 [0-10]
Speed Regulation	5.7 ± 5.5 [0-15]	5.0 ± 4.4 [0-13]
Lane Maintenance	5.8 ± 4.1 [0-13]	6.1 ± 5.2 [1-18]
Wide	2.5 ± 3.8 [0-13]	2.4 ± 5.3 [0-18]
Encroach	3.4 ± 3.0 [0-8]	3.6 ± 3.1 [0-9]
Signaling	.45 ± .69 [0-2]	.55 ± .82 [0-2]
Vehicle Position	1.8 ± 2.2 [0-7]	1.7 ± 1.6 [0-4]
Adjustment to Stimuli	.82 ± .98 [0-2]	.45 ± .69 [0-2]
Gap Acceptance	36 ± .50 [0-1]	.18 ± .60 [0-2]
Total Errors	19.0 ± 9.9 [6-43]	17.1 ± 8.9 [5-28]

Note. *M* = mean, *SD* = standard deviation

As shown in Table 3, high AED dosages were significantly associated with errors of lane maintenance and gap acceptance. No associations

were significantly associated with errors of lane maintenance and gap acceptance. No associations between driving errors and low AED dosage were significant.

Table 3

Spearman's Correlation Coefficient of Errors on High and Low Dosage AED Drives

	High Dosage		Low Dosage	
Driving Errors	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Visual Scanning	.05	.88	.07	.84
Speed Regulation	.05	.88	.30	.37
Lane Maintenance	.49	.13	-.33	.33
Wide	.67	.03*	-.44	.18
Encroach	.01	.97	.01	.98
Signaling	.15	.66	.32	.33
Vehicle Position	.36	.27	.38	.26
Adjustment to Stimuli	.51	.11	.48	.13
Gap Acceptance	.66	.03*	.00	1.0
Total Errors	.44	.18	.09	.78

Note. *r* = correlation coefficient, * denotes significance on a 2-tailed test, *p* < .05

Discussion

The findings suggest that occupational therapists need to consider the effects of AEDs when assessing fitness to drive in persons with seizures. Generally, the participants made more simulated driving errors while on their high

compared to low AED dosages. Consistent with a prior study (Crizzle et al., 2012), the most commonly committed errors in the present study were speed regulation and lane maintenance errors. Although individuals taking AED's may have more difficulties with speed regulation and lane

maintenance, the findings suggest that driving may be affected for anyone taking AEDs for any reason, including pain, migraines, and mood disorders, consistent with prior findings (Kaussner et al., 2010; Ramaekers et al., 2002). This has implications not only for persons with seizures but also for patients with other medical conditions who use AEDs.

We found that high AED dosages in our sample were significantly associated with errors of lane maintenance (driving wide) and gap acceptance. As AEDs impair aspects of cognition, namely attention (Drazkowski, 2007), information processing speed (Wesnes, Edgar, Dean, & Wroe, 2009), and concentration (Shorvon, 1996), it is possible that our sample had more difficulty with proper lane maintenance and gap acceptance when taking high AED dosages. As seven of the 11 patients were actually unmedicated in the low dosage condition, it is also possible that there may have been a deterioration of simulator performance, which perhaps may have inflated the error measure in the low dosage condition overall. Different AED classes may have variable effects on the central nervous system, and given that the group was administered the same drug treatment, it is difficult to draw any conclusions regarding a specific AED on simulated driving performance. It is possible that certain AEDs may impair driving performance more so than others. For example, prior studies have found that on-road and simulated driving performance was worse when taking CBZ when

compared to both OXC (Kaussner et al., 2010) and remacemide (Ramaekers et al., 2002).

Limitations

The primary limitation of the present study was the small sample size (potential for type II error). However, our sample acted as their own controls, and we did ensure practice effects were not confounded by drug dosage. Although we recruited 22 participants for over two years, only 11 participants met the criteria of driving under both high and low AED dosages while at the EMU. Due to the loss of participants over the study protocol, our power to determine statistically meaningful inferences concerning the effects of different AED dosages on simulated driving performance was substantially reduced. Even though we obtained medication profiles from the participants' medical records, without monitoring AED serum levels (e.g., blood tests), we did not determine the actual AED dosage in their system at the time of the driving assessment. As a result, we could not determine if patients were in a steady state or whether some tolerance had developed, although we attempted to assess patients on the simulator immediately after AEDs were administered at the EMU.

Implications for Further Research

Future prospective studies with larger homogenous samples are needed to discern the effects of specific AEDs and their respective dosages on driving performance in persons with seizures. Additionally, there is a need to determine if the underlying epileptic focus has an impact on

driving performance regardless of AED dosing.

While there were no differences between those with seizure and conversion disorders, there are important features that should be considered in future research. For example, epileptic seizures affect the brain not only when they occur but in the interictal period as well. Thus, any increase in their frequency (following lowering of drug dosages) could alter driving ability. Conversely, as non-epileptic seizures do not affect brain function, lowering of epileptic drugs in the non-epileptic group could lead to an improvement of brain

function and driving ability measures. Future studies should further assess those with seizures and conversion disorders to determine if there are any effects of AEDs on driving performance.

Additionally, future studies should also use AED serum levels to ascertain the effects of AED concentrations on driving performance.

Understanding the effects of AEDs on driving performance will enhance decision-making when prescribing AEDs, as well as occupational therapy practice with respect to driver assessment.

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