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Impairment due to cannabis and ethanol: clinical signs and additive effects

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ABSTRACT

Aims Studies have shown that the impairing effects of Δ-9-tetrahydrocannabinol (THC) are dose-related. Cannabis intake increases the risk of traffic accidents. The purpose of this study was to see how different clinical tests and observations were related to blood THC concentrations and to determine whether the combined influence of THC and ethanol was different from either drug alone. **Design** A retrospective cross-sectional forensic database study. **Setting** Drivers apprehended by the police suspected of driving under the influence of alcohol other drugs. **Participants** We investigated 589 cases positive for THC only. In addition, 894 cases with THC and ethanol were included. A comparison was made with 3480 drivers with only ethanol in their blood and 79 drivers who tested negative. **Measurements** Data were analytical results of blood samples and the 27 clinical tests and observations included in the Norwegian clinical test for impairment (CTI). **Findings** No relationship was found between blood THC concentration and most of the CTI tests. Blood THC concentration was, however, related to conjunctival injection, pupil dilation and reaction to light and to the overall risk of being judged impaired. When THC and ethanol were detected together the risk of being judged impaired was increased markedly. **Conclusions** This study demonstrates that cannabis impairs driving ability in a concentration-related manner. The effect is smaller than for ethanol. The effect of ethanol and cannabis taken simultaneously is additive. Conjunctival injection, dilated pupils and slow pupil reaction are among the few signs to reveal THC influence.

Keywords Cannabis, clinical test for impairment, drugged driving, ethanol.

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INTRODUCTION

Cannabis is a frequently used drug. It is also detected frequently in the blood samples of apprehended drivers [1,2] and in post-mortem samples from killed drivers [3]. In some studies, driving under the influence of cannabis has been found to occur more frequently than driving under the influence of alcohol [4].

Experimental laboratory research has shown a clear concentration–effect relationship between the active ingredient in cannabis; Δ^9-tetrahydrocannabinol (THC) and impairment [5–7], both in close-to-realistic driving simulators [8] and in on-the-road driving experiments [9–12]. For ethical considerations, however, it is not feasible to study the effects of higher THC levels. However, high blood THC concentrations are often found in drivers apprehended by the police on suspicion of driving under the influence of cannabis.

There is still a debate as to whether cannabis causes impairment which has an impact on traffic safety. Some studies have failed to identify an increased risk of road traffic accident. This has been explained by the suggestion that THC-impaired drivers compensate for their psychomotor impairment by driving more cautiously [3]. Some studies have, however, demonstrated an increased traffic accident risk for drivers who were regular cannabis users [13] or had THC in their blood samples [14,15].

In total, however, there is a paucity of studies identifying traffic-related impairment in real-life settings with drivers who have realistically high concentrations of

cannabis in their blood. We have investigated previously a relationship between high THC concentrations and impairment in apprehended drivers by comparing drivers with high concentrations with drivers who have lower concentrations [16]. The study identified a relationship between THC concentration and the risk of being judged impaired by a police physician. This approach could not, however, reveal the effect of lower THC concentrations, as these cases were used as comparators. Identifying an increased risk of impairment at lower THC concentrations, especially in real-life epidemiological studies, may have implications for the introduction of legal limits for THC and driving [12] as many, or even most, apprehended drivers have low THC concentrations in their blood [17].

Using a group of drug-free drivers as comparison could possibly overcome this problem. Previously, we have studied the effects of drugs such as opioids and carisoprodol by comparing them to drug-free drivers [18–20]. However, this could introduce an exaggerated picture of the drug effects, as drug-free drivers may be fundamentally different from drug-positive drivers. Using a reference group with a different drug in their blood (e.g. ethanol) and examining any additional effect of THC could help us to overcome this problem [21].

The standardized field sobriety test (SFST) was designed originally to reveal alcohol intoxication [22]. It usually includes horizontal gaze nystagmus, walk-and-turn test and one-leg stand. Some research, however, indicates that it may be poorly suited for revealing other types of impairment, e.g. cannabis [8]. In a laboratory-based study, researchers suggested that observations of head moves or jerks could increase the sensitivity of the SFST test to impairment by THC. In Norway, a more comprehensive clinical test for impairment (CTI) is performed shortly after apprehension on drivers suspected of driving under the influence of non-alcoholic drugs [23]. The CTI is performed by a police physician in conjunction with the collection of blood samples. However, it is not known how well this test, with a total of 27 subtests and observations, reveals cannabis-related impairment.

The aims of the present study were: to investigate if blood THC concentration was related to the risk of being judged impaired when comparing drivers with ethanol in their blood to drivers with both ethanol and THC in their blood; to look at the effects of a combination of THC and ethanol as such; and to investigate what elements of the Norwegian clinical test for impairment were possibly relevant for assessing the intake of cannabis.

MATERIALS AND METHODS

All the data were taken from an existing database at the Division of Forensic Toxicology and Drug Abuse (DFTDA) at the Norwegian Institute of Public Health and were handled anonymously by the researchers. The DFTDA analyses all blood samples from suspects of drugged driving in Norway. The database contains results from all cases of suspected driving under the influence of alcohol and non-alcohol drugs. The database was searched up to 2005 for positive THC-blood cases. There were 589 samples that contained only cannabis, with no other drugs or alcohol above detection limits. These cases have been reported previously [16]. We also included 894 cases where cannabis was detected in combination with ethanol alone. Finally, we included 3480 drivers with only ethanol in their blood and 79 drivers without any drugs detected in their blood. The former was taken from an earlier paper by Gustavsen and coworkers [24], the latter from an earlier paper by Bachs and coworkers [18].

Immediately after having drawn blood from the suspected driver, the Norwegian CTI is performed (Table 1). The CTI is based first on a short interview, in which the physician asks the suspected driver questions about drinking habits and drug history, as well as recent use. Then, the examining physician performs 27 observations and tests (including seven tests of alertness, cognitive function and vestibular function, four observations of the eyes, two observations on cardiac action, two observations pertaining to signs of intravenous drug abuse, four tests of motor activity/coordination and eight observations concerning appearance). Finally, on the basis of a broad and general impression, the examining physician concludes whether the suspected driver is 'not impaired' or 'impaired' [23].

Blood samples received at DFTDA were screened routinely for alcohol and common drugs of abuse (amphetamine, benzodiazepines, cannabis, cocaine and opiates) up to 2000 by immunological methods [1], and since then by liquid chromatography/mass spectrometry (LC/MS) for benzodiazepines [25]. The DFTDA does not screen the blood samples routinely for other drugs such as antihistamines, antidepressants or neuroleptics unless there is information on specific drug intake other than that revealed by the primary screening. Any positive results from the screening for cannabis were confirmed subsequently by gas chromatography/mass spectrometry (GC/MS) quantification of THC in blood. These methods have been described previously [16,26]. The limit of detection (LOD) for the confirmatory GC/MS analysis of THC in whole blood was 0.2 ng/ml, and the limit of quantification was 0.5 ng/ml. The inter-day coefficient of variation for the GC/MS analysis in whole blood for THC at 1.0 ng/ml was 10%. The limit of detection for the immunological screening method was set at 10 ng cannabinoids/ml to avoid too many negative THC confirmation results from the subsequent confirmatory analysis.

Table 1 Description of the 27 different subtests and observations conducted by the physician as part of clinical test for impairment (CTI). the physician's conclusion on the CTI is also included.

Test/observation	*Observations conducted by examining physician*	*% impaired*
Alertness		
Subdued consciousness	Responds normally to questions, has a normal vigilance	14.0
Not orientated for time and place	Can state time and place without being given cues	4.9
Eyes		
Abnormal eyes		36.9[a]
Tear shedding	Is there tear shedding?	1.7
Abnormal pupil size	Judge size by taking into consideration present light and compare with other person	30.9[a]
Abnormal reaction to light	Room should be dark or eyes closed for at least 1 minute. Judge reaction	21.5[a]
Vestibular function		
Horizontal gaze nystagmus	Pen is held 40 cm from eyes and moved laterally. There should be smooth movement of eyes and no nystagmus.	12.7
Rombergs test positiv	Standing steady on one leg for at least 5 seconds with arms stretched out and eyes closed. Judge body sway and other instabilities	34.6
Physical signs of intravenous (i.v.) abuse		
Needle marks	Are there needle marks?	24.7
Superficies thrombosis or phlebitis	Are there signs of old i.v. substance abuse?	10.3
Motor/coordination		
Gait on line abnormal	One foot in front of the other. Nine steps. Should be on line. Consider also failure to take instructions, not waiting for signal to start or latency before starting	7.0
Abnormal turning on line	Turn should be on line without side-steps	9.7
Finger-to-nose test positive	Standing with feet together and arms stretched to side and eyes closed, placing digit two of each hand on nose on command	12.4
Finger-to-finger positive	Standing with feet together and arms stretched to side and eyes closed, placing digit two of each hand together in front of body	22.3
Cognitive function		
Faulty counting backwards	Counting backwards from 107, 20 numbers to 87. Note faults and speed	17.9
Abnormal articulation	Is speech snuffled, slow, or with latency?	4.5
Not meaningful content	Is speech meaningful?	1.4
Pulse		
Pulse rate	What is the pulse rate (beats/minute)	
Regular heartbeat?	Is the pulse regular?	1.6
Appearance		
Abnormal smell on breath	Smell of alcohol, acetone and other strong smell of breath should be noted	9.5
Abnormal face/skin	Facial appearance should be assessed	24.9
Abnormal facial expression	Facial expression and gestures should be assessed	8.8
Involuntary movements	Judged throughout the whole session, have there been involuntary movements?	1.4
Hand tremor	Placing a piece of paper on the dorsal side of outstretched hands—is there any tremor?	13.1
General conduct abnormal	Suspect responds normally to questions, has a normal vigilance. Can comprehend messages, wait for signal to perform and perform without delay	19.2
Physical damage	Physical damage	11.6
Clothing untidy	Clothing untidy	10.5
Physician's conclusion		
Psychomotor impairment	The overall judgement from the physician, after the performance of all subtests/observations of CTI. Carried out at the end, but based freely on the CTI, adjusting for overall impression	49.6[a]

[a]Test with a concentration effect relationship between blood Δ-9-tetrahydrocannabinol (THC) and test outcome.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 16. Differences between the two groups were examined using either Pearson's χ^2 test for categorical data, a Student's *t*-test for continuous variables with a normal distribution or a Mann–Whitney *U*-test for variables without a normal distribution. The share of impaired drivers or relative risk as a function of the total number of drivers examined is given as a percentage with 95% confidence interval (CI). Using the risk ratios (RR) made it possible to investigate whether the effect of THC and ethanol together was additive or synergic. This was performed by calculating the synergy index (SI) using the formula $(RR_{THC+ethanol} - 1)/[(RR_{THC} - 1) + (RR_{ethanol} - 1)]$ for the different elevated THC and ethanol combinations [27], with 95% CI calculated by a method established by Rothman [28]. Levels of significance for all analyses were set to $P < 0.05$.

RESULTS

Clinical effects of THC as seen by the CTI

For the 589 suspected drivers with only THC in their blood, we had data on the CTI with varying degrees of response to the different tests and observations. The suspects were impaired on the tests and observations to a varying extent (Table 1), but a relationship between blood THC concentration and clinical effects was seen only for observations and tests concerning ocular phenomena (Table 2). With increasing blood THC concentrations the suspects more often had conjunctival injection, dilated pupils and decreased reaction to light. In approximately 5% of the suspects, small pupils were observed, but no concentration–effect relationship with blood THC was observed. One in every four drivers showed only one sign, but there was a significant overlap between these three positive signs and symptoms of eye involvement. As many as 47% of the subjects showed none of these signs of eye involvement.

Cannabis- and alcohol-positive samples and degree of impairment

Figure 1 shows the percentage of drivers that were judged impaired by the police physician after the CTI. More drivers with drugs detected in their blood sample were judged impaired than without. More drivers were considered impaired as the concentrations of THC increased. THC seemed to increase the degree of impairment in ethanol-impaired drivers. Similarly, the addition of some alcohol to even the lowest concentrations of THC increased the risk of being judged impaired. The percentage of impaired drivers also rose towards 100%, with

Table 2 The clinical tests and observations of the clinical test for impairment (CTI) relating to the eye that showed a positive relationship with blood Δ-9-tetrahydrocannabinol (THC) concentration in the suspected driver apprehended by the police and suspected of driving under the influence of non-alcoholic drugs, examined thereafter by a police physician. Figures are given as the number of positive observations over the number of observations (%; 95% confidence interval of %); shaded areas indicate significant findings.

	Blood THC concentration groups (in ng/ml)					
Observation	*0.30–1.00*	*1.01–1.60*	*1.61–2.90*	*2.91–4.80*	*4.81–10.10*	*>10.10*
Conjunctival injection	11/98 (11; 5–17)	13/111 (9; 4–14)	21/120 (18; 11–24)	11/71 (15; 7–24)	19/94 (20; 12–28)	11/29 (38; 20–56)
Pupils dilated	18/98 (18; 11–26)	18/114 (16; 9–22)	30/120 (25; 17–33)	25/71 (35; 24–46)	24/94 (26; 17–34)	11/31 (35; 19–52)
Slow or no pupil reaction upon light	14/94 (15; 8–22)	19/114 (17; 10–24)	13/117 (11; 5–17)	22/69 (32; 21–43)	18/91 (20; 12–28)	9/30 (30; 14–46)
At least one symptom of the eyes	31/92 (34; 24–43	34/108 (31; 23–40)	46/117 (39; 30–48)	38/68 (56; 44–68)	53/90 (59; 49–69)	17/28 (61; 43–79)

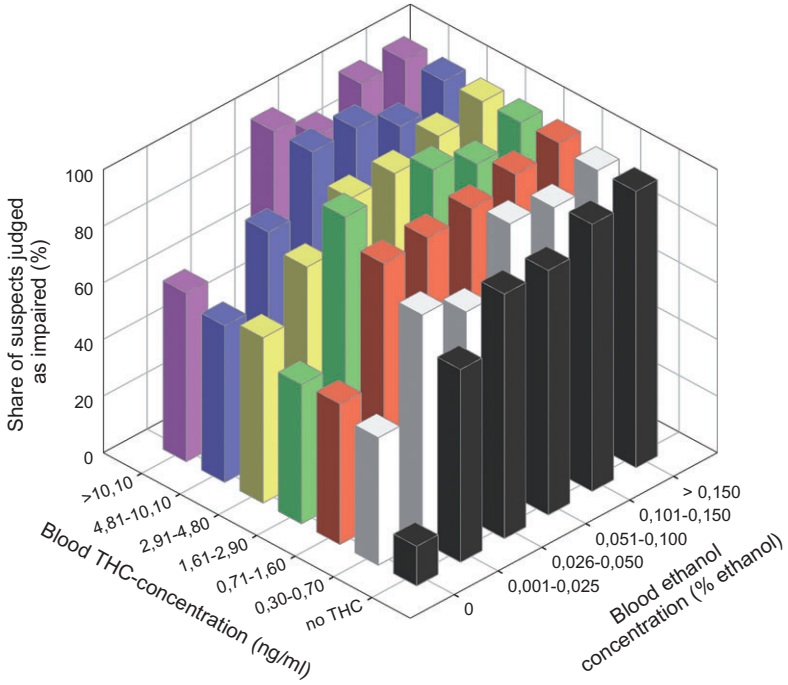

Figure 1 The share of suspected drivers judged impaired by the police physician according to blood alcohol concentration and blood Δ-9-tetrahydocannabinol (THC)-concentration. Data on impairment in cases of alcohol only were taken from an earlier study by Gustavsen and coworkers, with permission [24]. Data on impairment in cases containing THC only were taken from an earlier study by Khibani and coworkers, with permission [16]. Data on impairment in cases containing no drugs were taken from an earlier study by Bachs and coworkers, with permission [18]

Table 3 Number of individuals determined by the police physician to be impaired according to various blood ethanol and Δ-9-tetrahydrocannabinol (THC) concentrations. Figures are given as the number of positive observations over the number of observations (%; 95% confidence interval of %)

	THC concentration		
BAC	*THC not detected*	*THC-concentration 0.30–1.60 ng/ml*	*THC-concentration 1.60 ng/m and above*
Blood alcohol not detected	11/79 (14; 6–22)[a]	50/112 (45; 35–54)[b]	166/314 (53; 47–58)[b]
Low BAC; 0.001–0.050	253/327 (77; 73–82)[c]	99/109 (91; 85–96)	276/297 (93; 90–96)
High BAC; >0.050	2994/3153 (95; 94–96)[c]	92/95 (97; 93–100)	279/279 (100; 100–100)

[a]Data from an earlier study by Bachs and coworkers, with permission [18]; [b]data from an earlier study by Khiabani and coworkers, with permission [16]; [c]data from an earlier study by Gustavsen and coworkers, with permission [24]. BAC: blood alcohol concentration.

increasing blood THC concentrations at different blood alcohol concentrations (BACs). As we reached 100% impairment (or 0% 'not impaired') it was, however, difficult to identify the increase in risk between the different groups.

Table 3 shows that even smaller THC concentrations in blood (<1.60 ng/ml) involved an increased risk of being judged impaired, both when comparing low THC mono-cases with drug-free cases but, more importantly, when comparing low THC concentrations with alcohol to ethanol-only cases. Also, when a low concentration of alcohol was present in addition to THC there was an increased risk of being judged impaired. There were no signs that the effect of THC and ethanol together were more than additive, as all SI estimates were well below 1 (data not shown).

DISCUSSION

This study confirmed earlier findings of a positive concentration–effect relationship between blood THC concentration and impairment in a real-life group of apprehended drivers [16]. We were able to show an increased risk of being judged impaired not only for high THC concentrations, but also for lower concentrations. This was performed by comparing different THC concentrations to a drug-free population of apprehended drivers and by looking at the additional effects of THC with alcohol. Using a group with pure alcohol influence as a comparator to a group with alcohol and drug in their blood has proved to be a valid method of determining a drug's intoxicating effect [21]. Experimental studies on THC and alcohol have also shown that THC in combina-

tion with alcohol impairs drivers more than alcohol alone, adding to the growing body of evidence for the impairing effects of THC on driving [11]. The finding that low THC levels are impairing supports the idea of setting a low legal limit for THC and driving [12], if not a zero limit [17].

The impairing effects of alcohol and cannabis on performance have been reported previously as being similar in some respects and different in others. Researchers have also shown that THC may be less impairing than alcohol [10,14]. Our study also suggests considerable impairing effects when THC is combined with alcohol (i.e. as the percentage of impaired drivers reaches almost 100% among drivers with both alcohol and THC), confirming other findings on the additive effects of alcohol and cannabis [11]. Given estimates that at least 90% of the causes of car crashes can be traced to the driver [29], it is worth emphasizing that combined alcohol and THC impairment is considerable, and may have a serious impact on crash risks. Between BACs of 0.05 and 0.09, there is an 11-fold increased risk of fatal single-vehicle crash [30].

Our study also shows that even a small amount of alcohol, in addition to THC, increases impairment. This is in line with our knowledge of the impairing effects of alcohol [31]. Some smaller experimental studies on alcohol and THC have shown that the additive effects of these drugs are larger than either of the drugs alone [10,11,14,32–34]. Our study included analysis of THC in blood in 894 cases and allowed us to look at the concentration–effect of a psychoactive drug in a larger sample. Given the high incidence of impairment in the present material it would be difficult to demonstrate any synergy between the impairing effects of alcohol and THC, as others have demonstrated [3]. Our results can only confirm an additive effect.

The CTI was developed originally to reveal traffic-related impairment due to alcohol [35], but has been shown to be a valid instrument for also revealing impairment from other sedating drugs [20,23,36]. Many tests and observations, involving coordination, attention, cognition and psychomotor skills, are included to improve sensitivity. These tests and observations, similar to those included in the SFST, have been thought traditionally to be related to traffic skills, and thus have good face validity. However, their true external validity is not known; but this is true for all such tests ranging from laboratory investigations to the road driving trials. Nevertheless, when several different methods produce similar findings this strengthens the hypothesis.

Researchers in other countries have also found that most field tests are poor at detecting THC impairment [37]. It has been suggested to add extra observations, such as head jerks, to increase the sensitivity of tests such as the SFST to the impairing effects of THC [8]. The present investigation shows that, even when including an extensive number of tests and observations, THC impairment is difficult to detect. Conversely, we required the presence of a drug concentration–effect relationship to indicate a causal relationship. This might have been a very stringent criterion, and one reason for the many negative findings. A second reason may be low sensitivity of the CTI. In conclusion, the Norwegian CTI did not offer sensitive tests or observations that revealed THC impairment reliably, thus differing quite substantially from alcohol [36].

The exception was, to some extent, symptoms of the eyes. Conjunctiva injection was seen more often in suspects with increasing blood THC concentrations, and significantly more often above 2.9 ng/ml. There is evidence of cannabinoid receptors at different sites in the eyes (corneal epithelium, anterior eye and retina), and the observed reddening of the eye may be due to vasodilatation [38]. Although not observed regularly at low concentrations in the present study, injection can be present even at low blood THC concentrations [39].

There is more controversy about pupil diameter. Some groups have reported miosis [40,41], others no change in papillary size [42] and still others report dilated pupils [43,44]. We observed an increase in the number of suspects with dilated pupils at blood THC concentrations above 2.9 ng/ml. There was no relationship with blood THC concentrations for small pupil sizes. Nevertheless, even in the highest concentration ranges, no more than 35% of the suspects showed this symptom. Pupillary reaction to light is slow when the subject is under the influence of cannabis, especially during the first couple of hours after consumption [42].

The major strength of our study is that it is a real-life study, involving higher concentrations of THC in the blood than can be obtained in experimental studies due to ethical and medical considerations. Also, the suspects are most often experienced drug users [45], people missed in other investigations. However, the study has some limitations. It is an observational study with a risk of selection bias. We know from previous studies in Norway that apprehended drivers, suspected of driving under the influence of non-alcoholic drugs, often use multiple illegal substances [46], are frequently re-arrested for a similar offence [47] and have high mortality [48]. All these factors point to a marginalized group with a high problem load. To use a drug-free group as comparison [18] is not without problems. First, these drivers may not have the same stigmas of marginalization as the drug-positive drivers. Secondly, we may wonder why these drivers have attracted the attention of the police enough to be stopped, interviewed and be sent to the police physician for examination, when drug-negative. One

explanation could be that they were excessively tired or ill in some way, thus being impaired for other reasons. We therefore opted to include a group of alcohol-impaired drivers and observe how increasing THC concentrations added to this impairment. This may have reduced the selection bias, but we do not know how well this alcohol-impaired group really compares to the THC-positive group. However, the THC–ethanol-positive group will probably be more comparable to both the THC-positive and the ethanol-positive groups.

The CTI is easy to perform, requires few aids, is based on medical 'common sense' and over many years has been established as a reasonable method of judging impairment in drivers [36,49]. All these factors could contribute to a relatively high test reliability. However, numerous physicians perform this test under varying conditions with different degrees of motivation. The reliability of a test is not checked afterwards, and doctors may also have very variable amounts of experience in using CTI. Most doctors perform only a few tests per year, and none of the suspected drivers were examined by more than one physician. All these factors would, however, contribute to a lower reliability of CTI. Such a reliability problem would obscure the concentration–effect relationship in the present study and our figures would be distorted towards the null, thus leading to an underestimation of the observed effect.

Declarations of interest

None.

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