

MICRO REVIEW

Guideline for evaluating the effects of psychotropic drugs on motor vehicle driving performance in Japan: A tiered approach for the assessment of clinically meaningful driving impairment

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Abstract

In December 2022, the Ministry of Health, Labour and Welfare (MHLW) of Japan issued and implemented the guideline for evaluating the effects of psychotropic drugs on motor vehicle driving performance. This guideline recommends the use of a tiered approach to assess clinically meaningful driving impairment. It is noted that adverse events cannot be solely explained by pharmacokinetics, as the onset and duration of these events vary. Among these adverse events, those affecting alertness, such as drowsiness caused by psychotropic drugs on driving performance, are more frequently observed during initial treatment stages and dose escalation. Hence, when evaluating the effects of psychotropic drugs on driving performance, it becomes crucial to assess the persistence of clinically meaningful impairment. Therefore, the MHLW guideline, developed by the authors, emphasizes the need to assess the temporal profile of adverse events affecting driving in all clinical trials. Additionally, the guideline states that when conducting driving studies, the timing of multiple dosing should consider not only the pharmacokinetics of the investigational drug but also its tolerance.

KEYWORDS

blood alcohol concentration, driving impairment, guidelines, psychotropic drugs, temporal profile

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1 | INTRODUCTION

Recent psychotropic drugs have been shown to reduce sedative side effects making them more tolerable. The tolerability of psychotropic drugs is important in terms of not only the need for continued pharmacotherapy to prevent relapse or recurrence but also their impact on the patient's social life. In particular, automobile driving frequently serves as an essential means of transport in social life. Therefore, examining the effects of psychotropic drugs on driving performance and providing appropriate precautions regarding their effects on patients could not only help protecting patient safety, but also improve social functioning through the selection of appropriate therapeutic drugs.

Automobile driving is a complex activity involving a wide range of arousal, sensory-perceptual functions, cognitive functions, or psychomotor functions. Specifically, it is essential to determine which functional domains related to automobile driving are affected by a psychotropic drug and subsequently evaluate clinical significance of the magnitude of the effect. To facilitate the efficient and appropriate evaluation of the effects of psychotropic drugs on driving performance, we have developed a guideline, published by the Ministry of Health, Labour and Welfare (MHLW) of Japan on December 27, 2022.¹ This guideline, similar to that of the US Food and Drug Administration (US FDA), recommends a tiered approach,^{1,2} and the differences between the MHLW and US FDA guidelines have been reported previously.³ This article provides the specific information for planning clinical trials to assess the effects of psychotropic drugs on driving performance.

2 | OVERVIEW OF THE TIERED APPROACH IN THE MHLW GUIDELINE

In the MHLW guideline, the basic framework of the tiered approach for evaluating the effects of psychotropic drugs on driving performance is as follows.^{1,3}

STEP 1: Pharmacological evaluation

The pharmacological effects of the investigational drug and its active metabolites reported in nonclinical studies will be evaluated to determine which of the functional domains related to driving (i.e., alertness, sensory-perceptual functions, cognitive functions, or psychomotor functions) may be affected.

STEP 2: Pharmacodynamic evaluation

Clinical trials in early development, such as clinical pharmacodynamic trials, will be evaluated in terms of whether the investigational drug affects the functional domains related to driving identified in STEP 1.

STEP 3: Evaluation of the temporal profile of adverse events in clinical trials

In all clinical trials, the temporal profile of adverse events affecting automobile driving, including time of onset, duration, and tolerance, will be evaluated.

STEP 4: Driving study

If the accumulated information suggests an effect on the driving performance domains, driving studies will be conducted as appropriate.

The aim of pharmacodynamic trials in STEP 2 is to screen for the effects of the investigational drug on the functional domains identified in STEP 1 by using neuropsychological tests. However, assessing the clinical significance of the results remains challenging. The main purpose of exploratory, confirmatory, and long-term studies is to assess the efficacy and safety of the drug under development for the disease. When assessing the effects of the drug on driving performance, the aim of these studies is to clarify the temporal profile of adverse events affecting automobile driving (STEP 3). Additionally, the purpose of the driving study is to evaluate the presence or absence of clinically meaningful impairment with higher specificity (STEP 4).

3 | DATA TO BE COLLECTED IN ALL CLINICAL TRIALS: STEP 3

3.1 | Characteristics of psychotropic adverse events over time

Generally, adverse events include (1) time-limited events that occur and then rapidly diminish; (2) events that persist throughout the course of treatment; and (3) delayed events that are rare early in the treatment course and occur with continued treatment. Central nervous system disturbances caused by psychotropic drugs, such as drowsiness, are more common early in the treatment course and during dose escalation.

3.2 | Evaluation of temporal profiles

In all clinical trials, it is important to evaluate the temporal profile of adverse events affecting automobile driving, including time of onset, duration, and tolerance. In driving studies, it is necessary to set a time point for evaluating multiple dosing based on the pharmacokinetics of the investigational drug and the temporal profile of adverse events so that the persistence of impairment can be evaluated.

4 | EVALUATION OF CLINICALLY MEANINGFUL DRIVING IMPAIRMENT IN DRIVING STUDIES: STEP 4

4.1 | Blood alcohol concentration (BAC) as a benchmark

The purpose of assessing the effects of drugs on automobile driving ability is to predict and reduce the risk of road accidents. However, the effects of drugs on driving performance cannot be

TABLE 1 Summary of driving studies evaluating non-benzodiazepine hypnotics (GABA_A receptor agonists, melatonin receptor antagonists, and orexin receptor antagonists).

Authors (year)	Hypnotics	Status	Study design	Tests	Primary endpoint	References
Kuitunen (1994)	Zopiclone, triazolam	Healthy (n = 24)	Randomized double-blind, placebo-controlled, crossover	DS	Unspecified	12
Bocca et al. (1999)	Zopiclone, zolpidem, flunitrazepam ^a	Healthy (n = 16)		DS	Unspecified	13
Vermeeren et al. (2002)	Zaleplon, zopiclone ^a	Healthy (n = 30)		ORT	SDLP	14
Verster et al. (2002)	Zolpidem, zaleplon	Healthy (n = 30)		ORT	SDLP	15
Partinen et al. (2003)	Zolpidem, temazepam	PI (n = 23)		DS	Reaction time to collision	16
Staner et al. (2005)	Zopiclone, zolpidem, lormetazepam	PI (n = 23)		DS	Unspecified	17
Otmani et al. (2008)	Zolpidem, melatonin	Healthy (n = 16)		DS	Number of collisions	18
Boyle et al. (2008)	Eszopiclone	Healthy (n = 32), PI (n = 32)		ORT	Unspecified	19
Leufkens et al. (2009)	Zopiclone, temazepam	Healthy (n = 18)		ORT	SDLP	20
Bocca et al. (2011)	Zopiclone, zolpidem, flunitrazepam ^a	Healthy (n = 16)		DS	SDLP	21
Mets et al. (2011)	Ramelteon, zopiclone	Healthy (n = 30)		ORT	SDLP	22
Leufkens et al. (2014)	Zopiclone	Healthy (n = 16), PI (n = 32)		ORT	SDLP	23
Vermeeren et al. (2014)	Zolpidem, zopiclone ^a	Healthy (n = 40)		ORT	SDLP	24
Miyata et al. (2014)	Ramelteon, triazolam ^a	Healthy (n = 17)		DS	Unspecified	25
Vermeeren et al. (2015)	Suvorexant, zopiclone ^a	Healthy (n = 28)		ORT	SDLP	26
Vermeeren et al. (2016)	Suvorexant, zopiclone ^a	Healthy (n = 28)		ORT	SDLP	27
Vermeeren et al. (2019)	Lemborexant, zopiclone ^a	Healthy (n = 48)		ORT	SDLP	28
Iwamoto et al. (2022)	Zopiclone	Healthy (n = 28)		DS	SDLP	29
Muehlan et al. (2022)	Daridorexant, zopiclone ^a	Healthy (n = 60)		DS	SDLP	30

Abbreviations: DS, driving simulator; ORT, on-the-road test; PI, primary insomnia; SDLP, standard deviation of lateral position.

^aPositive control.

assessed based on the risk of actual automobile crashes because it would be unethical to use car crashes as an endpoint in randomized controlled trials. For this reason, in driving studies, it is common to use BAC as a benchmark to assess whether the effects of the investigational drug on driving performance are clinically meaningful. Epidemiological studies have reported a dose-response relationship between BAC and road traffic crashes, with an increased risk of road traffic crashes at BAC levels of 0.05% and above.^{4,5} In addition, BAC correlates with the standard deviation of lateral position (SDLP), which is the degree of weaving during driving and a standardized index used as a primary endpoint in driving studies worldwide.^{6,7} Alcohol acts as an agonist of γ -aminobutyric acid type A (GABA_A) receptors and also acts directly or indirectly on other neurotransmitter systems such as the glutamate, dopamine, serotonin, and opioid systems.^{8,9} Therefore, alcohol has a wide range of effects on the central nervous system and is biologically appropriate to be used as a benchmark.

4.2 | Clinically meaningful driving impairment: magnitude and persistence

In recent years, several driving studies have been carried out to evaluate the effects of hypnotics (Table 1). Table 1 shows driving studies for non-benzodiazepine sleep medications (GABA_A receptor agonists, melatonin receptor antagonists, and orexin receptor antagonists). The National Highway Traffic Safety Administration guideline was the first to recommend an anterospective tiered approach,² and after 2011, when this guideline was published, the SDLP was generally used as the primary endpoint (Table 2). The primary endpoint should be selected according to the characteristics of the investigational drug, and the MHLW and US FDA guidelines provide an example of the use of SDLP to assess drug-related drowsiness in driving studies.^{1,2} Recent psychotropic drugs have been shown to reduce sedative side effects, and it is important to consider whether these effects are clinically meaningful driving impairment. Therefore, after selecting the positive control and ensuring the sensitivity of the analysis, the difference in mean SDLP is used to assess superiority to a placebo. Recent driving studies have prespecified clinically meaningful SDLP reference values and assessed the clinical significance of the magnitude of the effect. In these analyses, the difference in SDLP between placebo and investigational drug administration is used to eliminate the influence of individual driving ability.^{10,11} The reference value corresponding to a BAC of 0.05% is then set for this difference in SDLP between investigational drug and placebo administration. More recently, non-inferiority examining has become more common in driving studies (studies in 2011 and before: 0%, studies after 2011: 50%). In recent driving trials, even if the mean difference in SDLP is statistically significant, if the upper limit of the confidence interval is below this reference value, that is, non-inferiority is demonstrated, the effect is judged not to be a clinically meaningful impairment. Although the SDLP reference values using BAC as a benchmark have been validated for the mean, reference values for

TABLE 2 Analysis methods of driving studies evaluating non-benzodiazepine hypnotics (GABA_A receptor agonists, melatonin receptor antagonists, and orexin receptor antagonists).

	No. of studies	Assessment time point			Primary endpoint		Statistical analysis	
		Studies with positive control		Single and multiple dosing	Studies with PE	SDLP as PE	Superiority to placebo	Non-inferiority
		No. of studies	Percentage					
2011 and before	11	27% (3)	91% (10)	9% (1)	64% (7)	71% (5/7)	100% (11)	0
After 2011	8	75% (6)	38% (3)	63% (5)	88% (7)	100% (7/7)	100% (8)	50% (4)

Note: Numbers in brackets indicate the number of studies. However, the numbers in brackets for "SDLP as PE" indicate the proportion of studies in which SDLP was the primary endpoint. Abbreviations: PE, primary endpoint; SDLP, standard deviation of lateral position.



individual subjects have not been established. This means that while it is possible to assess population effects, there are limitations in assessing clinically meaningful impairment in individual subjects.

In clinical practice, whether driving a car should be prohibited for the entire duration of treatment or only in the early stages is an important issue for not only patient guidance but also treatment selection. Recent driving studies have evaluated the effects of multiple rather than single dosing of an investigational drug, that is, the persistence of clinically meaningful impairment (studies evaluating single and multiple dosing in 2011 and before: 9%, studies after 2011: 63%). Therefore, evaluating the effects of initial and multiple dosing in driving studies can provide valuable information for real-world clinical practice. Multiple dosing should be continued at least until steady-state blood concentrations of the investigational drug and active metabolites have been achieved, and this period should be considered in cases of tolerance. As mentioned above, the temporal profiles of adverse events studied in clinical trials other than driving studies can be used as a reference for setting the assessment time points in multiple dosing.

5 | CONCLUSION

To ensure the best possible care for patients, healthcare professionals should be aware of the characteristics of each medicine. In the case of psychotropic drugs, understanding the extent and duration of their effects on driving performance is valuable information for treatment selection and patient counseling. Therefore, we recommend that the temporal profile of adverse events affecting driving should be assessed in all clinical trials and that the timing of multiple dosing in driving studies should consider the pharmacokinetics of the investigational drug and the tolerance observed in other clinical trials.

AUTHOR CONTRIBUTIONS

All authors developed the study concept. TN and KI wrote the first draft of the manuscript, 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

TN, AY, YK, MS, and HA have no conflicts of interest to declare. KI has received speakers' honoraria from Eisai, Kyowa, Meiji Seika Pharma, MSD, Otsuka, Sumitomo Pharma, Taisho, Takeda, Towa, and Viatrix, outside the submitted work. RY has received speakers' honoraria from Sumitomo Pharma, Eisai, Otsuka, and Takeda outside the submitted work. KK has received speaker's honoraria from Eisai, Daiichi-Sankyo, Otsuka, and UCB pharmaceutical companies,

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DATA AVAILABILITY STATEMENT

As this is a review, no data are available.

ETHICS APPROVAL AND INFORMED CONSENT

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

Informed Consent: N/A.

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

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DISCLOSURE STATEMENT

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.

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REFERENCES

1. Ministry of Health, Labour and Welfare. Guideline for evaluating the effect of psychotropic drugs on the performance to drive a motor vehicle. [in Japanese]. PSEHB/PED Notification No. 1227-3 and PSEHB/PSD Notification No. 1227-1 2022.
2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Evaluating Drug Effects on the Ability to Operate a Motor Vehicle, Guidance for Industry, November 2017.
3. Iwamoto K, Nakabayashi T, Yamaguchi A, Konishi Y, Saji M, Yoshimura R, et al. The new guideline for evaluating effects of psychotropic drugs on the performance to drive a motor vehicle in Japan: comparison with US FDA guideline. *Neuropsychopharmacol Rep*. 2023;43(2):172–6.
4. Krüger HP, Vollrath M. The alcohol-related accident risk in Germany: procedure, methods and results. *Accid Anal Prev*. 2004;36(1):125–33.
5. Blomberg RD, Peck RC, Moskowitz H, Burns M, Fiorentino D. The Long Beach/Fort Lauderdale relative risk study. *J Saf Res*. 2009;40(4):285–92.
6. Owens K, Ramaekers JG. Drugs, driving, and models to measure driving impairment. In: Verster JC, Pandi-Perumal SR, Ramaekers JG, de Gier JJ, editors. *Drugs, driving and traffic safety*. Basel: Birkhäuser Basel; 2009. p. 43–58.
7. Louwerens JW, Gloerich ABM, de Vries G, Brookhuis KA, O'Hanlon JF. The relationship between drivers, blood alcohol concentration



- (BAC) and actual driving performance during high speed travel. In: Noordzij PC, Roszbach R, editors. Alcohol drugs traffic safety. Volume T86. Amsterdam: Elsevier; 1987. p. 183–6.
8. Chastain G. Alcohol, neurotransmitter systems, and behavior. *J Gen Psychol*. 2006;133(4):329–35.
 9. Vengeliene V, Bilbao A, Molander A, Spanagel R. Neuropharmacology of alcohol addiction. *Br J Pharmacol*. 2008;154(2):299–315.
 10. O'Hanlon JF. Driving performance under the influence of drugs: rationale for, and application of, a new test. *Br J Clin Pharmacol*. 1984;18(Suppl 1):121s–29s.
 11. Verster JC, Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *Int J Gen Med*. 2011;4:359–71.
 12. Kuitunen T. Drug and ethanol effects on the clinical test for drunkenness: single doses of ethanol, hypnotic drugs and antidepressant drugs. *Pharmacol Toxicol*. 1994;75(2):91–8.
 13. Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. *Psychopharmacology*. 1999;143(4):373–9.
 14. Vermeeren A, Riedel WJ, van Bortel MP, Darwish M, Paty I, Patat A. Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol. *Sleep*. 2002;25(2):224–31.
 15. Verster JC, Volkerts ER, Schreuder AH, Eijken EJ, van Heuckelum JH, Veldhuijzen DS, et al. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharmacol*. 2002;22(6):576–83.
 16. Partinen M, Hirvonen K, Hublin C, Halavaara M, Hiltunen H. Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. *Sleep Med*. 2003;4(6):553–61.
 17. Staner L, Ertlé S, Boeijinga P, Rinaudo G, Arnal MA, Muzet A, et al. Next-day residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring. *Psychopharmacology*. 2005;181(4):790–8.
 18. Otmani S, Demazières A, Staner C, Jacob N, Nir T, Zisapel N, et al. Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers. *Hum Psychopharmacol*. 2008;23(8):693–705.
 19. Boyle J, Trick L, Johnsen S, Roach J, Rubens R. Next-day cognition, psychomotor function, and driving-related skills following nighttime administration of eszopiclone. *Hum Psychopharmacol*. 2008;23(5):385–97.
 20. Leufkens TR, Vermeeren A. Highway driving in the elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg, and placebo. *J Clin Psychopharmacol*. 2009;29(5):432–8.
 21. Bocca ML, Marie S, Lelong-Boulouard V, Bertran F, Couque C, Desfemmes T, et al. Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. *Psychopharmacology*. 2011;214(3):699–706.
 22. Mets MA, Kuipers E, de Senerpont Domis LM, Leenders M, Olivier B, Verster JC. Effects of alcohol on highway driving in the STISIM driving simulator. *Hum Psychopharmacol*. 2011;26(6):434–9.
 23. Leufkens TR, Ramaekers JG, de Weerd AW, Riedel WJ, Vermeeren A. Residual effects of zopiclone 7.5 mg on highway driving performance in insomnia patients and healthy controls: a placebo controlled crossover study. *Psychopharmacology*. 2014;231(14):2785–98.
 24. Vermeeren A, Vuurman EF, Leufkens TR, Van Leeuwen CJ, Van Oers AC, Laska E, et al. Residual effects of low-dose sublingual zolpidem on highway driving performance the morning after middle-of-the-night use. *Sleep*. 2014;37(3):489–96.
 25. Miyata A, Iwamoto K, Kawano N, Kohmura K, Yamamoto M, Aleksic B, et al. The effects of acute treatment with ramelteon, triazolam, and placebo on driving performance, cognitive function, and equilibrium function in healthy volunteers. *Psychopharmacology*. 2015;232(12):2127–37.
 26. Vermeeren A, Sun H, Vuurman EF, Jongen S, van Leeuwen CJ, van Oers AC, et al. On-the-road driving performance the morning after bedtime use of Suvorexant 20 and 40 mg: a study in non-elderly healthy volunteers. *Sleep*. 2015;38(11):1803–13.
 27. Vermeeren A, Vets E, Vuurman EF, van Oers AC, Jongen S, Laethem T, et al. On-the-road driving performance the morning after bedtime use of suvorexant 15 and 30 mg in healthy elderly. *Psychopharmacology*. 2016;233(18):3341–51.
 28. Vermeeren A, Jongen S, Murphy P, Moline M, Filippov G, Pinner K, et al. On-the-road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers. *Sleep*. 2019;42(4):zsy260. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448281/>
 29. Iwamoto K, Iwata M, Kambe D, Imadera Y, Tachibana N, Kajiyama Y, et al. Residual effects of zopiclone on driving performance using a standardized driving simulator among healthy volunteers. *Psychopharmacology*. 2022;239(3):841–50.
 30. Muehlan C, Brooks S, Vaillant C, Meinel M, Jacobs GE, Zuiker RG, et al. Driving performance after bedtime Administration of Daridorexant, assessed in a sensitive simulator. *Clin Pharmacol Ther*. 2022;111(6):1334–42.

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