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Title: Assessing the validity of eyelid parameters to detect impairment due to benzodiazepines

Running head: Eyelid parameters detects benzodiazepine impairment

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Declaration of Interests

V.E. Wilkinson, M.L. Jackson, J. Westlake, B. Stevens, M. Barnes, J. Cori, P. Swann: no conflict of interest to disclose. Dr Howard has received funding from The CRC for Alertness, Safety and Productivity, ResMed Foundation, Edansafe, and Prevention Express; received non-financial support from Sleep Diagnostics; and is a consultant for the National Transport Commission and Vicroads.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/hup.2723](https://doi.org/10.1002/hup.2723)

Keywords: behavioural lapses, eyelid parameters, ocular measures, eye blinks, benzodiazepines, temazepam

Abstract

Objective

Benzodiazepines impair driving ability and psychomotor function. Eyelid parameters accurately reflect drowsiness, however the effects of benzodiazepines on these measures have not been extensively studied. The aim of this study was to investigate the effect of benzodiazepines on eyelid parameters, and evaluate their accuracy for detecting psychomotor impairment.

Methods

Eyelid parameters were recorded during a psychomotor vigilance task (PVT) and driving simulation over two days, baseline and after 20mg oral temazepam. The utility of eyelid parameters for detecting PVT lapses was evaluated using receiver operating characteristic curves and cut-off levels indicating impairment (≥ 1 and ≥ 2 PVT lapses/min) were identified. The accuracy of these cut-off levels for detecting driving simulator crashes was then examined.

Results

PVT and driving simulator performance was significantly impaired following benzodiazepine administration ($p < 0.05$). Average eyelid closure duration (Inter-Event Duration (IED)) was a reliable indicator of PVT lapses (area under the curve (AUC) 0.87-0.90). The cut-off value of eyelid closure duration derived from PVT AUC was able to predict driving simulator crashes with moderately high sensitivity and specificity (76.23%, 75.00%).

Conclusions

Eyelid parameters were affected by benzodiazepines and accurately detected the psychomotor impairment. In particular, eyelid closure duration is a promising real-time indicator of benzodiazepine impairment.

1. Introduction

Benzodiazepines are independent contributors to driving impairment and increased crash risk (Dunbar et al., 1987; Martin et al., 2013; Rapoport et al., 2009). Roadside blood alcohol concentration (BAC) testing campaigns have been used to infer alcohol related impairment and reduce alcohol related crashes. Similarly, random roadside drug testing occurs in some jurisdictions, such as across Australia, but the sensitivity of testing for benzodiazepines is poor (Beirness et al., 2016) and, unlike roadside BAC testing, the experience of roadside drug testing does little to deter drug driving (Horyniak et al., 2017). Recently, devices which measure drowsiness through eyelid parameters have become commercially available. These measures are accurate at measuring drowsiness and drowsiness related errors or crashes in laboratory (Jackson et al., 2016b; Johns et al., 2008; Wilkinson et al., 2013) and field settings (Ftouni et al., 2013; Lee et al., 2015; Liang et al., in press). This allows for real-time on-road monitoring of drowsiness levels with alerts to drivers if they reach a level indicative of severe impairment that is unacceptable for driving. Whether performance impairment due to benzodiazepine administration can similarly be identified through eyelid parameters currently remains unexplored.

Eye movements are altered by drugs with sedative-like properties, such as benzodiazepines, and therefore may have utility for assessing ability to drive safely. Benzodiazepines decrease saccade and smooth pursuit velocity, reflecting their sedating effect on the central nervous system, but their impact on other ocular measures has not been studied (Fafrowicz et al., 1995; Padoan et al., 1992; Roy-Byrne et al., 1993; van Steveninck et al., 1991). Saccadic eye

movement variables, such as accuracy, velocity, and acceleration are altered with benzodiazepine administration, and these changes are correlated with self-rated sedation ratings (Ball et al., 1991). Temazepam and diazepam appear to have greater effects on saccadic velocity than other benzodiazepines (Bittencourt et al., 1981) and diazepam also increases the duration of “fixations”, during reading (Stern et al., 1974). There is only limited research evaluating the relationship between eyelid parameters and psychomotor performance following benzodiazepine administration (Kroboth et al., 1998).

Eyelid parameters are good indicators of drowsiness in the laboratory (Jackson et al., 2016a; Johns et al., 2008; Schleicher et al., 2008; Wierwille and Ellsworth, 1994), with the ability to detect impairment leading to drowsiness related errors (Anderson et al., 2013; Jackson et al., 2016b; Wilkinson et al., 2013). In particular, eyelid closure duration and the ratio of amplitude to velocity of eyelid movements are accurate indicators of drowsiness related psychomotor errors (Wilkinson et al., 2013) and have the potential to be used to monitor for drowsiness in real-life situations, such as driving (Johns et al., 2008). In this study we evaluated the accuracy of eyelid movement parameters for detecting impaired performance on psychomotor vigilance following benzodiazepine administration.

2. Methods

Objective assessment of vigilance with concurrent measurement of eyelid movement parameters was undertaken during baseline and benzodiazepine administration conditions in a laboratory-based experimental study, using a randomised crossover design.

2.1 Participants

Healthy males and females were recruited by advertisement from the general community. Participants were required to be aged between 18-70 years with a current drivers licence. Participants were reviewed medically by the study physician and excluded if they had any medical conditions that could affect neurocognitive or motor function or be a contraindication to benzodiazepine administration. Participants were also excluded if they were regular smokers, consumed five or more caffeinated beverages daily, used sedative medication, had

significant daytime sleepiness (Epworth Sleepiness Scale (ESS) >11) (Johns, 1991), high sleep apnea risk on a validated screening survey (Maislin et al., 1995), or visual impairment not corrected with glasses.

The protocol was approved by the Austin Health Human Research Ethics Committee and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12609000289213).

2.2 Outcome Measures

2.2.1. Psychomotor Vigilance Task (PVT)

The hand-held reaction time task, PVT, was used to assess sustained attention through measuring reaction time in response to a visual stimulus (Dinges and Powell, 1985). Decreased PVT performance indicates impaired attention with slowed reaction times and increased errors and lapses, and is sensitive to impairment due to alcohol, circadian effects and sleep deprivation (Banks and Dinges, 2007; Dinges and Powell, 1985; Dorrian et al., 2005; Howard et al., 2007). A 10 minute PVT is believed to be the optimal length with the most reliable and frequently reported measure being the number of lapses (reaction time > 500ms) (Basner and Dinges, 2011).

2.2.2. AusEd Simulated Driving Task

The AusEd driving simulator consists of a computer display of a road and uses a steering wheel and brake and accelerator pedals to simulate driving a car (Desai et al., 2007). The road components and time of presentation of vehicles were identical for each simulated driving session. A monotonous night-time drive on a two lane highway with curved and straight sections was used, and included standard lane divisions and road edges marked with reflective posts. Participants were instructed to maintain their position in the middle of the left-hand lane on the road (in accordance with Australian driving regulations), keep their speed within 60-80 km/h on the speedometer, and brake in response to other vehicles. A 60 minute drive was chosen as previous studies have demonstrated fatigue effects within this time frame (Vakulin et al., 2007). Crash events were used as the outcome variable. Braking reaction time, lane deviation and speed deviation were also recorded.

2.2.3. Eyelid Movement Parameters

Eyelid movement parameters were measured using the Optalert Drowsiness Measurement System (ODMS) (Optalert™, Sleep Diagnostics Pty Ltd, Melbourne, Australia), a device which records eight eyelid variables using infrared light positioned on a pair of glasses (Johns et al., 2007). Five of these eight variables have been shown to have utility in detecting drowsiness (Wilkinson et al., 2013).

ODMS analysis focussed on the following five eyelid variables on a minutely basis:

- *Inter-Event Duration (IED)*: blink duration measured in seconds from the moment of maximum closing velocity to maximum opening velocity.
- *Blink Total Duration (BTD)*: duration of blinks from the commencement of closing to complete re-opening, measured in seconds.
- *Percent Time with Eyes Closed (%TEC)*: proportion of time with eyes closed, calculated from the velocity of eyelid movement during closure.
- *Positive Amplitude-Velocity Ratio (+AVR)*: ratio of maximum amplitude to maximum velocity for the closing phase of blinks.
- *Johns Drowsiness Scale (JDS)*: composite drowsiness measure calculated using weighted ocular movement values, with higher scores indicating greater drowsiness (range 0 – 10) (Johns et al., 2007).

2.3 Experimental Procedure

Initial medical screening was completed at the Sleep Laboratory, Austin Health, where written informed consent was obtained. An experienced researcher fitted ODMS glasses to ensure accurate measurement of eyelid data and participants familiarised themselves with task procedures. Participants maintained an eight hour in bed sleep schedule (22:00h – 06:00h), confirmed by sleep diary, for the week prior to each testing session.

Testing was conducted on two separate days, in a randomised order, with at least one week separating the sessions to ensure wash out of the drug. Performance measures were conducted at 09:00h for the rested baseline session (baseline) and, on a separate day, 11:30h for the

benzodiazepine session (BZ)), 2 hours post-ingestion. Participants performed a breath test at the start of each session using a calibrated Alcometer (model SD_400, Lion Laboratories, Glamorgan, UK) to ensure no alcohol was consumed prior to the commencement of each testing day.

In the BZ condition, participants were administered a usual clinical dose (20 mg) of temazepam. In the baseline condition, participants received a placebo. Participants were blinded to the type of tablet being taken, and were told it “may or may not” make them sleepy. Performance measures were conducted two hours post-administration when peak plasma levels would be expected to be reached.

The 1.5 hour test battery consisted of vigilance tests and subjective drowsiness and performance questionnaires. The vigilance tests were conducted in randomised order, including the 10 minute PVT and 60 minute driving simulation, in a soundproofed room with dim lighting. ODMS was recorded during all testing sessions with video monitoring to ensure synchronisation with vigilance tests.

2.4 Data Analysis

Outcome variables were analysed in one minute bins for PVT (lapses) and driving simulation (crashes). The number of lapses (reaction time >500ms) per minute on the PVT were determined. The first

five minutes of the driving simulation were excluded from the analysis, to reduce the impact of learning effects at the start of the drive, as per standard procedures (Desai et al., 2007). PVT and driving simulation data were compared to the corresponding time matched ODMS eyelid data in one minute bins. Data were excluded if ODMS signal quality was poor.

Behavioural and eyelid data for each condition is presented as median and interquartile range (IQR). Data was compared using the Wilcoxon signed-rank test due to skewness of the data. Significance level was set at $p=0.05$. Receiver operating characteristic (ROC) curve analysis

was conducted for all eyelid variables to determine their accuracy in identifying PVT lapses during any one minute bin in the baseline and BZ conditions. ROC curve analysis was undertaken separately for one or more, and two or more PVT lapses per minute. Data was clustered by participant to account for multiple minutes of PVT replication (Janes et al., 2009; Pepe et al., 2009). Eyelid variable cut-off values indicating an impairment level resulting in lapses in vigilance (PVT lapses ≥ 2) with high sensitivity and a corresponding specificity $>50\%$ were determined using the ROC curve. The accuracy (sensitivity and specificity) of these cut-off levels in detecting driving simulator crashes was then assessed. Statistical analyses were conducted using STATA 11 (StataCorp, College Station, TX: StataCorp LP).

3. Results

Data was utilised from the 15 participants who completed both days of the protocol (14 male, mean age 37.9 (± 11.6), mean BMI 29.0 (± 5.1) and median ESS score of 5.5 (IQR 3-8)). Initially 25 participants had available PVT data for both conditions. For available PVT data, the time matched Optalert data and corresponding driving data was available for 15 participants. Missing data was due to equipment errors along any stage of the experimental process, either due to poor Optalert eye tracking data (fitting errors, head positioning), inability to time match data, or errors in downloading data. The ten participants whose data was not included (6 male, mean age 45.4 (± 15.0), mean BMI 28.4 (± 6.9) and median ESS 7 (IQR 4-8)) did not have significantly different baseline characteristics.

Psychomotor performance was significantly impaired during the BZ condition compared to baseline (Table 1), including slower reaction time and more frequent lapses. More driving simulator crashes occurred in the BZ condition than baseline with 61.5% of participants having at least one crash in the BZ condition compared to 33.3% in the baseline condition (Table 1, $p < 0.05$). Braking reaction time and lane deviation were increased in the BZ condition (not significant) and speed deviation was significantly increased in the BZ condition (Table 1).

3.1 PVT lapses and Eyelid Variables: ROC Curve Analysis

A summary of eyelid variables during the PVT (Figure 1) and driving simulation (Table 2) are presented for the baseline and BZ conditions. Significant differences from baseline were found during the PVT following benzodiazepine administration for all eyelid variables and for all variables other than JDS during the driving simulation.

ROC area under the curve (AUC) and 95% confidence intervals (CIs) clustered by participant are presented in Figure 2 and 3 for analysis of eyelid variables compared to one or more lapses per minute, and two or more PVT lapses by minute for the conditions of baseline and BZ. In the baseline condition 7/15 participants had episodes of two or more PVT lapses within a minute (11/15 had at least one lapse) compared to 12/15 in the BZ condition (13/15 had at least one lapse). The percentage of minutes with two or more lapses was 5.33% in the baseline condition and 37.33% in the BZ condition.

All chosen eyelid variables had moderate or good ability to discriminate PVT lapses (Figure 2 and 3). Eyelid variables during the BZ condition were more predictive of PVT lapses than during the baseline condition. Eyelid variables showed moderate to good discriminatory ability in the baseline (AUC>0.666 for one or more lapses and AUC >0.7348 for two more lapses) and BZ conditions (AUC>0.7082 for one or more lapses and AUC >0.7751 for two more lapses). In the baseline condition, the eyelid variables with the best discriminatory ability were JDS when detecting one or more PVT lapses (0.7453, 95% CI 0.6010 – 0.9052) and %TEC detecting two or more PVT lapses (0.8522, 95% CI 0.6235-0.9554). The eyelid variables with the greatest discriminatory ability in the BZ condition were JDS when analysing one or more PVT lapses (AUC 0.8752, 95% CI 0.7204-0.9736) and IED when analysing two or more PVT lapses (AUC 0.9016, 95% CI 0.8069 – 0.9647). Overall, the eyelid variables with the greatest accuracy in detecting PVT lapses were IED and JDS (Figure 2 and 3), when looking at both baseline and BZ conditions and using one or more and two or more PVT lapses. +AVR also had high accuracy in the BZ condition.

3.2 Driving Simulator Crashes and Eyelid Variables

Cut-off values were chosen from the ROC curves for eyelid variables detecting two or more PVT lapses per minute. Cut-off values were selected to have high sensitivity with a corresponding specificity >50% and are displayed in Table 3.

The sensitivity and specificity for detecting driving simulator crashes using the selected cut-off values were determined for all eyelid variables. Overall, IED, BTD and JDS had the greatest utility for detecting driving simulator crashes. BTD had the greatest accuracy for detecting crashes in both the baseline (sensitivity= 77.78, specificity= 88.18%) and BZ (84.07%; 84.49%) conditions. IED had moderately high sensitivity and specificity for the baseline (76.92%; 70.41%) and BZ (76.23%; 75.00%) conditions. Similarly, JDS also had a moderately high sensitivity and specificity for baseline (89.74%; 68.32%) but lower sensitivity for the BZ (52.46%; 79.85%) condition. %TEC and +AVR had poor to moderate ability in detecting driving simulator crashes in both conditions with high sensitivity (76.52% - 100%) but low specificity (0.00% - 66.60%).

4. Discussion

Eyelid movement parameters were altered by administration of benzodiazepines and were able to accurately detect lapses in visual attention. Similarly to previous studies evaluating eyelid movements to detect drowsiness related impairment (Anderson et al., 2013; Wilkinson et al., 2013), a variable measuring the average duration of eye closure (IED) had the best discrimination for detecting neurobehavioural lapses caused by benzodiazepines, as well as JDS a composite of eyelid movements unique to the ODMS. This suggests there is potential to use eyelid parameters to determine whether someone is impaired due to benzodiazepines and may be at increased risk of attentional failure. This study used a dosage of benzodiazepine that is commonly prescribed, hence, performing tasks such as driving or operating machinery could readily occur under these conditions.

Using eyelid parameters to indicate psychomotor impairment was accurate in detecting PVT lapses in the baseline and benzodiazepine conditions. Eyelid parameters assessing eyelid

closure duration detected two or more attention lapses in a minute on the PVT with very high accuracy (ROC AUC 0.9016 for benzodiazepines using IED). Analysis of PVT data using one or more lapses in a minute was marginally less accurate (AUC 0.8676). This reduced accuracy may be because one PVT lapse in a minute could be a reflection of boredom or distraction, rather than true impairment, while two lapses within a minute is a rarer occurrence in an alert state.

Driving simulator studies often extrapolate performance on simulators to on-road driving performance, although there are many other factors which influence on-road driving and the relationship between impairment and crashes is not as clear. However, several aspects of on-road driving are measured by and correlate well with simulators, such as visual tracking, coordination, attention, reaction and vigilance (Jackson et al., 2013; Philip et al., 2005; Thiffault and Bergeron, 2003). When using cut-off levels determined by the PVT receiver operating characteristic curve analysis to find whether these eyelid parameters predicted driving simulator crashes, the blink duration measures of BTD and IED had the highest accuracy in the benzodiazepine condition with moderately high levels of sensitivity and specificity.

Overall, the greatest accuracy in detecting impairment was found using the IED variable, a measure of eye blink duration. IED was found to increase (slower blink duration) following benzodiazepine administration. Eye movements, such as saccades and fixations, slow following benzodiazepine administration (Fafrowicz et al., 1995; Roy-Byrne et al., 1993, Padoan et al., 1992; Stern et al., 1974; van Steveninck et al., 1991) although no previous studies have investigated the effect of benzodiazepines on eye blink duration, or how the link between eye blink duration and psychomotor impairment is affected by benzodiazepines. Other eyelid variables, such as +AVR, were also accurate indicators of psychomotor impairment following benzodiazepine administration. +AVR measures a ratio of maximum amplitude to velocity during eye closure, a variable affected by the slowing of eyelid movements. JDS, a composite measure used in the commercial version of ODMS to determine excessive sleepiness and

increased crash risk, also provided a high level of accuracy in detecting psychomotor impairment.

A previous study using a validated test of sleep onset to determine the accuracy of the ODMS in a sleep restricted state not impaired by drugs or alcohol found the IED and BTD variables to be the most useful (Wilkinson et al., 2013) and other studies have found JDS a strong predictor of drowsiness (Anderson et al., 2013). Comparing the values found in the previous study to the values found in the baseline session of the current study to determine the validity of using the PVT at lapses of more than one or two to indicate impairment, found similar levels of accuracy across all variables. The previous study found receiver operating characteristic curve values of 0.722 – 0.835 (95% CI 0.642 – 0.897) across the same eyelid variables measured in this study (Wilkinson et al., 2013).

A single physiological indicator and cut-off level for detecting impairment from many common causes would be ideal in a commercially available impairment management system. The ODMS used in this project was designed to detect impairment due to sleepiness when unaffected by drugs or alcohol. Interestingly we found that several eyelid parameters that were accurate at detecting drowsiness related impairment in previous studies were also good at detecting impairment secondary to benzodiazepines, raising the possibility of using the same eyelid parameters for detecting impairment from a range of causes. While the effect of sleepiness on eyelid parameters such as blink duration has been more thoroughly researched (Caffier et al., 2003; Caffier et al., 2005; Hakkanen et al., 1999; Ingre et al., 2006), relatively little has been published with regards to the impact of alcohol and drugs on these eyelid parameters. As this study was conducted in the laboratory, further research in controlled on-road and field studies needs to be conducted to determine the true utility of eyelid parameters for detecting impairment which increases crash risk from drowsiness or drugs. Another limitation of this study is that there was a difference in the timing of the baseline and benzodiazepine sessions after administration of the tablet, which may have affected the blinding of participants to the drug condition. Participants completed the sessions in a randomized order and were blinded to what the tablet contained and told that it may or may not

make them sleepy, therefore we believe this would have minimized any likelihood that participants would be aware of which condition they were undertaking. Additionally, it is unlikely that an awareness of condition would influence continuously measured ocular movements, such as eyelid closure speed and duration, which are predominantly non-volitional movements.

Hypnotic medications, particularly temazepam, are widely prescribed for the treatment of insomnia and anxiety (Calem et al., 2012) and have the potential to carry next-day hangover effects. Of particular concern is epidemiological evidence indicating that benzodiazepines are associated with an increased risk of traffic accidents (Barbone et al., 1998). Thus it is increasingly important that non-invasive measures of drug and alcohol related impairment are developed and validated. The current study makes initial steps towards such a methodology in a healthy, benzodiazepine-naïve sample, however further validation is required in sleep disordered populations who are currently using benzodiazepines and may exhibit subjective and behavioural tolerance to the drug. Alternatively there may be a compounding negative effect of sleep disorders and benzodiazepine use on eye blink parameters. Indeed, it has been shown that eye blink parameters such as IED and AVR are impaired in patients with obstructive sleep apnea relative to healthy individuals (Cori et al., 2018). However, whether benzodiazepines further worsen these parameters remains to be assessed.

The current study found that eyelid parameters, particularly blink duration measures, were accurate at detecting psychomotor impairment on a simple task following benzodiazepine administration. Eyelid parameters have potential to be used to detect performance impairment due to benzodiazepines use in situations such as driving, and the impact of these substances on eyelid parameters needs to be considered when they are used for drowsiness monitoring.

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Table 1: Summary of PVT measures (reaction time, lapses) and Driving Simulation measures (crashes, brake reaction time, lane deviation, speed).

		PVT			Driving Simulation		
		Reaction Time (msec)	Lapses (N)	Crashes (N)	Brake reaction time (msec)	Lane deviation (cm)	Speed deviation (km/hr)
Baseline (n=15)							
	<i>Mdn (IQR)</i>	240.49 (216.31-257.53)	1 (0-5)	0 (0-1)	0.95 (0.86-1.16)	61.50 (52.46-80.62)	2.39 (1.94-5.39)
BZ (n=15)							
	<i>Mdn (IQR)</i>	295.27 (217.86-573.97)*	9 (2 - 28)*	1 (0-38)	1.17 (0.95-1.29)	77.97 (55.33-143.59)	5.62 (2.54-16.41)

PVT (psychomotor vigilance test), BZ (benzodiazepine), Mdn (median), *IQR* (interquartile range)

* performance significantly worse in BZ conditions compared to baseline $p < 0.05$

Table 2: Summary of eyelid variables during Driving Simulation

Eyelid parameters – PVT	
Baseline (n=15)	BZ (n=15)

IED	<i>Mdn</i> (<i>IQR</i>)	0.09 (0.0705 – 0.1310)	0.1090 (0.0750 – 0.1850)
BTD	<i>Mdn</i> (<i>IQR</i>)	0.2760 (0.2320 – 0.3660)	0.3310 (0.2520 – 0.4330)
% TEC	<i>Mdn</i> (<i>IQR</i>)	0.03700 (0.0030 – 0.4230)	0.0830 (0.0170 – 1.5070)
+AVR	<i>Mdn</i> (<i>IQR</i>)	1.174 (1.0620 – 1.4710)	1.3070* (1.1340 – 1.6200)
JDS	<i>Mdn</i> (<i>IQR</i>)	2.2000 (0.9000 – 4.0000)	3.2000 (1.6000 – 4.7000)

IED (Inter-Event Duration), BTD (Blink Total Duration), %TEC (Percent Time with Eyes Closed), +AVR (Positive Amplitude-Velocity Ratio), JDS (Johns Drowsiness Scale), *Mdn* (median), *IQR* (interquartile range), BZ (benzodiazepine).

* performance significantly worse in BZ condition compared to baseline $p < 0.05$

Table 3: Cut-off values for eyelid variables with sensitivity and specificity values for chosen cut-offs.

	Baseline	BZ
IED Cut-off	0.131	0.150
Sensitivity	100.00%	98.08%
Specificity	50.50%	50.00%
BTB Cut-off	0.346	0.413
Sensitivity	85.71%	84.31%
Specificity	50.00%	50.00%
%TEC Cut-off	0.093	0.240
Sensitivity	85.71%	88.24%
Specificity	50.00%	50.00%
+AVR Cut-off	1.147	1.164
Sensitivity	85.71%	98.04%
Specificity	50.00%	50.00%

JDS Cut-off	3.800	4.500
Sensitivity	71.43%	95.65%
Specificity	51.35%	50.00%

IED (Inter-Event Duration), BTD (Blink Total Duration), %TEC (Percent Time with Eyes Closed), +AVR (Positive Amplitude-Velocity Ratio), JDS (Johns Drowsiness Scale), BZ (benzodiazepine)

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Title:

Assessing the validity of eyelid parameters to detect impairment due to benzodiazepines

Date:

2020-02-05

Citation:

Wilkinson, V. E., Jackson, M. L., Westlake, J., Stevens, B., Barnes, M., Cori, J., Swann, P. & Howard, M. E. (2020). Assessing the validity of eyelid parameters to detect impairment due to benzodiazepines. HUMAN PSYCHOPHARMACOLOGY-CLINICAL AND EXPERIMENTAL, 35 (2), <https://doi.org/10.1002/hup.2723>.

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