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

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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 2 days, baseline, and after 20-mg 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 per 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 < .05). Average eyelid closure duration (inter-event duration) was a reliable indicator of PVT lapses (area under the curve [AUC] of 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% and 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.

KEYWORDS
behavioural lapses, benzodiazepines, eye blinks, eyelid parameters, ocular measures, temazepam

1 INTRODUCTION

Benzodiazepines (BZs) are independent contributors to driving impairment and increased crash risk (Dunbar, Penttila, & Piikkiainen, 1987; Martin et al., 2013; Rapoport et al., 2009). Roadside blood alcohol concentration 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 BZs is poor (Beirness & Smith, 2017), and unlike roadside blood alcohol concentration testing, the experience of roadside drug testing does little to deter drug driving (Horniak et al., 2017). Recently, devices that measure drowsiness through eyelid parameters have become commercially available. These measures are accurate at measuring drowsiness and...
Objective assessment of vigilance with concurrent measurement of eyelid movement parameters was undertaken during baseline and BZ 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 driver’s license. 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 BZ 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 apnoea 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

The hand-held reaction time task, psychomotor vigilance task (PVT), was used to assess sustained attention through measuring reaction time in response to a visual stimulus (Dinges & 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 & Dinges, 2007; Dinges & Powell, 1985; Dorrian, Rogers, & Dinges, 2005; Howard et al., 2007). A 10-min PVT is believed to be the optimal length with the most reliable and frequently reported measure being the number of lapses (reaction time > 500 ms; Basner & 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/hr on the speedometer, and brake in response to other vehicles. A 60-min 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
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Diagnetics Pty Ltd, Melbourne, Australia), a device that records eight eyelid variables using infrared light positioned on a pair of glasses (Johns, Tucker, Chapman, Crowley, & Michael, 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 minute 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; and
- 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 8 hr in bed sleep schedule (22:00–06:00 hr), 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 1 week separating the sessions to ensure washout of the drug. Performance measures were conducted at 09:00 hr for the rested baseline session (baseline) and, on a separate day, 11:30 hr for the BZ session, 2 hr postingestion. 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 2 hr postadministration when peak plasma levels would be expected to be reached.

The 1.5-hr test battery consisted of vigilance tests and subjective drowsiness and performance questionnaires. The vigilance tests were conducted in randomised order, including the 10-min PVT and 60-min 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 1-min bins for PVT (lapses) and driving simulation (crashes). The number of lapses (reaction time > 500 ms) per minute on the PVT was determined. The first 5 min 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 with the corresponding time matched ODMS eyelid data in 1-min bins. Data were excluded if ODMS signal quality was poor.

Behavioural and eyelid data for each condition are presented as median and interquartile range (IQR). Data were compared using the Wilcoxon signed-rank test due to skewness of the data. Significance level was set at $p = .05$. Receiver operating characteristic (ROC) curve analysis was conducted for all eyelid variables to determine their accuracy in identifying PVT lapses during any 1-min 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 were clustered by participant to account for multiple minutes of PVT replication (Janes, Longton, & Pepe, 2009; Pepe, Longton, & Janes, 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 were utilised from the 15 participants who completed both days of the protocol (14 male, mean age of 37.9 [±11.6], mean body mass index of 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 were available for 15 participants. Missing data were due to equipment errors along any stage of the experimental process, either due to poor Optalert eye tracking data (fitting errors and head positioning), inability to time match data, or errors in downloading data. The 10 participants whose data were not included (six male, mean age of 45.4 [±15.0], mean body mass index of 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 with 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 with 33.3% in the baseline condition (Table 1, $p < .05$). 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).
TABLE 1  Summary of PVT measures (reaction time and lapses) and driving simulation measures (crashes, brake reaction time, lane deviation, and speed)

<table>
<thead>
<tr>
<th></th>
<th>PVT</th>
<th>Driving simulation</th>
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<tr>
<td></td>
<td>Reaction Time (ms)</td>
<td>Lapses (N)</td>
</tr>
<tr>
<td>Baseline (n = 15)</td>
<td>240.49 (216.31–257.53)</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>BZ (n = 15)</td>
<td>295.27 (217.86–573.97)*</td>
<td>9 (2–28)*</td>
</tr>
</tbody>
</table>

Abbreviations: BZ, benzodiazepine; IQR, interquartile range; PVT, psychomotor vigilance test.
*Performance significantly worse in BZ conditions compared with baseline p < .05.

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 BZ 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 Figures 2 and 3 for analysis of eyelid variables compared with one or more lapses per minute, and two or more PVT lapses per 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 with 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 (Figures 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 or more lapses) and BZ conditions (AUC > 0.7082 for one or more lapses and AUC > 0.7751 for two or 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, 0.9736]) and IED when analysing two or more PVT lapses (AUC of 0.9016, 95% CI [0.8069, 0.9647]). Overall, the eyelid variables with the greatest accuracy in detecting PVT lapses were IED and JDS (Figures 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% and specificity = 88.18%) and BZ (84.07% and 84.49%) conditions. IED had moderately high sensitivity and specificity for the baseline (76.92% and 70.41%) and BZ (76.23% and 75.00%) conditions. Similarly, JDS also had a moderately high sensitivity and specificity for baseline condition (89.74% and 68.32%) but lower sensitivity for the BZ (52.46% and 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 BZs 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 BZs, as well as JDS a composite of eyelid movements unique to the ODMS. This suggests that there is potential to use eyelid parameters to determine whether someone is impaired due to BZs and may be at increased risk of attentional failure. This study used a dosage of BZ 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 BZ 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 of 0.9016 for BZs using IED). Analysis of PVT data using one or more lapses in a minute was marginally less accurate (AUC of 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, whereas 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 that influence on-road driving and the relationship between impairment and crashes is not 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, Croft, Kennedy, Owens, & Howard, 2013; Philip et al., 2005; Thiffault & Bergeron, 2003). When using cut-off levels determined by the PVT ROC 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 BZ 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 BZ administration. Eye movements, such as saccades and fixations, slow following BZ

![Diagram of eyelid variables during psychomotor vigilance task](image-url)
administration (Fafrowicz et al., 1995; Padoan et al., 1992; Roy-Byrne et al., 1993; Stern et al., 1974; van Steveninck et al., 1991) although no previous studies have investigated the effect of BZs on eye blink duration, or how the link between eye blink duration and psychomotor impairment is affected by BZs. Other eyelid variables, such as +AVR, were also accurate indicators of psychomotor impairment following BZ 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 with 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

<table>
<thead>
<tr>
<th>Eyelid parameters—PVT</th>
<th>Baseline (n = 15)</th>
<th>BZ (n = 15)</th>
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<tbody>
<tr>
<td>IED Median (IQR)</td>
<td>0.09 (0.0705–0.1310)</td>
<td>0.1090 (0.0750–0.1850)</td>
</tr>
<tr>
<td>BTD Median (IQR)</td>
<td>0.2760 (0.2320–0.3660)</td>
<td>0.3310 (0.2520–0.4330)</td>
</tr>
<tr>
<td>%TEC Median (IQR)</td>
<td>0.03700 (0.0030–0.4230)</td>
<td>0.0830 (0.0170–1.5070)</td>
</tr>
<tr>
<td>+AVR Median (IQR)</td>
<td>1.174 (1.0620–1.4710)</td>
<td>1.3070* (1.1340–1.6200)</td>
</tr>
<tr>
<td>JDS Median (IQR)</td>
<td>2.2000 (0.9000–4.0000)</td>
<td>3.2000 (1.6000–4.7000)</td>
</tr>
</tbody>
</table>

Abbreviations: BTD, blink total duration; BZ, benzodiazepine; IED, inter-event duration; IQR, interquartile range; JDS, Johns Drowsiness Scale; %TEC, percent time with eyes closed; +AVR, positive amplitude-velocity ratio.

*Performance significantly worse in BZ condition compared with baseline p < .05.

**FIGURE 2**  Receiver operating characteristic curves of eyelid variables for discrimination of one or more psychomotor vigilance task lapses using (a) inter-event duration (IED), (b) blink total duration (BTD), (c) percent time with eyes closed (%TEC), (d) positive amplitude-velocity ratio (+AVR), and (e) Johns Drowsiness Scale (JDS) in the baseline and benzodiazepine (BZ) conditions.
impairment, we found similar levels of accuracy across all variables. The previous study found ROC 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 BZs, raising the possibility of using the same eyelid parameters for detecting impairment from a range of causes.

Although the effect of sleepiness on eyelid parameters such as blink duration has been more thoroughly researched (Caffier, Erdmann, & Ullsperger, 2003; Caffier, Erdmann, & Ullsperger, 2005; Hakkanen, Summala, Partinen, Tihonen, & Silvo, 1999; Ingre, Akerstedt, Peters, Anund, & Kecklund, 2006), relatively little has been published with regard 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

**TABLE 3** Cut-off values for eyelid variables with sensitivity and specificity values for chosen cut-offs

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>BZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>IED cut-off</td>
<td>0.131</td>
<td>0.150</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100.00%</td>
<td>98.08%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.50%</td>
<td>50.00%</td>
</tr>
<tr>
<td>BTD cut-off</td>
<td>0.346</td>
<td>0.413</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85.71%</td>
<td>84.31%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.00%</td>
<td>50.00%</td>
</tr>
<tr>
<td>%TEC cut-off</td>
<td>0.093</td>
<td>0.240</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85.71%</td>
<td>88.24%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.00%</td>
<td>50.00%</td>
</tr>
<tr>
<td>+AVR cut-off</td>
<td>1.147</td>
<td>1.164</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85.71%</td>
<td>98.04%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.00%</td>
<td>50.00%</td>
</tr>
<tr>
<td>JDS cut-off</td>
<td>3.800</td>
<td>4.500</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>71.43%</td>
<td>95.65%</td>
</tr>
<tr>
<td>Specificity</td>
<td>51.35%</td>
<td>50.00%</td>
</tr>
</tbody>
</table>

Abbreviations: 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.

**FIGURE 3** Receiver operating characteristic curves of eyelid variables for discrimination of two or more psychomotor vigilance task lapses using (a) inter-event duration (IED), (b) blink total duration (BTD), (c) percent time with eyes closed (%TEC), (d) positive amplitude-velocity ratio (+AVR), and (e) Johns Drowsiness Scale (JDS) in the baseline and benzodiazepine (BZ) conditions.

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study is that there was a difference in the timing of the baseline and BZ sessions after administration of the tablet, which may have affected the blinding of participants to the drug condition. Participants completed the sessions in a randomised 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 minimised 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 nonvolitional 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 BZs 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, BZ-naïve sample; however, further validation is required in sleep disordered populations who are currently using BZs and may exhibit subjective and behavioural tolerance to the drug. Alternatively, there may be a compensatory negative effect of sleep disorders and BZ 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 apnoea syndrome–A pilot study. Sleep Medicine, 6(2), 155–162. https://doi.org/10.1016/j.sleep.2004.11.013

The current study found that eyelid parameters, particularly blink duration measures, were accurate at detecting psychomotor impairment on a simple task following BZ administration. Eyelid parameters have potential to be used to detect performance impairment due to BZs 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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CONFLICT OF INTEREST

V. E. Wilkinson, M. L. Jackson, J. Westlake, B. Stevens, M. Barnes, J. Cori, P. Swann have no conflict of interest to disclose.

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