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Research Article

Marijuana and alcohol increase crash avoidance reaction time in a driving simulator test at blood concentrations below commonly-used per se 'Cut-offs' for Intoxication

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Abstract

The present study demonstrates marijuana- and alcohol-induced impairment of a driving-relevant measure in a driving simulator task at (estimated) blood alcohol and THC concentrations that are below the per se cut-off for impaired driving in several states. The subject was an adult male with a history of occasional alcohol use (2-3 times/week for the past 6 months) and past but very infrequent use of marijuana, i.e., less than once/month for the past 6 months. The testing procedure was a crash avoidance test using a fixed base driving simulator. In this procedure, while driving at 55 mph, the subject was required to make an 'emergency' steering maneuver to avoid crashing into a 'stalled car' that appeared on the roadway immediately (40 meters) ahead. In the absence of any drug treatment, after training the subject effectively made this avoidance maneuver in >98% of trials (20 trials/session), with a crash avoidance response latency of approximately 450-475 msec from the onset of the car ahead until an abrupt crash avoidance steering response of >10 degrees. On two test days separated by 14 days, the subject was tested for crash avoidance reaction time following oral alcohol (beer consumption) use and, on another occasion, following oral marijuana use (approximately 10 mg in a 'candy'). The testing involved a pre-drug test and several post-treatment tests, and one final post-treatment test 24 hours later. On both test days, blood samples were collected at various times after drug administration and throughout behavioral testing. Both alcohol and marijuana treatment significantly increased crash avoidance reaction time (from approximately 475 msec to > 550 msec). Plasma alcohol concentrations of 42 mg/dl, 79 mg/dl and up to 99 mg/dl (corresponding to BAC values of 39, 67 and 86 mg/dl, respectively) were associated with alcohol impaired driving over the time period from 45 minutes to 175 minutes after the onset of drinking. On the marijuana test day, plasma concentrations of THC were 4.7 and 2.4 ng/ml (corresponding to blood THC concentrations of 2.9 and 1.5 ng/ml, respectively) at times when significant impairment of driving was observed. This is the first study to demonstrate dramatic driving simulator performance impairment at a THC blood concentration less than 3 ng/ml, which is the below the 5 ng/ml cut-off for marijuana-impaired driving in several states (e.g., Washington, Colorado). These data further suggest that the crash avoidance reaction task might be useful in further studies on the effects of marijuana, alcohol and other drugs (prescription, non-prescription and also drugs of abuse) on driving performance.

Introduction

Alcohol use and alcohol-impaired driving continues to be a significant problem. In 2017, crashes involving drunk drivers claimed nearly 11,000 lives in the US, with fatalities occurring on average every 48 minutes [1]. Most states use a Blood Alcohol Concentration (BAC) of 80 mg/dl as the per se cut-off for drunk driving. By contrast, the state of Utah

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recently moved to a 50mg/dl cut-off for drunk driving [2]; this value is in agreement with many other countries in the world, where the drunk driving cut-off also has been lowered to 50 mg/dl within the past 20 years [3]. The move to reduce the BAC cut-off for drunk driving is in part the result of research demonstrating a significant crash risk with BAC levels 50 mg/dl. NHTSA has advocated for reducing the BAC cut-off from 80 mg/dl to 50mg/dl across the US [4].

Marijuana continues to be the most commonly used illicit drug in the USA, with over 20 million people in the US reporting that they used marijuana within the past month [5]. With medical and legal marijuana continuing to be approved in many states, the frequency of use is likely to increase further [6]. Bonar recently reported that more than 50% of medical marijuana patients in the state of Michigan admitted to driving within one hour of use, and nearly 20% reported driving while high [7]. It has been reported that legalization of cannabis is associated with increased reports of cannabis-related crash fatalities [8], although other studies have reported no significant change as a consequence of legalization [9]. Similarly, reports on the effects of marijuana on driving in general are somewhat inconsistent [10]. Conducted a meta-analysis and reported that the risk of being involved in a crash significantly increased after marijuana use. Marijuana also has been shown to impair driving simulator performance [11,12]. In contrast, a large case-control study conducted by the National Highway Traffic Safety Administration found no significant increased crash risk attributable to cannabis after controlling for drivers' age, gender, race, and presence of alcohol [13].

Compared to alcohol, there is less consensus regarding the establishment of a legal cut-off for marijuana-impaired driving. In states where marijuana is not legal for medical or recreational use, any amount of marijuana in the blood is deemed illegal.. In those states where marijuana is legal for medical or recreational use, different states use different cut-offs: 1, 2, or 5 ng/ml; some states with recreational and/or medical marijuana have no 'cut-off' concentration [14].

The wide variability between states regarding the identification of a blood THC concentration for driving impairment, and the fact that some states have opted NOT to have a THC cut-off, relates to some of the challenges/problems of identifying the relationship between blood concentrations and effects of THC. This problem relates at least in part to the complicated pharmacokinetics of THC in the blood. THC exhibits biphasic pharmacokinetics. After reaching a peak (125-150 ng/ml) within minutes of inhalation, THC concentrations decline rapidly to approximately 10-20 ng/ml within 60-90 minutes (mostly via redistribution), followed by a much slower elimination phase, with a half-life of approximately 24 hours [15-17]. In addition, THC is sequestered in body fat and there is the potential for redistribution from fat back to the bloodstream [18]. The pharmacokinetics of orally administered THC are significantly different from smoked marijuana, with a much lower peak concentration (5-10 ng/ml for 20 mg oral) and a later onset to peak concentration of 1-2 hours [16,17,19]. Another factor which complicates the issue of establishing a cut-off for THC concentrations and driving impairment is the potential contribution of 11-OH THC, an active metabolite of THC [20]. All of these issued complicate significantly the question of establishing a legal cut-off for THC-impaired driving.

Moderate to heavy use of regular marijuana is likely to be associated with significant tolerance [21,22]. Because marijuana possession and use has been an illegal activity until only recently in the US, the vast majority of laboratory studies examining the effects of marijuana have been conducted in subjects with a history of moderate to heavy use, often without a drug-naïve reference control group. Thus, there is a paucity of laboratory studies on the effects of marijuana on driving behavior in non-users or even in subjects with very limited experience with marijuana.

On November 6, 2018 citizens in the state of Michigan voted to enact Michigan Regulation and Taxation of Marijuana Act (MRTMA), which would legalize and tax the sale for marijuana to adults >21 years old. Effective December 6, 2018 the possession and use of limited quantities of marijuana were no longer illegal for residents >21 years old. Passage of this law created an opportunity to study the effects of marijuana on driving simulator behavior in a subject that did not have a history of significant marijuana use.

We describe herein a driving simulator task that measures a defensive driving behavior in response to a surprise event, i.e., swerving to avoid an imminent crash. We further report the results of an open label study on the effects of marijuana on driving simulator performance in a subject with a known history of very limited marijuana use. For reference purposes, the study also included driving simulator assessments following a challenge with alcohol. We believe this is the first-ever study of the effects of marijuana on driving simulator performance in a subject with a life history of virtually no marijuana use (< 10 lifetime uses) and absolutely no history of driving following marijuana use. We report the effects of alcohol and marijuana on this crash avoidance reaction time response, and we provide data comparing blood alcohol concentrations (BACs), THC and metabolite concentrations with driving simulator performance.

Methods

Subject

An adult male subject with a history of very limited marijuana use (fewer than 10 lifetime exposures; none in the 8 weeks prior to testing) and occasional alcohol use (less than 3 occasions/week and less than 3 drinks/occasion for the past 12 months); the subject has never had a DUI or DUID; the subject was not taking any CNS active drugs (legal or illegal) at the time of the study; the subject was experienced (more than 10 driving experiences) with the driving simulator in general and the crash avoidance procedure (more than 4 driving experiences). This study was approved by the Wayne State University Internal Review Board (WSU IRB #066716B3E).

Apparatus and crash avoidance testing procedure

The studies were conducted using a fixed-base driving

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simulator (2001 Chevrolet) using Hyperdrive Hardware and DriveSafety software. For each test session, the subject drove 55 mph in the middle lane of a 3-lane roadway with no ambient traffic and was presented with 20 crash avoidance trials with a variable distance between the trials (shortest: 300 meters; longest: 600 meters). Each crash avoidance trial consisted of a 'stalled car' appearing on the screen 40 meters ahead of the driver; pilot studies examining a range of 'car-ahead' distances (30-60 meters) revealed that a 40-meter distance was far enough ahead for a sober and minimally-trained subject/driver to successfully avoid a crash in > 98% of the trials, but was close enough that even the most experienced driver would not have any (spare) time to 'wait' before initiating an avoidance maneuver. Driving speed was 55 mph because pilot studies also had revealed that a driving speed of <45 mph allowed drivers to 'wait' before reacting (increasing reaction time values on control trials), whereas a driving speed of >65 mph resulted in a dramatic increase in the frequency of car crashes and loss of control of the vehicle on the roadway, but with no change in reaction time. For the various trials, the 'stalled car' appeared at different relative positions in the lane ahead of the simulator; when the 'stalled car' appeared on the right edge of the driver's lane, the instruction was to swerve to the left to avoid a crash; when the 'stalled car' appeared on the left edge, the instruction was to swerve to the right. These opposite reactions were obvious and natural, but they were necessary to prevent a driver from 'cheating' by drifting away from the middle of the lane in advance of the 'stalled car'. There also were trials where the 'stalled car' appeared in the middle of the lane; in this situation, the driver was instructed to swerve to the right or left, depending on their preference. The subject did not know the position of the upcoming 'stalled car' on the various trials.

The subject was instructed to keep his eyes on the roadway and not on the speedometer, with driving speed advice/coaching (slow down a little; speed up a bit) provided by a laboratory team member so the driver would not check the speedometer to maintain driving speed. For each test session, videotaping of the 'roadway' and the driver's face were used to create synchronized picture-in-picture videos, which were viewed by an observer who was unaware of the treatment condition and scored each trial by assessing whether the driver's eyes were or were not on the roadway at the moment when the 'stalled car' first appeared.

Drug Treatment and Testing Procedures

On two occasions separated by 14 days, the subject was tested before and after the administration of either oral marijuana (approximately 10 mg in an oral 'candy') or alcohol (6 bottles of beer; Blue Moon^{R}, 12 ounces; 5.4% ethanol; consumed in two rapid drinking bouts of 3 beers in 15 minutes). Each drug challenge day consisted of a pre-drug test and multiple post-drug tests (20 crash avoidance trials). Following the pre-drug test, the subject left the laboratory area, administered the treatment, and returned for the post-drug crash avoidance tests. Each experiment concluded with a 24 hr post-treatment test.

On the marijuana and alcohol challenge days, blood samples were obtained 10-15 minutes after completion of selected crash avoidance tests. Fresh blood samples were centrifuged (3500 rpm for 10 minutes) and the plasma was decanted off and stored frozen at -20°C until analysis within 60 days of sample collection. Frozen samples were packaged in dry ice and shipped to NMS Laboratories (Grove City, PA). Concentrations of Ethanol, THC and THC metabolites in plasma are stable when samples are stored at -20 degrees Centigrade for up to 12 months [23]. THC analysis included quantification of THC and its metabolites 11-OH-THC and THC-COOH; ethanol analysis was for ethanol only. The reporting limits for quantitation of THC, 11-OH-THC and THC-COOH were 0.5, 1 and 5 ng/ml, respectively; the reporting limit for quantitation of ethanol was 10 mg/dl. Estimates of whole blood concentrations of ethanol were calculated by multiplying the plasma concentration by a factor 1.18 [24]. Estimates of whole blood THC, 11-OH-THC and THC-COOH were calculated by multiplying the respective plasma concentration by a factor of 1.6 [25].

Beer goggles control experiment

In a separate experiment, the subject performed two separate crash avoidance tests in a 'no drug' condition, once while wearing 'beer goggles' and on a subsequent occasion while wearing standard laboratory safety goggles. The beer goggles were reported by their manufacturer (Fatal Vision^{R}; Innocorp; Verona, WI) to produce a visual disruption similar to a high BAC (170-200 mg/dl). Palumbo, et al. [26] have reported that beer goggles potentiate the disruptive effects of texting on driving behavior (lateral control) in a driving simulator. Although beer goggles cause significant visual distortion, they have no psychoactive component that would increase reaction time. The 'beer goggles' experiment therefore tested the hypothesis that the effects produced by marijuana or alcohol on reaction time were not simply the result of changes in visual perception.

Independent Variables, Dependent Variables and Statistical Analyses: Separate statistical analyses were conducted for each drug test. The independent variable in each analysis was the time after drug treatment. The dependent variable was the crash avoidance reaction time; this value was defined as the time from the appearance of the 'stalled car' until the time at which the driver made a significant steering maneuver (swerve) to avoid a crash; because small steering movements (5 degrees to -5 degrees) are a regular part of driving even on a straight roadway, a 'significant crash avoidance steering maneuver' was defined as the first steering measurement with an absolute value of >10 degrees. Crash avoidance reaction times (in msec) were compared at various times Pre- and Post-treatment via Analysis of Variance (ANOVA); post hoc comparisons were conducted using the Student Neuman Keuls (SNK) test. Because the driving simulator samples and records car data outputs at a rate of 60 samples/second (60 cps computer speed), this measure of reaction time had a resolution of 16.67 msec (1/60th of a second). A trained and blinded observer (blinded regarding treatment condition) viewed picture-in-picture video of all crash avoidance trials to determine whether the subject was

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looking at the roadway at the moment the stalled car appeared. Data from crash avoidance trials were excluded from statistical analysis if this review revealed that the driver was not looking at the roadway (e.g., speedometer check) at the moment when the 'stalled car' appeared. Overall, approximately 5% of the trials were excluded for this reason. The criterion for statistical significance was $p<0.05$ in all analyses.

Results

Marijuana effects

Marijuana 'Pre-treatment' driving data was unobtainable due to a computer error. However, both 'Pre-treatment' and '24 hour Post-treatment' values measured in the alcohol study (see below) were comparable to '24 hr Post-treatment' of the marijuana study; therefore, the '24 hr Post-treatment' measure was used as the primary point of reference for statistical comparison. Figure 1 illustrates that marijuana significantly increased crash avoidance reaction times ($F[6,105]=6.93$, $p<0.001$). Post hoc Student Neuman Keuls (SNK) analysis revealed significant increases in reaction times at 120, 150 and 180 minutes when compared to the 24-hour 'post-treatment' test.

Not including the 24-hour post treatment THC blood value of zero, estimated THC blood concentrations ranged from 1.5 ng/ml to 2.9 ng/ml throughout the study. 11-OH THC estimated blood concentrations were slightly higher than parent THC at the various time points, and estimated blood THC-COOH concentrations were 5-10 times higher than THC, and it was present in measureable quantities before either THC or 11-OH-THC. The significant increase in crash avoidance reaction time was observed during the time interval 120-180 minutes post ingestion when THC blood concentrations were estimated to be 2.9 ng/ml and 1.5 ng/ml respectively, and 11-OH-THC concentrations were estimated to be 3.1 ng/ml and 2.1 ng/ml, respectively, with subject reports of feeling 'high' (10/10). In contrast to the alcohol challenge (see below), there was no incidence of yawning observed throughout any test sessions for the marijuana experiment.

Alcohol effects

Figure 2 illustrates that alcohol significantly increased crash avoidance reaction times ($F[7,118]=15.92$, $p<0.001$); post hoc Student Neuman Keuls (SNK) analysis revealed significant increases in reaction times at 60, 90, 120 and 150 minutes when compared to both 'pre' and 'post-treatment' tests.

Not including the pre-treatment and 24-hour post treatment BAC values of zero, estimated BAC values ranged from 39-86 mg/dl throughout the study. The significant increase in crash avoidance reaction time observed at 60 minutes occurred as BAC increased from 39 mg/dl (45 min) to 67 mg/dl (75 min), i.e., below the legal BAC cut-off of 80 mg/dl. Crash avoidance performance continued to be impaired as BAC increased to 84 mg/dl (125 min) and further to 86 mg/dl (165 min).

The subject reported feeling 'significantly inebriated' during the period 90-150 minutes after the pre-test (0 minutes); this corresponded with observations of yawning (2-8x/session) during the test drives at 90-180 minutes.

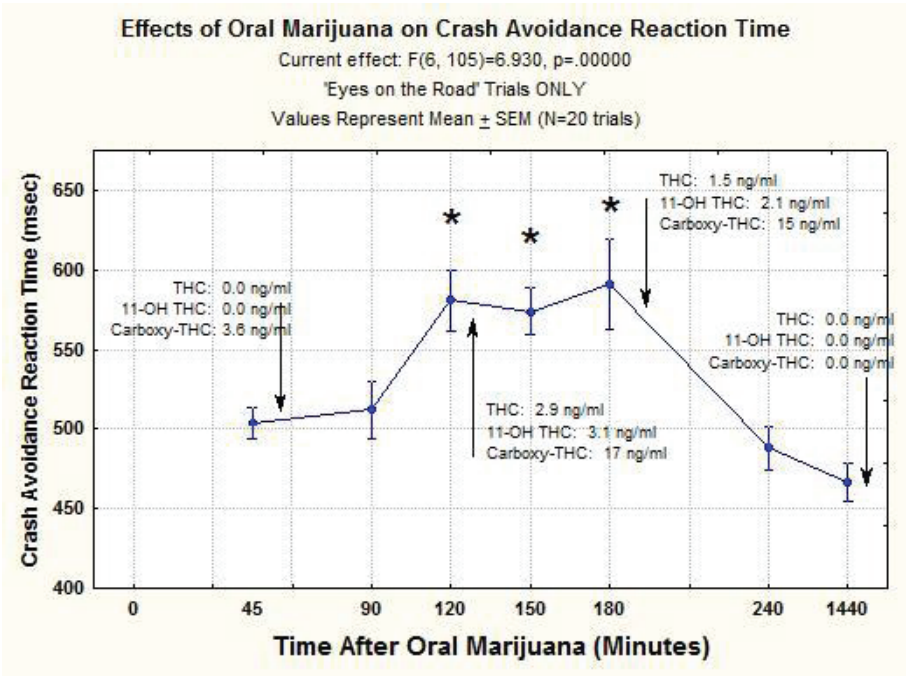

Figure 1: Plotted are the Mean + SEM (n=18-20 trials) Crash Avoidance Reaction Times (in msec) at various times after oral administration of marijuana (approximately 10 mg 'candy'). Vertical arrows indicate the times at which blood samples were collected and the blood concentrations of THC and its metabolites determined in that sample. Concentrations of THC, 11-OH THC and THC-COOH were measured in plasma, and blood concentrations were estimated using the correction factor of 1.6 ([blood] = [plasma]/1.6; Giroud et al., 2001).

* - Crash avoidance reaction time at the indicated test was significantly different from Post-test (1440 hr) values, ANOVA followed by post hoc Student Newman Keuls test.

0.00 ng/ml = Not Detectable (ND); Reporting Limits for THC, 11-OH THC and THC-COOH were 0.5 ng/ml, 1.0 ng/ml and 5 ng/ml, respectively.

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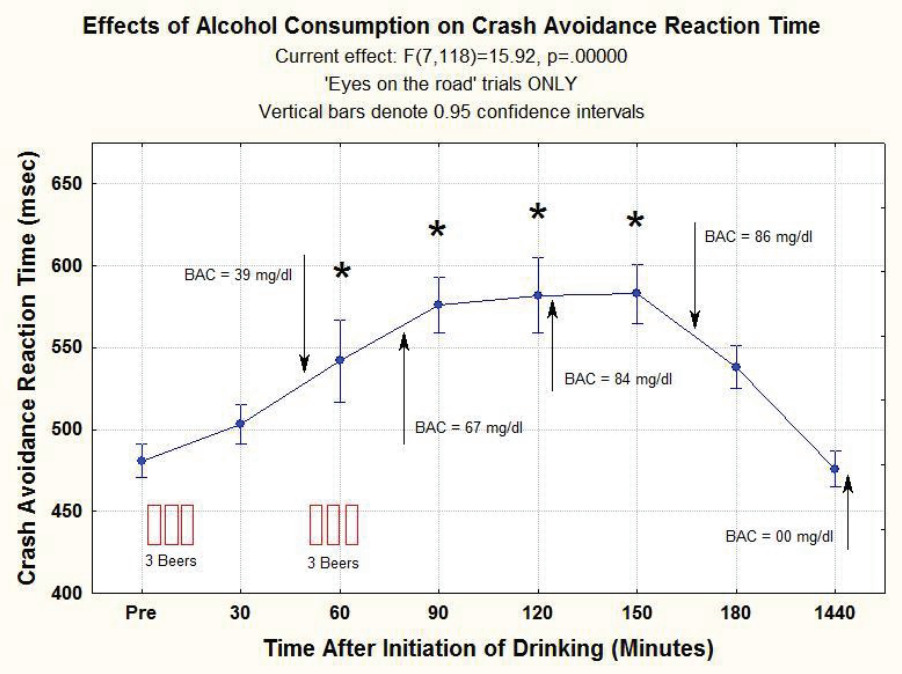

Figure 2: Plotted are the Mean + SEM (n=18-20 trials) Crash Avoidance Reaction Times (in msec) before (Pre) and at various times after consumption of alcohol. Alcohol was administered in two 'doses' of 3 beers each over a 15-minute period; one dose was administered immediately after the Pre-test, and the second dose was administered at approximately 50 minutes after the Pre-test. Vertical arrows indicate the times at which blood samples were collected. Ethanol concentrations were measured in plasma, and blood ethanol concentrations were estimated using the correction factor of 1.16 ([blood] = [plasma]/1.16; Payne et al., 1968).
* - Crash avoidance reaction time at the indicated test was significantly different from Pre-test and Post-test (1440 hr) values, ANOVA followed by post hoc Student Newman Keuls test;
BAC = 0.00 mg/dl = Not Detectable; Reporting Limit = 10 mg/dl

Beer goggles study

Beer goggles dramatically impaired visual perception in the subject as judged by extreme difficulty walking a straight line or catching a thrown ball. Conversely, wearing beer goggles did not affect crash avoidance reaction time in the driving simulator test. There was no difference in the mean avoidance reaction time between clear laboratory goggles ('control'; 466 +12 msec (Mean +SEM)), and beer goggles [464 +9 msec] ($F[1,34]<1.0$, ns).

Discussion

In an experienced driver with a history of occasional alcohol use and very infrequent marijuana use, consumption of each drug significantly increased crash avoidance reaction times. Conversely, wearing 'beer goggles' dramatically affected visual performance tasks (walk a straight line; catch a ball), but did not affect crash avoidance reaction time. These data suggest that the crash-avoidance reaction time procedure described above using a fixed-base driving simulator is a reliable and sensitive tool for studying the effects of alcohol, marijuana and perhaps other drugs (prescription, non-prescription and illegal) on reaction time in a defensive driving performance task. Future work with laptop, gaming chair or even virtual reality applications might allow for more widespread applications of this crash avoidance task for the study of drugs on this important defensive driving maneuver.

Significant impairment of crash avoidance behavior was observed during the driving test at 60 minutes post-alcohol, where the BAC (estimated from plasma) ranged from 39 mg/dl shortly before testing to 67 mg/dl shortly afterward. This finding is consistent with the argument for decreasing the legal BAC in the US from 80 mg/dl to 50 mg/dl [4], a move which has already been undertaken by many countries [14].

There is less clarity regarding a cut-off value for marijuana impaired driving for many reasons. In the present study, significant impairment as exhibited by increased crash avoidance reaction time was observed when the whole blood THC concentrations (estimated from plasma) were 2.9 ng/ml (125 minutes) and 1.5 ng/ml (190 minutes). These values are significantly lower than the effect-based threshold values of 13.1 ng/ml (to mimic 80 mg/dl EtOH) and 8.2 ng/ml (to mimic 50 mg/dl EtOH) as reported by Hartmann, et al. [11] in a driving simulator study. There are several possible reasons for this difference. First, the primary measure in the Hartman, et al. [11] study was maintaining lane control as measured by standard deviation of lane position (SDLP), which might be less sensitive to the effects of marijuana when compared to crash avoidance. Second, it is possible that THC tolerance is responsible for the difference. The subject in the present study was a very infrequent user, virtually a novice, whereas in the Hartman, et al. [11] study the subject histories ranged from occasional use (<1x/mo) to relatively frequent use (2-3 x/wk). Chronic marijuana use produces significant tolerance for a number of effects [21,22]. Consistent with this idea, preliminary results from studies in medical marijuana patients

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(virtually all of whom are chronic marijuana users) suggest that they are indeed less affected by marijuana administration when compared to the subject in the present study (Alali et al., in preparation). Finally, the route of administration and associated pharmacokinetics in the two studies - oral in the present study and smoked in the Hartmann, et al. [11] study- might account for the differences observed in the effect-based threshold value [11,17,19]. All of the above point to the challenge of identifying a single cut-off value for marijuana-induced driving impairment.

Consistent with previous reports, plasma concentrations of the inactive THC metabolite (THC-COOH) were consistently higher than concentrations of the parent THC compound, and were measurable before THC parent concentrations were measureable [27]. It should also be noted that 11-OH-THC concentrations closely paralleled those of the parent THC; this is consistent with previous reports following oral THC administration [16,17,19]. Given the significant biological activity of 11-OH-THC [20], these findings suggest that measurements of this metabolite might also need to be considered when discussing a possible per se 'cut-off' for marijuana-intoxicated driving.

In summary, the results of the present studies suggest that the crash-avoidance reaction time procedure described above is a robust, reliable and sensitive tool for studying the effects of, and possible tolerance to, marijuana, alcohol and other drugs (prescription, non-prescription and illegal) on defensive driving performance.

Limitations of the present study

The present study used an open label design with a single subject; however, the present findings are robust and statistically reliable. The crash avoidance reaction test procedure exhibits high test-retest reliability within subjects and is therefore suitable for multiple tests with different treatments, thus making longitudinal studies in a single subject highly valuable. The present study was conducted in a driving simulator and not on a real road under real driving conditions; however, driving simulator studies have been shown to be a very safe and effective tool for studying, understanding and predicting future real world driving experiences. Finally, there was not much 'open driving' in the study to examine for possible differential effects of the various drugs on driving behavior (e.g., lateral control, speed, aggression, risk-taking); however, the degree of simplicity and standardization used in the present study was important for the purpose of obtaining multiple crash avoidance reaction trials.

Declarations

Ethics approval and consent to participate: The study was conducted under Wayne State University (WSU) Internal Review Board (IRB) Approval #066716B3E; the subject provided written informed consent.

Availability of data and materials: The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Authors, Alali, Taneja, Malone, Mohammed, D Head and Commissaris participated in the research design. Authors Alali, J Stewart, Nwobi, Murdock, M Stewart and McQueen participated in the research conduct, under oversight from Author Commissaris. Authors Alali, Nwobi, Murdock, T Head, Malone and Mohammed participated in data analysis, under the guidance of Author Commissaris. Author Alali wrote the initial draft of the manuscript, Authors J Stewart, D Head and Commissaris contributed substantially to the draft revision process, and all authors contributed to the final version.

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