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MICRO REVIEW

Effects of frequently prescribed antiseizure medications on motor vehicle driving performance: Narrative review based on a tiered approach for the assessment of clinically meaningful driving impairment in the Ministry of Health, Labour, and Welfare guideline

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Abstract

Patients with epilepsy often require long-term treatment with antiseizure medications, and their impact on daily activities, particularly driving, is of significant concern. The recently published "Guideline for Evaluating Effects of Psychotropic Drugs on the Performance to Drive a Motor Vehicle" in Japan provides a framework that can be referred to for not only the evaluation of new drugs but also the reevaluation of approved drugs. This study conducted a literature review regarding the effects of carbamazepine, valproate, lamotrigine, lacosamide, and levetiracetam, which are frequently prescribed for epilepsy, on driving performance following the guideline's tiered evaluation approach. Analyses of pharmacological, pharmacodynamic, and adverse events suggested that these drugs primarily affect arousal function. Driving studies showed that acute administration of carbamazepine, but not chronic monotherapy with carbamazepine, valproate, lamotrigine, and levetiracetam, significantly impairs driving performance. Epidemiological studies have not identified a definitive association between these drugs and traffic accidents. Initial administration of these five antiseizure medications may affect driving performance, warranting special attention, but the influence appears to diminish with continued use. Nevertheless, while long-term administration of these five drugs may not have a clinically meaningful effect on driving performance, safe driving is not guaranteed for each individual patient, and appropriate individualized guidance is important in clinical practice.

KEYWORDS
antiseizure medication, driving performance, drug evaluation, guideline, traffic accident

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1 | INTRODUCTION

The tolerability of antiseizure medications (ASMs) is crucial for patients with epilepsy because of the necessity of long-term use and the need to consider carefully their effects on daily functioning, particularly on driving. Patients with epilepsy must be seizure-free for a certain period to be deemed fit to drive, making medication adherence and the absence of drug-related adverse events paramount.

While the effects of ASMs on driving performance remain incompletely understood, the Driving Under the Influence of Drugs, Alcohol, and Medicines (DRUID) project by the European Union classifies the effect of all medicinal drugs, including ASMs, on automobile driving into four risk categories. These classifications are based on a combination of pharmacological and pharmacodynamic data, evidence from experimental and epidemiological studies, and adverse events.[1] Each ASM possesses a unique pharmacological profile and is presumed to have different effects on drowsiness, dizziness, and cognitive function.[2] Nonetheless, in many countries, effective risk communication between physicians and patients regarding pharmacological treatment and automobile driving is considered crucial to prevent traffic accidents.[1] Practical regulations are implemented in these countries, considering both ASM treatment and patients' social activities.

The recently published "Guideline for Evaluating Effects of Psychotropic Drugs on Motor Vehicle Driving Performance to Drive a Motor Vehicle" in Japan[3] provides a framework that can be referred to for not only the evaluation of new drugs but also the reevaluation of approved drugs. In this study, we conducted a literature review regarding the effects of carbamazepine, valproate, lamotrigine, lacosamide, and levetiracetam, which are frequently prescribed for epilepsy, on driving performance following the guideline's tiered evaluation approach.[4]

2 | METHODS

The target drugs were carbamazepine, valproate, lamotrigine, lacosamide, and levetiracetam, which are frequently prescribed oral monotherapy for adult focal or generalized seizures in Japan and worldwide.[5] The search databases included PubMed and Pharmaceuticals and Medical Devices Agency (PMDA) approval application summaries. Clinical trial results for evaluation of adverse events were searched in the PMDA database, which publishes the results of all trials used in regulatory submissions. To determine the risk of the drugs, in principle, the referenced evidence was based on healthy adults (excluding older adults). We employed a tiered approach, investigating pharmacological and pharmacodynamic evaluations, adverse events in exploratory, confirmatory, and long-term studies, and driving studies, as recommended in the guideline.[3,4] Additionally, considering previously approved drugs, we included epidemiological research. A flowchart of the tiered approach used in this study is shown in Figure 1. Specifically, pharmacological evaluations identified functional domains (arousal, sensory-perceptual, cognitive, and psychomotor functions)[3] affected by the drugs, while pharmacodynamic evaluations examined their influences on these domains. The risk of traffic accidents significantly increases with a blood alcohol concentration (BAC) above 0.05%.[4] Therefore, the pharmacodynamic evaluation focused on neuropsychological tests that have been examined for their association with BAC, as exemplified in the guideline. Among the studies, this minimized false positives and false negatives, allowing for test result interpretation. Adverse event data from clinical trials were analyzed to assess the time course of events affecting driving. Driving studies evaluated clinically meaningful driving impairment,[4] while epidemiological studies examined the relationship between drug use and occurrence of traffic accidents. The search period was up to June 2023, and only English-language literature was selected from PubMed.

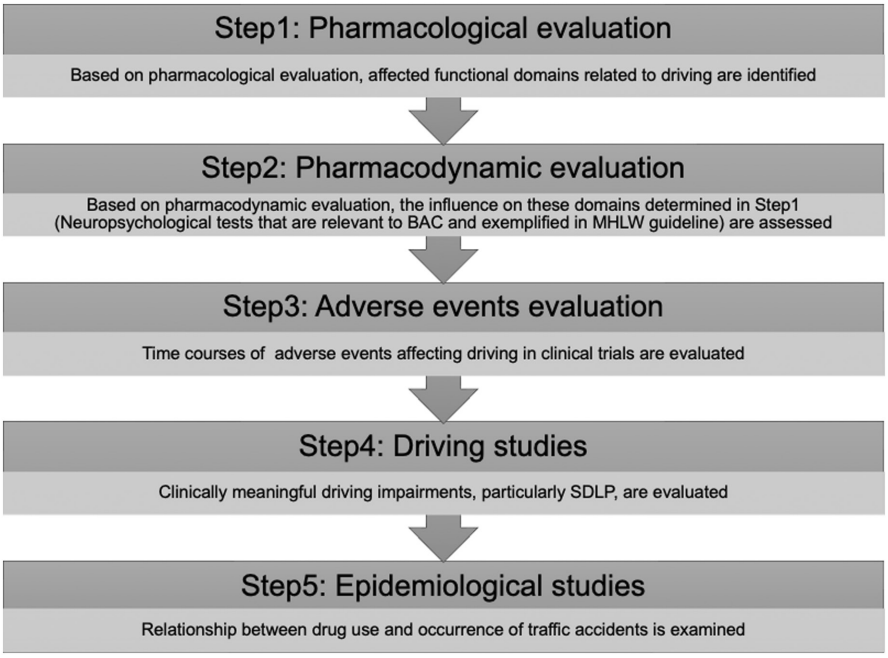

FIGURE 1 Flowchart of the tiered approach for evaluating the effects of antiseizure medications on motor vehicle driving performance. BAC, blood alcohol concentration; MHLW, Ministry of Health, Labour, and Welfare; SDLP, standard deviation of lateral position.

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3 | RESULTS

3.1 | Pharmacological evaluation

The mechanisms of action of ASMs are generally complex. However, here, carbamazepine, valproate, lamotrigine, and lacosamide are classified as voltage-gated sodium channel (VGSC) modulators that inhibit VGSC, while levetiracetam is categorized as a synaptic vesicle protein 2A (SV2A) modulator acting on SV2A. VGSC and SV2A modulators are presumed to have inhibitory effects on excitatory neurotransmission. Additionally, valproate inhibits γ-aminobutyric acid (GABA) transaminase, increasing GABA levels in the brain, leading to known inhibitory enhancement.[5] According to a report by Willems et al.[2] that examined the relationship between the mechanism of action and the side effect profile of ASMs, VGSC, and SV2A modulators have less impact on arousal function than benzodiazepines. However, carbamazepine, valproate, lamotrigine, lacosamide, and levetiracetam may also affect sensory-perceptual functions,[2] indicating the need to evaluate their effects on arousal and sensory-perceptual functions in pharmacological assessments.

3.2 | Pharmacodynamic evaluation

The dosage, duration of administration, assessment methods, and timing of assessment varied across studies. The extracted trial results are summarized in Table 1. While multiple studies reported that carbamazepine affects sensory-perceptual functions, few studies have examined its influence on arousal function.[6–14] Additionally, reports assessing the effects of valproate,[15] lamotrigine,[10,13,16–18] lacosamide,[14] and levetiracetam[8,9,19–21] on arousal and sensory-perceptual functions were either limited or not found. None of the drugs were sufficiently studied for their effects on arousal function, and it was not possible to determine whether arousal or sensory-perceptual functions were primarily affected by these drugs through pharmacodynamic evaluations. Therefore, it was deemed necessary to examine the influence of these drugs on driving based on the occurrence of adverse events in clinical trials.

3.3 | Evaluation of adverse events

Regarding adverse events affecting driving, arousal-related events such as drowsiness and somnolence, and sensory-perceptual-related events such as dizziness were defined, and with adverse events whose causality were not ruled out. Trials for carbamazepine, lamotrigine, lacosamide, and levetiracetam were identified, excluding valproate, but no information on time course aspects such as onset and the duration of adverse events was available (Table S1). Considering the high incidence of adverse arousal-related adverse events in these trials and the pharmacological evaluation of valproate,[5] these drugs appear to affect primarily arousal function, making interpretation of driving study results using the standard

TABLE 1 Results of pharmacodynamic evaluations in clinical trials targeting healthy subjects: Comparison with placebo or no medication.

			Effect on functional domains related to driving			
	Dosage (mg/day)	Duration of administration	Arousal function	Sensory-perceptual functions	Cognitive functions	Psychomotor functions
Carbamazepine	200–1200	Single dosing–12 weeks	↓(2)[7,13] ↔(1)[12]	↓ (2)[7,13]	↓ (1)[7] ↔(4)[6,10,12,14]	↓(3)[7,9,11] ↔(4)[6,8,10,12]
Valproate	951	4 weeks	–	–	–	↔(1)[15]
Lamotrigine	50–300	Single dosing–12 weeks	↔(1)[10]	↔(1)[13] ↓(1)[18]	↔(2)[10,16]	↔(3)[10,16,17]
Lacosamide	300	6 weeks	–	–	↔(1)[14]	-
Levetiracetam	500–2000	Single dosing–8 weeks	↔(2)[20,21]	–	↑(1)[19]	↔(2)[8,9]

Note: Results evaluated by neurocognitive tests recommended in the MHLW guideline. ↓, Statistically significant worsening; ↔, No statistically significant difference; ↑, Statistically significant improvement; –, No data available. *N*, Number of trials. Superscript numbers represent reference numbers.

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deviation of lateral position (SDLP; weaving during driving), which is a standardized index, feasible.

3.4 | Driving studies

Two driving studies with carbamazepine administered to healthy individuals and two driving studies with carbamazepine, valproate, lamotrigine, and levetiracetam administered to patients with epilepsy were identified. Although acute administration of carbamazepine significantly increased SDLP,[22,23] no significant difference in SDLP was found between patients with epilepsy under monotherapy with carbamazepine, valproate, lamotrigine, and levetiracetam and healthy controls.[24] Moreover, SDLP in patients taking carbamazepine, valproate, lamotrigine, levetiracetam, and other ASMs did not significantly differ from that in healthy controls.[25] This suggests that continued carbamazepine administration does not result in clinically meaningful driving impairment. Considering the pharmacokinetics, carbamazepine induces cytochrome P450, leading to decreased blood levels over days of administration, which may affect driving performance in the initial phase. The acute effects of valproate, lamotrigine, and levetiracetam are unclear and warrant caution, but continued administration is not believed to result in clinically meaningful driving impairment. Although no driving studies were found for lacosamide, the incidence of arousal-related adverse events with lacosamide was lower than that for carbamazepine-controlled release, which has a similar effect to carbamazepine on half-life and wakefulness, suggesting that its influence on driving performance may not be greater than that of carbamazepine. However, considering the results of epidemiological studies is also considered appropriate.

3.5 | Epidemiological studies

Four reports were identified from different populations. A spontaneous reporting epidemiological study showed more spontaneous reports of traffic accidents with lamotrigine,[26] but epidemiological studies using patient registry databases did not show any association between traffic accidents and ASMs.[27–29] The increased risk of traffic accidents with lamotrigine does not undermine the results suggesting no association between ASMs and traffic accidents. Moreover, the risk of traffic accidents with lacosamide did not exceed that of carbamazepine, valproate, lamotrigine, and levetiracetam.[26] From epidemiological studies, it was considered that the continued administration of the five ASMs does not result in clinically meaningful driving impairment.

4 | DISCUSSION

Five frequently prescribed drugs for epilepsy—carbamazepine, valproate, lamotrigine, lacosamide, and levetiracetam—were reviewed

TABLE 2 Summary of the tiered approach in the MHLW guideline for frequently prescribed antiseizure medications for epilepsy.

		Tiered evaluation approach in MHLW guideline				
Drug class	Drugs	Pharmacological evaluation	Pharmacodynamic evaluation	Adverse events evaluation	Driving studies	Epidemiological studies
VGSC modulator	CBZ	Primarily arousal and sensory functions	Arousal function: ↓/↔ Sensory functions: ↓ Cognitive functions: ↓/↔ Psychomotor functions: ↓/↔	Primarily arousal function	Acute: ↓ (Healthy) Chronic: ↔(Patient)	No significant association between traffic accidents and antiseizure medication in patient registry databases More spontaneous reports of traffic accidents with lamotrigine
	VPA		Arousal function: NA Sensory functions: NA Cognitive functions: NA Psychomotor functions: ↔		Acute: NA Chronic: ↔(Patient)	
	LTG		Arousal function: ↔ Sensory functions: ↓/↔ Cognitive functions: ↔ Psychomotor functions: ↔		Acute: NA Chronic: ↔(Patient)	
	LCM		Arousal function: NA Sensory functions: NA Cognitive functions: ↔ Psychomotor functions: NA		NA	
SV2A modulator	LEV		Arousal function: ↔ Sensory functions: NA Cognitive functions: ↑ Psychomotor functions: ↔		Acute: NA Chronic: ↔(Patient)	

Note: ↓, Statistically significant worsening; ↔, No statistically significant difference; ↑, Statistically significant improvement; NA, No data available or not assessed.

Abbreviations: CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MHLW, Ministry of Health, Labour, and Welfare; SV2A, synaptic vesicle glycoprotein 2A; VGSC, voltage-gated sodium channel; VPA, valproate.

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and are summarized in Table 2. The pharmacological effects of ASMs are complex because their mechanism of action is not clearly understood and each agent has multiple points of action.[5] Drugs affecting arousal could potentially impair driving, although their sedative effects are also influenced by individual differences. Although limited ASMs have been evaluated in driving studies,[22,23] according to the tiered approach proposed in the guideline,[3,4] these five ASMs may result in clinically meaningful driving impairment under acute administration, but not under chronic administration.

The evidence referenced in this study varies in terms of trial design, drug dosage, participant characteristics, evaluation methods, etc. Additionally, there are many other ASMs besides those discussed in this study, highlighting the ongoing need to accumulate evidence. It is also important to note that the effects of the ASMs considered in this study were evaluated under monotherapy conditions. In clinical practice for epilepsy treatment, attention should be paid to factors such as drug dosage, drug interactions, and pharmacokinetics. While minimizing the impact on driving is important, seizure control remains paramount, and there should not be a set upper limit on the dose of therapeutic agents within the tolerated range. Even if a drug has minimal impact on driving, it does not guarantee safe driving by individual patients. Therefore, to ensure safe driving for each patient, it is crucial to provide individualized guidance in clinical practice.[3]

AUTHOR CONTRIBUTIONS

KI and TN developed the study concept with NO; KI wrote the first draft of the manuscript; TN, AY, YK, MS, RY, KK, HA, MA, and NO made critical revisions to the manuscript. All authors contributed to and have approved the final manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

KI has received speakers' honoraria from Eisai, Kyowa, Meiji Seika Pharma, MSD, Otsuka, Sumitomo Pharma, Takeda, Towa, and Viatris, outside the submitted work. RY has received speakers' honoraria from Sumitomo Pharma, Eisai, Otsuka, and Viatris, outside the submitted work. KK has received speaker's honoraria from Eisai, Daiichi-Sankyo, Otsuka, and UCB pharmaceutical companies, outside the submitted work. MA has received subsidies from Kyowa Kirin. NO has received research support or speakers' honoraria from, or has served as a joint researcher with, or a consultant to, Sumitomo Pharma, Otsuka, Viatris, Eisai, Mochida, Kyowa Pharmaceutical Industry, Nihon Medi-Physics, Nippon Chemiphar, Medical Review, Nippon Boehringer Ingelheim, and SUSMED, outside the submitted work. The other authors have no conflicts of interest to declare. Board member is coauthor: R. Yoshimura is an editorial board member of *Neuropsychopharmacology Reports* and a coauthor of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were generated.

DISCLOSURE

The views expressed in this article are those of the authors and do not necessarily reflect the official views of the Pharmaceuticals and Medical Devices Agency.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Reviewer Board: N/A.

Informed Consent: N/A.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

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