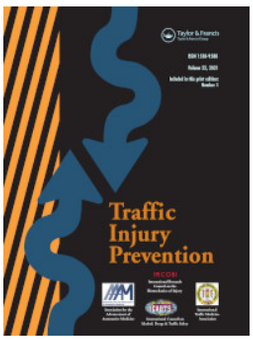

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A comparison of driving related skills impaired by ethanol and zopiclone

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ABSTRACT

Objective: Ethanol and zopiclone are both sedating drugs that impair traffic relevant skills, but that show vast differences in epidemiological traffic risk. One explanation for this could be that they impair various kinds of skills differently, but this is less previously studied. The aim of this study was to compare effects of zopiclone and ethanol on a large battery of computerized psychomotor and cognitive tests according to different test classifications.

Methods: Ethanol (50 grams), zopiclone 5 mg, zopiclone 10 mg or placebo was administered in a randomized trial with a cross-over design. Blood was sampled nine times after administration and analyzed for zopiclone and ethanol using fully validated methods. The computerized tests Connors Continuous Performance Test (CPT), Stockings of Cambridge (SOC) and choice reaction time (CRT) was performed at baseline and after administration. The three tests yielded fifteen different test components, which were categorized according to the three well-known behavior levels (automative behavior, control behavior and executive planning). Secondly, they were categorized into tests measuring "reaction time", "impulsivity" and "attention/cognition".

Results: On all tests belonging to behavior level 1 and on all tests measuring "reaction time", more subjects were impaired by zopiclone than ethanol. On all tests measuring "impulsivity", more subjects were impaired by ethanol than zopiclone.

Conclusion: Zopiclone and ethanol both lead to impairment, but have a different profile on what kind of tests and neurocognitive functions they mostly impair. This could be important in the understanding of the differences in traffic risk connected to these two drugs.

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Introduction

Ethanol and zopiclone are both sedating $GABA_A$ acting drugs, but ethanol also acts on several other receptor systems, one of them being the NMDA-receptors (Narahashi et al. 2001), in addition to e.g., glycine, neuronal nicotinic and 5-hydroxytryptamine type 3 ($5\text{-}HT_3$)- receptors and involvement of dopamine transmission. It is well documented from experimental studies that both ethanol and zopiclone impair traffic relevant psychomotor and cognitive tests, when zopiclone is tested in therapeutic doses and ethanol is tested in doses up to about 0.12 g/dL (Berghaus and Grellner 2010; Schnabel and Krüger Hp 2010; Gunja 2013). On the other hand, the documentation for epidemiological risk of traffic accidents is much more comprehensive for ethanol than for zopiclone, as ethanol is thoroughly documented to substantially increase crash risk, while probably only minor increase in crash risk is seen for zopiclone (Gjerde et al. 2011).

One possible explanation for this difference in traffic risk related to ethanol and zopiclone could be that they impair different kind of relevant skills. This could be investigated by categorizing psychomotor and cognitive tests and investigate which group is most affected by intake of ethanol and which group is most affected by intake of zopiclone. According to Walsh et al, three core levels of behavior will cover different traffic relevant tasks (Walsh et al. 2008). These core levels include automative behavior (well-learned, automatic action patterns), control behavior or maneuvering level (controlled action patterns) and executive planning behavior or strategic level (general plans for interactions with ongoing traffic). Different computerized tests will be included in these behavior levels (Walsh et al. 2008). As an alternative to these core levels, experimental tests could be categorized by dividing them into which types of skills they measure, e.g., test measuring reaction time as opposed to test measuring other aspects like impulsivity. For impairment regarding both reaction time and impulsivity, increase in crash risk is expected (Fillmore et al. 2008; Christoforou et al. 2013). Different laboratory tests are also shown to be relevant for driving, as measured by standard deviation of lateral position (Huizinga et al. 2019).

The experimental documentation for traffic relevant impairment from ethanol and zopiclone is performed using

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different types of psychomotor and cognitive tests (Leufkens and Vermeeren 2009; Schnabel and Krüger Hp 2010; Bocca et al. 2011). In the very few experimental studies that have compared ethanol and zopiclone, it is only concluded which drug that overall gives the most pronounced impairment. In previous articles, zopiclone given in a high dose (10 mg) yielded more overall impairment than 50 mg of ethanol, both as measured by a simplified field-sobriety test (Hjelmeland et al. 2015), and as measured by computerized performance tests (Gustavsen et al. 2011). A previous study indicated that one test measuring reaction time was most impaired by zopiclone and one test measuring number of errors was most impaired by ethanol (Gustavsen et al. 2011). To the best of our knowledge, which group of tests is most impaired by ethanol and which group of tests is most impaired by zopiclone, has not been systematically studied in the previous literature.

Also, acute tolerance to ethanol is relatively well documented (Mellanby 1920), and this is also shown for different benzodiazepines (Ingum et al. 1994), and indicated in one study for zopiclone (Gustavsen et al. 2012). If an experimental study has measured performance at two time points where the blood drug concentrations are quite similar; one on the ascending blood drug concentration limb and one on the descending concentration limb, the differences in test results would give an impression of the extent of acute tolerance seen for the drug. To the best of our knowledge, the previous research on acute tolerance for zopiclone did not investigate if the development of acute tolerance was different according to which type of psychomotor or cognitive test was performed.

The first aim of the present study was to investigate if ethanol and zopiclone impair traffic relevant psychomotor and cognitive tests differently i.e., which tests were impaired most by intake of ethanol and which most by zopiclone. The second aim of this study was to compare test performance on the ascending and descending concentration limb for zopiclone and to investigate which types of tests are most prone to acute tolerance.

Materials and methods

Study design and blood sampling

The present results are from a randomized, placebo-controlled, double blind, cross over trial administering zopiclone 5 mg, zopiclone 10 mg, ethanol 50 gram or placebo, to 16 healthy, male individuals, recruited by advertisements at the University area. The median age was 23.5 years (range 20-28 years) and the median weight was 76.5 kg (range 69-88 kg). All participants were students at the University of Oslo or at the Norwegian Business School.

The protocol has been published previously (Ethics committee reference number was S-07288a) (Gustavsen et al. 2011). Briefly, drug administration of zopiclone, ethanol or placebo was performed after baseline blood sampling, and nine blood samples were retrieved until 10 hours post dosing. The subjects attended a research unit at 8 am for four different study days and received in randomized order one of the four different study regimens. Each of the subjects received the different study regime once. The study drugs were given blinded to the subjects and the investigators. A GMP (good manufacturing practice)-certified pharmacy at Oslo University Hospital prepared a study medicine package of two capsules and one drink.

The blood analyses were performed using protein precipitation followed by liquid chromatography mass spectrometry (LC-MS) analysis for zopiclone (Gjerde et al. 2010) and headspace GC analysis for alcohol (Kristoffersen et al. 2006). The limit of quantification for zopiclone was 7 ng/ml, the interassay precisions for low and high quality of control samples were 12% and 5% ($n = 14$), respectively, and the accuracy expressed as bias was 1.2% and −7%. The limit of quantification for ethanol was 0.04 g/kg. Repeatability, expressed as relative standard deviation, was <1.3%, between assay reproducibility was <2.9% and accuracy was <-6.7% deviation from theoretical value. Blood samples were refrigerated (5 °C) immediately after the samples were collected and for a maximum 24 h after sampling. They were then either analyzed or frozen (–20 °C) for later analysis.

Computerized tests

A battery of computerized tests was performed at baseline and then at 0.5-1.5 h and 3-4 h after intake of study drug (the interval was due to time demanding tests), for simplicity hereafter referred to as 1.0, and 3.5 h after intake of study drug. The test battery was also performed 6.5 h after intake, but no test results showed deteriorated performance at this time point. The tests were administered in the same order at baseline and after drug administration and also in the same order at all study days. A training session was performed for each participant one week ahead of the first study day.

The computerized tests performed were: 1. Connors Continuous Performance Test (CPT) Version II for Windows (Epstein et al. 2003). The test subjects are placed in front of a screen and instructed to press the spacebar on the computer's keyboard in response to any letter excluding "X" appearing on the screen. The test measures how fast the test subject responds to a stimulus and how often the subject responds incorrectly (i.e., hits the spacebar when the letter "X" appears on the screen). One test session lasted for 14 min. 2. The Stockings of Cambridge (SOC) test, which is a computerized version of the Tower of London (TOL) test (Shallice 1982). In the TOL test the subject is presented with two vertical columns of colored balls, one which represents the desired arrangement. The other must be rearranged to match the first, moving one ball at a time. The objective is to use the minimum number of moves in the shortest possible elapsed time. The computerized SOC session lasted for 10 min. 3. Choice reaction time (CRT), where a series of stimuli, which may be auditory and/or visual, is presented to the test subject using an electronic apparatus or a computer screen. The subject is instructed to respond appropriately and rapidly through hand movements to pre-selected

signals. The subject is graded on the speed and accuracy of the performance. One test session lasted for 7 min.

Twenty-three test components were available from the three computerized tests. Of these test components, fifteen that were relevant to measure impairment were selected. They were firstly categorized into three behavior levels (automative, control and executive behaviors). Secondly, another categorization was performed according to which skills the test measured. The test components were categorized into three optional groups measuring "impulsivity", "reaction time and related functions" (hereafter named "reaction time") and "attention/cognition". A description of each test component, the categorization into behavior levels and the optional categorization is presented in Table A1 (see online supplement).

Presentation of results

In the present study, we investigated impairment for each test component in the 16 subjects. For each subject we compared the result after drug treatment with the result after placebo at corresponding time points. The main data presentation is percentage of the 16 individuals that showed impaired performance compared to placebo 1.0 h after intake of zopiclone 5 mg, zopiclone 10 mg or ethanol 50 g, respectively, for each of the single tests. The effect size of impaired results after drug treatment differed between test components and subjects. Therefore, the results were also standardized according to the Dunlap's d formula (Dunlap et al. 1996), making it possible to compare effect sizes across tests using different scales of measurements. The formula used is $d = t^*(2^*(1-r)/n)^{1/2}$, where t is the t-value from the paired samples t-test (placebo performance compared to each drug performance 1 h after intake), r is the correlation coefficient between the placebo performance and each drug performance and n is the number of subjects. The mean effect size on all tests belonging to each behavior level and each optional categorization was then compared between ethanol and zopiclone using Student's t-test.

Mean results with standard deviation for the difference between drug and placebo performance were calculated for ethanol, zopiclone 5 mg or zopiclone 10 mg.

Acute tolerance was determined for various test components by comparing the fraction of subjects impaired by drug compared to placebo, 1.0 h and 3.5 h after drug intake, if the drug concentrations at these time points were similar. A less pronounced drug impairment at the descending limb of the drug concentration curve (at 3.5 h), was regarded as acute tolerance.

Results

The blood zopiclone concentrations of the 16 individuals after 1.0 and 3.5 h are presented in Table 1, showing that the median and mean concentrations of zopiclone for blood samples retrieved 1.0 h and 3.5 h after intake were quite equal for both doses. Also, the blood ethanol concentrations of the 16 individuals after 1.0 and 3.5 h are presented in Table 2, showing that the median and mean concentrations of ethanol for blood samples retrieved 1.0 h after intake was higher than 3.5 h after intake.

The percentages of subjects demonstrating impaired performance according to the three behavior levels are presented in Figure 1a. For all test components at behavior level 1, more subjects showed deteriorated performance after intake of one or both doses of zopiclone compared to ethanol. For behavior level 2 and 3, the results were more variable.

Figure 1b shows the performance of the computerized test components when they are regrouped according to which skills they measure (impulsivity, reaction time or attention/cognition). In all four test components categorized to indicate impulsivity, a higher proportion of individuals show deteriorated performance after intake of ethanol compared to zopiclone. For all test components that measure reaction time, a higher proportion of individuals showed deteriorated performance after intake of one or both doses of zopiclone compared to ethanol. For the test components that are categorized to measure "attention/cognition", results were variable.

In Table A2 (see online supplement), the effect size standardized according to Dunlap's d formula is presented for each test and each drug intake. This shows that effect sizes were higher for zopiclone 10 mg compared to ethanol, for all tests belonging to behavior level 1 and tests measuring reaction time. For all tests measuring impulsivity, effect sizes were higher for ethanol compared to both doses of zopiclone. In Table 3, the mean effect sizes for ethanol and zopiclone 10 mg are presented for each behavior level and each optional categorization. The mean effect sizes was significantly higher for zopiclone 10 mg compared to ethanol on tests belonging to behavior level 1 ($p = 0.011$) and on tests measuring reaction time ($p = 0.001$). The mean effect

Table 1. Concentrations of zopiclone in blood (ng/ml) 1.0 and 3.5 h after intake. The median, mean, total range and interquartile (IQ) range is shown.

	Concentrations in blood 1.0 h after intake				Concentrations in blood 3.5 h after intake			
Zopiclone dose	Median	Mean	Range	IQ range	Median	Mean	Range	IQ range
5 mg	17.1	19.0	11-34	12-26	16.7	17.8	14-25	16–20
10 mg	37.3	39.1	16-77	23-51	35.4	34.3	23–45	30-37

Table 2. Concentrations of ethanol in blood (g/dL) 1.0 and 3.5 h after intake. The median, mean, total range and interquartile (IQ) range is shown.

	Concentrations in blood 1.0 h after intake				Concentrations in blood 3.5 h after intake			
Ethanol dose	Median	Mean	Range	IQ range	Median	Mean	Range	IQ range
50 g	0.057	0.078	0.057–0.098	0.072–0.084	0.037	0.051	0.037–0.065	0.045–0.055

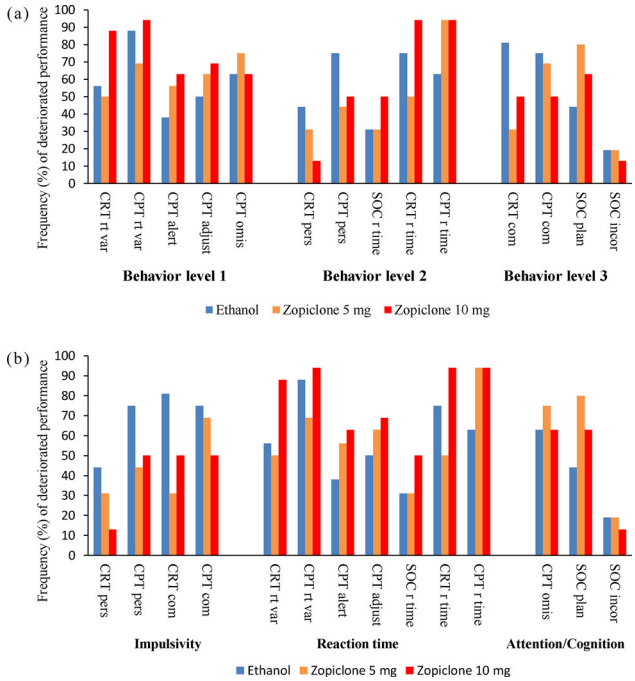

Figure 1. a. Fractions (in percent) of the 16 individuals that showed deteriorated performance after intake of active drug compared to placebo performance 1.0 h after intake. The test components are sorted in order of the three core levels of behavior: 1 (automative behaviors), 2 (control behaviors) or 3 (executive behavior). b. Proportions (in percent) of the 16 individuals that showed deteriorated performance after intake of active drug compared to placebo performance 1.0 h after intake. The four test components to the left (CRT pers, CPT pers, CRT com and CPT com) are specific measures of impulsivity. In the middle, seven test components (CRT rt var, CPT rt var, CPT alert, CPT adjust, SOC r time, CRT r time and CPT r time) which measures reaction time are presented. To the right the test components (CPT omis, SOC plan and SOC incor) which measures attention/cognition are shown.

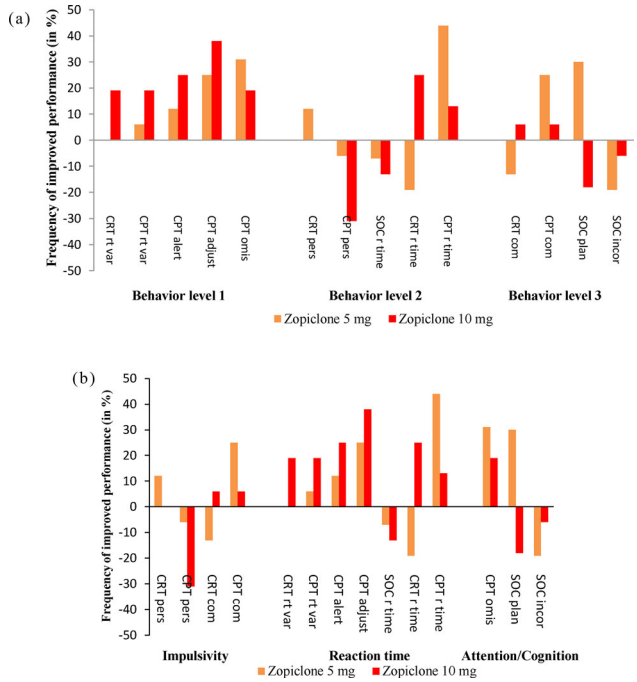

Figure 2. a. Change in (placebo-compared) performance (fractions in percent of the 16 individuals) for the 14 test components from 1.0 h to 3.5 h after intake of zopiclone. A positive bar shows lower percentage of deteriorated subjects for performance after 3.5 h compared to performance after 1.0 h (acute tolerance) and a negative bar shows more deteriorated subjects. The test components are sorted in order of the three core levels of behavior: 1 (automative behaviors), 2 (control behaviors) or 3 (executive behavior). b. Change in (placebo-compared) performance (fractions in percent of the 16 individuals) for the 14 test components from 1.0 h to 3.5 h after intake of zopiclone. A positive bar shows lower percentage of deteriorated subjects for performance after 3.5 h compared to performance after 1.0 h (acute tolerance) and a negative bar shows more deteriorated subjects. The test components are sorted in order as components that measure "impulsivity", "reaction time" or "attention/cognition".

Table 3. Mean Dunlap's d effect sizes for ethanol 50 gram and zopiclone 10 mg according to different behavior levels and optional categorizations.

Group	Number of tests	Mean effect size zopiclone 10 mg	Mean effect size ethanol 50 grams	P
Behavior level 1	5	0.97	0.20	0.011*
Behavior level 2	5	0.62	0.55	0.845
Behavior level 3	4	0.19	0.32	0.743
Reaction time	7	1.08	0.35	0.001*
Impulsivity	4	0.14	0.79	0.002*
Attention/Cognition	3	0.43	0.13	0.354

sizes were significantly higher for ethanol compared to zopiclone 10 mg on tests measuring impulsivity ($p = 0.002$).

Also, in Table A3 (see online supplement), the difference from placebo performance is seen for each test result and each drug 1 h after intake. This shows larger differences from placebo performance and also more significant results for zopiclone compared to ethanol within all tests belonging to behavior level 1 and tests categorized to measure reaction time. For tests categorized to measure impulsivity, larger differences from placebo performance and more significant results were seen for ethanol compared to zopiclone.

The percentage of subjects demonstrating impaired performance in the different test components 3.5 h after intake was generally lower than shown in Figure 1a and b, and the detailed data for performance 3.5 h after intake are not shown.

For ethanol, the concentrations differed at 1.0 and 3.5 h after intake and acute tolerance could therefore not be investigated. For zopiclone, however, the concentrations in blood at 1.0 and 3.5 h were quite similar, and acute tolerance could be studied.

Figures 2a and b show the change in placebo-compared performance 1.0 h after zopiclone intake compared to the placebo-compared performance 3.5 h after zopiclone intake. An improvement of performance would be an indication of acute tolerance. This is seen as a positive bar and shows a lower fraction of impaired subjects at 3.5 h compared to 1.0 h. A negative bar indicates more deteriorated subjects at 3.5 compared to 1.0 h and lack of acute tolerance.

Figure 2a shows the tests when they are categorized according to the three behavior levels. For level 1, acute tolerance to zopiclone was indicated for all tests, while acute tolerance was more variable for level 2 and 3.

In Figure 2b the tests are sorted according to which skills they measure ("impulsivity", "reaction time" or "attention/

cognition"). Acute tolerance was seen for six of the seven tests that measure reaction time. For the test components categorized to measure impulsivity and attention/cognition, acute tolerance was more variable. It should especially be noted that for the three test components that originate from the SOC test, acute tolerance was not observed.

Discussion

The present study showed that both zopiclone and ethanol lead to impairment, but zopiclone causes the most pronounced impairment on psychomotor or cognitive test components related to reaction time, while ethanol shows the most pronounced effect on test components measuring impulsivity. When test components are divided according to behavior level, zopiclone mostly impaired level 1. Also, acute tolerance is shown for zopiclone, but mostly on tests measuring reaction time and tests belonging to behavior level 1.

The results from the present study indicate some differences in the pharmacodynamic effects of ethanol and zopiclon, although both are sedating drugs. This could be related to the different receptor profiles of the two drugs. While zopiclone acts solely on $GABA_A$-receptors, ethanol has a wider range of action, which is also largely based on $GABA_A$-receptors, but also includes other receptor systems like e.g., 5-hydroxytryptamine type 3 ($5\text{-}HT_3$)-receptors and especially NMDA-receptors (Narahashi et al. 2001). Ethanol is also shown to reduce inhibition, which might be related to enhanced impulsivity (Heinz et al. 2011). The present findings could indicate that $GABA_A$-effects mostly are responsible for causing impaired reaction time, while the effect of ethanol on other neurotransmitter systems could contribute to enhanced impulsivity. The mean effect size for ethanol on tests measuring reaction time is comparable to what is previously shown to accompany a blood alcohol concentration of 0.5 g/kg (Jongen et al. 2014). Such an effect size of about 0.30-0.40 is considered a relatively weak effect, while effect sizes higher than 0.7, as indicated for zopiclone for reaction time tests in the present study, is considered to be a relatively strong effect.

Although it should be noted that zopiclone and ethanol both show impairment on the different performance skills, the differences in the profile of the impairing effects between ethanol and zopiclone could be clinically important. It is well documented from epidemiological studies that use of ethanol is accompanied by a much higher crash risk compared to use of zopiclone (Gjerde et al. 2011). One could question if these documented differences in traffic accident risk from zopiclone and ethanol (Gjerde et al. 2011) could imply that the enhanced impulsivity would add increased traffic risk to that related to increased reaction time. Although some previous studies have tried to link drug intake to impairment of reaction time and impulsivity or even traffic risk (Fillmore et al. 2008; Christoforou et al. 2013), the direct comparison of reaction time related effects and impulsivity on traffic risk is not previously investigated. Although comparing the present results to the previously documented crash risk from ethanol compared to zopiclone could indicate that impulsivity represents a higher risk than increased reaction time, it is however difficult to conclude, as the usage pattern for ethanol and zopiclone in epidemiological studies differ, with possible less presence of high dose intakes for zopiclone compared to ethanol. Also, it should be noted that impairing effects not included in the present test battery, as for instance aggression, could be important for differences in observed epidemiological traffic related risk.

The findings in the present study could also be important when experimental studies are planned. If impairment from zopiclone in comparison with the "verum" ethanol should be measured (Walsh et al. 2008), a test measuring reaction time is more likely to show reduced performance after zopiclone administration, while enhanced impulsivity is more likely to be found after ethanol intake.

Regarding acute tolerance to zopiclone, it is more difficult to explain from a pharmacological point of view why this is considerable for reaction time tests and very variable for other tests. For chronic tolerance, which develop when an individual adapts to constant exposure to a drug over weeks or months, it is well known that different impairing effects show different degree of tolerance (Barker et al. 2004). For acute tolerance, however, this is not extensively studied earlier. As zopiclone acts solely on the $GABA_A$- receptors, it could be speculated that differences within the receptor complex and/or downstream effects could develop and being expressed as acute tolerance.

The strength of the present study was the randomized, controlled design and the measurement of blood concentrations of both ethanol and zopiclone. A well-known problem regarding zopiclone is the instability in biological samples (Nilsson et al. 2010), but this was handled by quick cooling after sampling. The three ways of presenting the impairment in relation to placebo performance: both according to number of subjects and according to the Dunlap's d effect size as well as mean differential results on all tests, showing similar results, strengthen the findings. One limitation is that the classification of the different tests could be subject to different solutions. The classification into behavior levels is relatively well documented (Walsh et al. 2008), while the classification into which skills the test measure was a result of a thorough discussion in the research group. It should also be noted that although median and mean concentrations of zopiclone was quite equal 1.0 and 3.5 h after drug intake, the ranges were wide, and acute tolerance was therefore not perfectly measured in all individuals. For ethanol, the concentrations 1.0 and 3.5 h after ingestion differed, making the assessment of acute tolerance more difficult. This difference between ethanol and zopiclone concentrations could be related to the pharmacokinetic differences between the two drugs.

In conclusion, the present study showed that although both zopiclone and ethanol impair computerized cognitive and psychomotor tests components, there were differences in which test components they mostly affected and for which test components acute tolerance developed. The

findings might be of importance when the differences in traffic accident risks of these two drugs should be understood.

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Data availability statement

Anonymous data could be provided by contacting the authors.

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