



News Release

University of Colorado Denver | Anschutz Medical Campus

For Immediate ReleaseContact: David Kelly, 303-315-6374, david.kelly@ucdenver.edu**New drugged driving laws have little or no impact on traffic deaths***All 50 states urged to adopt such laws*

DENVER (Jan. 14, 2013) –A new study by economists at the [University of Colorado Denver](#) and Montana State University reveals that so-called “per se” drugged driving laws have no discernible impact on traffic fatalities.

Per se laws set thresholds for controlled substances above which drivers are considered impaired.

Since 1990, 11 states have passed zero-tolerance drugged driving laws making it illegal to drive with detectable levels of a controlled substance in the system. Five other states have passed similar laws specifying nonzero limits for controlled substances or their metabolites..

“These laws are intended to make the job of prosecuting drugged drivers easier,” said Daniel Rees, professor of economics at the [University of Colorado Denver](#) who co-authored the study with D. Mark Anderson, assistant professor of economics at [Montana State University](#). “In states without these laws, prosecutors must rely on field sobriety tests or evidence that a motorist was driving erratically in order to prove impairment.”

The Office of National Drug Control Policy (ONDCP) recently announced a goal of reducing drugged driving by 10 percent within three years. In an effort to achieve this goal, the ONDCP is encouraging all 50 states to prohibit driving with detectable levels of a controlled substance in the system.

Although there is anecdotal evidence that the new drugged driving laws make prosecution easier, this is the first study to examine their effectiveness.

Using state-level data from the Fatality Analysis Reporting System (FARS) for the period 1990-2010, Anderson and Rees examined the relationship between adopting controlled substance thresholds for drivers and traffic fatalities. They found that the relationship is statistically indistinguishable from zero and concluded that there is no evidence that these limits reduced traffic deaths.

“Our study is particularly timely given that Washington voters recently passed Initiative 502, which legalized the recreational use of marijuana but prohibited driving with THC levels equal to, or greater than, 5 nanograms per milliliter of blood,” Anderson said. “Setting a THC standard for drivers may, in the future, be viewed by voters as a necessary complement to legalizing marijuana for recreational or medicinal use.”

The FARS data represent a census of all fatal injuries resulting from motor vehicle accidents in the United States and include information on when the accident took place. Using this data, Anderson and Rees distinguished between nighttime and daytime traffic fatalities. They also distinguished between weekend and weekday traffic deaths.

Although the percentage of drivers testing positive for marijuana and other controlled substances is highest during the night and on weekends, they found no evidence that these laws, which have been adopted by 16 states, led to a reduction in traffic fatalities at either time.

“There is strong evidence that drivers under the influence of marijuana have slower reaction times than drivers who are not under the influence of marijuana,” Rees said. “As currently implemented, these laws have no discernible impact on traffic fatalities.”

The study, which is under review, is available as an IZA working paper at: http://www.iza.org/en/webcontent/personnel/photos/index_html?key=4915. IZA is a private, independent research institute. For more information about IZA see: <http://www.iza.org/en/webcontent/about/index>

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Setting thresholds for controlled substances above which drivers are automatically considered impaired has no discernible impact on traffic deaths.

All 50 states urged to adopt them

DENVER (Jan. 14, 2013) –A new study by economists at the [University of Colorado Denver](#) and Montana State University reveals that so-called “per se” drugged driving laws have no discernible impact on traffic fatalities.

As of now, 11 states have passed zero-tolerance drugged driving laws making it illegal to drive with detectable levels of a controlled substance in the system. Five other states have passed similar laws specifying nonzero thresholds for controlled substances or their metabolites above which drivers are automatically considered impaired.

“These laws are intended to make the job of prosecuting drugged drivers easier,” said Daniel Rees, professor of economics at the [University of Colorado Denver](#) who co-authored the study with D. Mark Anderson, assistant professor of economics at [Montana State University](#). “In states without such laws, prosecutors must rely on field sobriety tests or evidence that a motorist was driving erratically in order to prove impairment.”

The Office of National Drug Control Policy (ONDCP) recently announced a goal of reducing drugged driving by 10 percent within three years. In an effort to achieve this goal, the ONDCP is encouraging all 50 states to adopt thresholds for controlled substances above which drivers are automatically considered impaired. Although there is anecdotal evidence suggesting that adopting these thresholds make drugged driving easier to prosecute, this is the first study to examine their effectiveness.

Using state-level data from the Fatality Analysis Reporting System (FARS) for the period 1990-2010, Anderson and Rees examined the relationship between adopting per se standards and traffic fatalities. They found that the relationship is statistically indistinguishable from zero and concluded that there is no evidence that adopting these standards reduces traffic deaths.

“Our study is particularly timely given that Washington voters recently passed Initiative 502, which legalized the recreational use of marijuana but prohibited driving with THC levels equal to, or greater than, 5 nanograms per milliliter of blood,” Anderson said. “Setting a threshold for THC above which the driver is automatically considered impaired may, in the future, be viewed by voters as a necessary complement to legalizing marijuana for recreational or medicinal use.”

The FARS data represent a census of all fatal injuries resulting from motor vehicle accidents in the United States and include information on when the accident took place. Using this information, Anderson and Rees distinguished between traffic

fatalities that occurred at night and those during the day. They also distinguished between traffic deaths that happened during the week and those that occurred from Friday night through Monday morning.

Although the percentage of drivers testing positive for marijuana and other controlled substances is highest at night and on weekends, they found no evidence that adopting thresholds for controlled substances above which drivers are automatically considered impaired led to reductions in traffic fatalities during these times.

“There is strong evidence that drivers under the influence of marijuana have slower reaction times than drivers who are not under the influence of marijuana,” Rees said. “As currently implemented, these laws have no discernible impact on traffic fatalities.”

The study, which is under review, is available as an IZA working paper at: http://www.iza.org/en/webcontent/personnel/photos/index_html?key=4915. IZA is a private, independent research institute. For more information about IZA see: <http://www.iza.org/en/webcontent/about/index>

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Memorandum

TO: Drug Policy Task Force

FROM: Marijuana DUID Working Group

DATE: September 6, 2011

The working group met seven times from June through August 2011 to carefully discuss existing research and to hear testimony from 8 experts (see attached summaries). At the working group meeting on August 31, 2011, the members decided to inform the Drug Policy Task Force of the complex issues associated with setting a *per se* limit for active THC-blood levels. While there are many areas of agreement which will result in recommendations to the Task Force, the group was unable to come to consensus regarding a *per se* limit. The reasons for the lack of consensus are both scientific and pragmatic, and are summarized below.

- High levels of active THC may remain in the blood long after use, perhaps up to 24 hours, whereas driving impairment that would negatively affect driving occurs closer to the time the THC was consumed.
- Whereas BAC (Blood Alcohol Content) can be accurately measured and correlated with driving impairment, this is more difficult with cannabis.
 - Alcohol is water soluble; cannabis is stored in the fat and is metabolized differently, making a direct correlation with behavior difficult to measure.
 - One expert equated 2 ng/ml of active THC to .05 BAC and 5 ng/ml of active THC to .08 BAC.
 - Blood tests are not readily available to law enforcement officers at traffic stops; as time passes the THC levels will decline.
- Research is currently underway in California and The Netherlands that will likely improve our understanding of nanogram levels of THC and behavioral impairment.
- The experts agree that chronic use, such as that by medical marijuana patients, can lead to drug tolerance but impairment may still be present when chronic users consume THC and drive.
- While the science is clear that use of cannabis leads to immediate behavioral impairment which can negatively affect driving, there is a lack of consensus among the experts about the duration of impairment (approximately 2-4 hours for smoking, 8 hours for edibles).
- Discussions by the experts of the *per se* limit related to driving impairment ranged from 1-2 ng/ml to 15 ng/ml.
 - A low threshold may include individuals whose driving ability was not impaired because consumption occurred many hours prior to the blood test.
 - A low threshold may not necessarily imply driving impairment, especially for chronic users.
 - A high threshold may make prosecution for nanogram levels below the designated number very difficult, possibly resulting in dismissed cases.
 - The proportion of drivers, especially chronic users, whose behavior may not be impaired while testing positive at, for example, 5 ng/ml is unknown.
- Administrative sanctions (such as revocation of a driver's license) for impaired driving due to active THC in the blood are a critical ingredient to a successful *per se* law but will require that a fiscal note be attached to proposed legislation.
- Additional non-scientific concerns were identified by members of the working group:
 - Prosecutors want a *per se* limit to use in court and with juries, however, this "system efficiency" requires scientific consensus across many studies and experts, and such consensus remains

debatable; the state toxicologist lab director told the Working Group that 15 out of 16 cannabis cases where she testified were successfully prosecuted. State Judicial reports that 90% of marijuana-related driving filings resulted in a conviction.

- The Department of Transportation reports the following number of drivers involved in fatal vehicle accidents tested positive for marijuana:
 - 2006---21
 - 2007---33
 - 2008—31
 - 2009—37
 - 2010—32
- Some members question if the current system is broken and if a *per se* limit might result in both unintended and intended consequences:
 - Establishing *per se* levels may communicate to the public that it is permissible to drive after the consumption of small amounts of cannabis.
 - Does establishing a *per se* law encourage what is illegal behavior by Federal law?
 - Not having a *per se* level might undermine the public education campaign (“the jury didn’t convict me”).
 - Having a *per se* law sends a message that driving while impaired will not be tolerated.
 - Since the scientific community lacks complete consensus, establishing a *per se* limit that affects individuals who are competent to drive while testing positive for THC might undermine confidence in the justice system and lead to contempt for the law.
- The Federal government may link highway funding to establishing a *per se* limit for the consumption of cannabis.

RECAP

Drug Policy Task Force – Marijuana *Per Se* (DUID) Working Group/Meetings

Working Group Members

- Grayson Robinson, Arapahoe County Sheriff
- Sean McAllister, Private Defense Attorney
- Christine Flavia, Division of Behavioral Health
- Heather Garwood, Colo. Judicial Department
- Rod Walker, Colo. Springs Police Department
- Laura Spicer, Drug Addictions Counselor
- Mike Elliott, Medical Marijuana Industry Group
- Mark Hurlbert, DA, 5th Judicial District

EXPERT TESTIMONY	SUMMARY POSITION
Paul Armentano, NORML Dep Director	Measurement problem Need better development of cannabis DUI tests
Cindy Burbach, State Toxicology Lab Director	No measurement problem tolerance/1-2 nanogram limit
Dr. Carl Hart, Columbia University	Measurement problem Nanogram information is not sufficient to determine cognitive functioning
Glenn Davis/CDOT, Manager of Impaired Driving Programs, DRE (Drug Recognition Evaluator) Coordinator	(Measurement problem not applicable) By the end of 2011 there will be 200 DREs in the state; need 250-300 for rural/frontier parts of the state
Dr. Jan Ramaekers, Behavioral Toxicology of Medicinal Drugs and Drugs of Abuse, Maastricht University, The Netherlands	No measurement problem --Cannabis in the blood can be measured and is correlated with driving impairment --THC at 2ng/ml is equivalent to .05 BAC; 5ng/ml=.08 BAC --Two thresholds for driving impairment would not distinguish between the amount of THC actually consumed
Alan Shackelford, Amarimed of Colorado (written letter)	Measurement problem --Little correlation between any given blood level of THC or THC metabolites and impaired driving --An arbitrarily determined limit would therefore adversely affect patients without improving public safety
Dr. Franjo Grotenhermen, International Association for Cannabis as Medicine (written letter)	Measurement problem No good correlation between THC concentrations in blood and impairment blood tests; cannot accurately show driving impairment
Dr. Marilyn Huestis, Chief, Chemistry and Drug Metabolism, U.S. Dept. of Health and Human Services	No Measurement problem Many advocate for zero tolerance limit; a limit of 5 ng/ml in whole blood is most likely too high although a step in the right direction

Discussion Points from Expert Testimony

Paul Armentano/NORML Deputy Director

- Acute marijuana intoxication impairs psycho-motor performance
- Peak problems occur in the first 20 to 60 minutes
- Impaired performance is subtle unless used with alcohol
- Marijuana use alone shows increase in weaving, issues in tracking hand/eye coordination, decision making impact, impact in braking, slower speeds, over-estimation of time and users are aware of their impairments
- The way THC is taken into the body, stored in the body and expelled through the body makes it difficult to have a per se level. Alcohol is water soluble and therefore tests differently in the body. THC is fat soluble and manifests completely differently in the body. This is why it's hard to have a per se level for MJ.
- THC is at its peak level within a few minutes. But peak impairment is 20-40 minutes later, when THC levels are actually lower. THC levels are higher at the beginning, impairment is higher later when THC levels are lower.
- There's a wide variance on different people's tolerance
- Current studies are retrospective, we need more prospective studies
- Proposed per se standards are convenient, are they necessary or efficacious?
- **Better development of cannabis DUI tests**

Cindy Burbach/State Toxicology Lab Director

- 15 states have per se levels, all the rest have zero tolerance
- Marijuana metabolizes quickly in the blood
- Cannabinoids- duration effects 2-4 hours (smoking), up to 8 hours for edible. Detectable in the blood (THC) 2-4 hours
- THC peaks in the blood within 30 minutes – different peak times for edibles. Typical high is 2 hours.
- At a nanogram level of 5 we're going to miss a lot of people driving under the influence. This is a problem in other countries around the world.
- MJ positive samples have surpassed alcohol levels in the state labs and the sample load has gone up significantly.
- "Tolerance" does not necessarily equate to not "Impaired". True. There are two different types of tolerance, but there is no such thing as no tolerance to Executive Cognitive Functioning.
- DUI results in a revocation, DWAI does not result in revocation of driver's license.
- Five nanograms is a very high level and you'll miss a lot of people. **Cindy suggests one or two nanogram limit or no tolerance.** With 5 you'll miss many people. Netherlands has ½ nanogram or single nanogram limit.

- We need to refer to either plasma or whole blood data, you can't refer to both. Plasma is cleaner.
- We need to look at NEW studies.

Dr. Carl Hart/Columbia University

- Effects of marijuana are brief. Those who smoke approx. 4 times/week, see minimal differences in performance
 - **Nanogram info is not sufficient to determine cognitive functioning.**
 - Marijuana and limited cognitive effects: slowing of performance/inhibits control problems. Impairment peaks in 15 minutes for smokers. Impact DAYS later is impossible, despite blood levels.
 - THC/Marijuana stays in the system for weeks. But it is not pharmacologically active, meaning that it is having no impact.
 - What law enforcement does to test sobriety is excellent. Roadside sobriety maneuvers used for alcohol would be appropriate for marijuana. Heel to toe; stand on one foot, hands out eyes closed. Advantage in lab is comparison w/ baseline.
 - Slowing of cognitive performance is main effect.
 - Driving requires complex memory; a series of steps to remember versus declarative memory (which is remembering one thing, like what state do you live in?)
-

Glenn Davis/CDOT, Manager of Impaired Driving Programs, Drug Recognition Expert (DRE) Coordinator

- 178 officers trained in DRE in 2011, soon to be 200
- What is the process of taking someone from a roadside test to a blood sample?
 - Person stopped for traffic violation such as weaving
 - Ask driver to get out of car to do roadside (can be any SFT officer)
 - If person shows impairment, regardless of what it is, they get arrested. They can choose breath test, blood test or refuse both. If officer has probable cause, can arrest the driver.
 - If arrestee shows nothing on breath test but clearly impaired then the officer can mandate a blood test. DRE can do the blood test, or blood can be drawn at a hospital, or by a paramedic
 - If person refuses roadside and refuses blood test do you call in DRE.
 - DRE is used only with cooperative person.
- DRE officers get 24 hours of DRE training

- ARIDE trained officers get 16 hours of training
- Why are traffic fatalities going down?
 - Engineering of roadways
 - Vehicles are safer
 - High visibility enforcement (such as The Heat Is On campaign)
 - A lot of dedicated law enforcement
 - Many DUI filings 26,600 in 2010
 - Arrests have gone down. Patterns in arrest based on economy. A lot of variables influence impaired driving arrests, people don't have as much money to go a bar and drink so there is less drinking and driving.
 - One of the reasons fatality counts are down is because guardrails are now cable and not steel. Cable bounces car back into its lane.
- We have not seen evidence of an increase in marijuana-related accidents
- **There will soon be 200 DRE's in the state but we need 250 to 300 DRE's to serve the underserved (rural/frontier) parts of the state. We don't have enough funds state or locally to support this**
- Currently DREs are peace officers. Is this necessary?

Dr. Jan Ramaekers/ Behavioral Toxicology of Medicinal Drugs and Drugs of Abuse, Maastricht University, The Netherlands

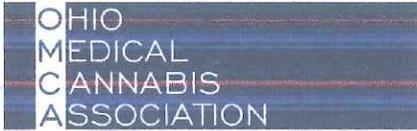
- Driving tests are being standardized by measuring driving function with road task tracking. A subject drives for an hour at 65 miles per hour on a highway, needs to drive as straight as possible in the right driving lane. Eventually what is calculated is the weaving motion of the vehicle over a one hour drive. The weaving index is a very sensitive measure of fatigue (fatigue can be induced by several reasons). Even people who have taken a placebo will often weave as the task is so monotonous. The task itself induces tiredness in subjects, and weaving motions increase over time.
- The test model described above is the most important model because it is a sensitive measure of fatigue and it is calibrated with blood/alcohol up to .13 BAC.
- Another important point is that this test is standardized, and researchers can correlate outcomes with blood alcohol outcomes.
- Given these two tests (weaving plus BAC), it can be shown that there is an exponential rise in weaving based on BAC
- Testing is done on people between 18-35 years, cannabis by itself increased weaving motion and these effects were comparable with blood alcohol levels of .05. Tests are comparable to or more significant than that of a blood alcohol levels of .05 to .08. Cannabis alone increased weave motion in a dose-dependent manner.

- Combined cannabis plus alcohol in ANY dose is bigger than either alone.
- There is a relationship between recent use of cannabis and crashes.
- These point correlations were confirmed through epidemiological data, crash info, real life parameters.
- There are not many epidemiological studies available.
- Drivers under the influence of a drug would have higher culpability rates/risk than those not under the influence, and this increases with dose and concentration of THC.
- A majority of the research has been conducted in occasional users and occasional users have been used to determine thresholds.
- Another study had people smoke MJ in a lab, different doses, and then test their blood every five minutes or so. Outcomes from this study were published in 2006. From this data, researchers concluded that impairment occurs with blood serum concentrations between 2 and 5 nanograms. This does not mean at this level each and every individual is impaired, it just means the group as a whole is at risk of impairment.
- Frequent users (daily users) do develop behavioral tolerance.
- Frequent users are not unimpaired. A substantial proportion shows impairment even though the group as a whole shows tolerance.
- Regarding per se levels that define impairment, to capture each and every individual including heavy users you would have to increase the nanogram level to a level of 15 or 30 .
- If you define a per se limit, are you defining it for the population at large or each individual? The numbers would vary greatly depending on the population you're defining per se for.
- A per se limit is to protect the general population.
- If you compare driving impairment between occasional and frequent users, the occasional users are much more likely to be impaired.
- People do adapt to the drug, some adapt much better than others. You can't say each and every individual will be affected. But you also can't say that each and every individual user will be impaired.
- **In the Netherlands there is a 'Fitness to Drive' law. Daily cannabis smokers are deemed unfit to drive and their licenses are revoked.** A study by Pope in 2001 looked at smokers who went into abstinence for 3 weeks. After those three weeks the performance levels of daily users returned to 'normal' levels. Also, soon after stopping using cannabis, the baseline levels for frequent users were lower than infrequent users.

Alan Shackelford/Amarimed of Colorado (written letter)

Dr. Franjo Grotenhermen/International Association for Cannabis as Medicine (written letter)

Dr. Marilyn Huestis/Dept. of Health and Human Services, Chief, Chemistry and Drug Metabolism (written letter)



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Ohio Medical Cannabis Amendment

Be it resolved by the people of the State of Ohio: That the Constitution of the State of Ohio be amended by adopting a section to be designated as Section 12 of Article XV thereof, to read as follows:

Article XV: Section 12. Medical Cannabis.

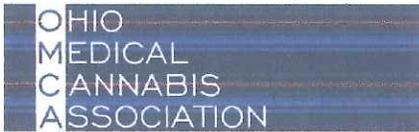
Section 1. Rights.

In accordance with Article 1: Bill of Rights, Section 1 of the Constitution of the State of Ohio:

- (A) Residents of the State of Ohio, who have attained the age of majority and who are diagnosed with a debilitating medical condition, shall be eligible residents for the purpose of using medical Cannabis, also known as medical marijuana or medical marihuana, to alleviate their suffering.
- (B) Eligible residents shall have the right to use medical Cannabis to alleviate their suffering and to possess an amount of medical Cannabis sufficient to meet their medical needs.
- (C) Eligible residents shall have the right to be free of discrimination and interference from the State of Ohio with regard to their use of medical Cannabis.
- (D) Eligible residents shall have the right to privacy and confidentiality with respect to their use of medical Cannabis, including but not limited to any records kept by the State pertaining to such use.
- (E) Eligible residents shall have the right to produce their own medical Cannabis, and to acquire medical Cannabis sufficient to alleviate their suffering from state-licensed providers without fear of arrest, prosecution or undue interference by the state.
- (F) Eligible residents shall have the right to access goods and services to enable their use of medical Cannabis.
- (G) Within the State of Ohio, it shall be a legal right for individuals or organizations, deemed eligible by the Ohio Commission of Cannabis Control, to grow, process, distribute, transport, purchase or sell medical Cannabis in its various forms to eligible residents according to rules and regulations as established by the Ohio Commission of Cannabis Control.
- (H) The State of Ohio shall support, uphold and defend these rights.

Section 2. Limitations.

- (A) Nothing in this Amendment requires the use of Cannabis as a medical treatment.
- (B) Nothing in this Amendment shall prohibit the reasonable regulation and control of the commercial production and distribution of medical Cannabis by the Ohio Commission of Cannabis Control as set forth in Section 3.
- (C) Nothing in this Amendment shall prohibit the sale of medical Cannabis to eligible residents, nor prevent research or educational institutions from studying the medicinal properties of medical Cannabis; nor prohibit the reasonable application of fines or fees pursuant to the regulation and control of medical Cannabis within the State in accordance with Section 4. The sale of Cannabis is sale of tangible personal property for purposes of collection of State and local sales taxes.
- (D) Debilitating medical conditions include, but are not limited to the following: glaucoma; multiple congenital cartilaginous exostosis; multiple sclerosis; nail-patella syndrome; positive status for human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS); Alzheimer's disease; amyotrophic lateral sclerosis; cancer; celiac disease; Crohn's disease; hepatitis C; myelomalacia; post traumatic stress; rheumatoid arthritis; sickle cell anemia; injury or disease to the spinal cord, spinal column, or vertebra; Tourette's syndrome; a chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe or chronic pain, severe or chronic nausea, seizures, including those characteristic of epilepsy, or severe or persistent muscle spasms; and any additional medical condition or its treatment that may be designated by the Commission or set forth by the General Assembly pursuant to Section 3.



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(E) Nothing in this Amendment authorizes any person to engage in, and does not prohibit the imposition of civil, criminal or other penalties for undertaking any task under the influence of Cannabis, when doing so would constitute negligence or professional malpractice; or to operate, navigate or be in actual physical control of any motorized conveyance while under the influence of Cannabis.

(F) An eligible resident shall not be considered to be under the influence of medical Cannabis solely because of the presence of active or inactive metabolites of Cannabis in the eligible resident's urine, blood, tissue, hair or skin or as detectable by any other measure of body chemistry. The legal definition of impairment as a result of medical Cannabis use and applicable testing to determine such impairment shall be based on scientific evidence of impairment.

(G) The possession of drug paraphernalia used by an eligible resident to consume, possess or store medical Cannabis shall not be grounds for arrest or prosecution of the eligible resident, or of agents who are serving the eligible resident.

Section 3. The Commission.

(A) There is hereby created the Ohio Commission of Cannabis Control, which shall support and uphold the rights enumerated in Section 1; license, regulate and control medical Cannabis in Ohio; and ensure statewide compliance with this Amendment.

(B) The appointments to the Board of the Commission shall total nine members: three members to serve an initial one year term, three members to serve initial two year terms and three members to serve initial three year terms. Three members are to be registered Ohio voters, who shall also be eligible residents after regulations to be established by the Commission are in place; two members are to be licensed practitioners; one member is to be a farmer, who shall be a license or permit holder after implementation of a licensing and permitting system by the Commission; one member is to represent the Ohio Civil Rights Commission; and two members are to be licensed attorneys. Each Commissioner shall be an Ohio resident. No more than four (4) members shall be affiliated with the same political party. Initial appointments to the Commission shall be selected by the Committee to Represent the Petitioners for this Amendment. Succeeding terms of the Commission shall be three years in length and members shall be selected by the Governor and approved by the Senate. No vacancy in the Commission shall impair the right of the remaining Commissioners to exercise all powers of the Commission.

(C) The Board of the Commission shall be duly constituted and conduct its first official meeting within ninety (90) days of an affirmative vote by the electors of the state. The Commission shall have regulations in place within 270 days of an affirmative vote. Implementation of the licensing and permitting systems created by this Amendment shall take place within 360 days of an affirmative vote.

(D) The Commissioners shall have the authority to enact and amend regulations, recommendations or findings as they pertain to medical Cannabis in accordance with this Amendment, and to the procedures in the Ohio Administrative Procedure Act.

(E) The proposed regulations shall support, uphold and defend the Rights enumerated in Section 1 and shall include provisions for the protection from arrest and prosecution of eligible residents, providers and other entities who provide legal access to medical Cannabis for the benefit of eligible residents. The Commission shall license or authorize other personnel to regulate medical Cannabis within the State.

Section 4. Funding.

(A) The General Assembly shall provide adequate funds to cover the costs of implementing the provisions set forth by this Amendment, based on recommendations set forth by the Commissioners.

(B) Fines, regulatory fees, licensing fees and permit fees shall be determined by the Commission. Fines, regulatory fees, license fees and permit fees shall be based upon anticipated costs and expenses for the necessary operations of the Commission in a manner that shall not be cost prohibitive for eligible residents or providers.

(C) All operating expenses of the Commission shall be funded by the reasonable fees and fines adopted to implement the activities authorized by this Amendment.

Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users

Johannes G. Ramaekers · Eef L. Theunissen ·
Marjolein de Brouwer · Stefan W. Toennes ·
Manfred R. Moeller · Gerhold Kauert

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Abstract

Introduction Previous research has shown that heavy cannabis users develop tolerance to the impairing effects of Δ^9 -tetrahydrocannabinol (THC) on neurocognitive functions. Animal studies suggest that chronic cannabis consumption may also produce cross-tolerance for the impairing effects of alcohol, but supportive data in humans is scarce.

Purpose The present study was designed to assess tolerance and cross-tolerance to the neurocognitive effects of THC and alcohol in heavy cannabis users.

Methods Twenty-one heavy cannabis users participated in a double-blind, placebo-controlled, three-way study. Subjects underwent three alcohol-dosing conditions that were designed to achieve a steady blood alcohol concentration of about 0, 0.5, and 0.7 mg/ml during a 5-h time window. In addition, subjects smoked a THC cigarette (400 μ g/kg) at 3 h post-onset of alcohol dosing during every alcohol condition. Performance tests were conducted repeatedly between 0 and 7 h after onset of drinking and included measures of perceptual motor control (critical tracking task), dual task processing (divided-attention task), motor

inhibition (stop-signal task), and cognition (Tower of London).

Results Alcohol significantly impaired critical tracking, divided attention, and stop-signal performance. THC generally did not affect task performance. However, combined effects of THC and alcohol on divided attention were bigger than those by alcohol alone.

Conclusion In conclusion, the present study generally confirms that heavy cannabis users develop tolerance to the impairing effects of THC on neurocognitive task performance. Yet, heavy cannabis users did not develop cross-tolerance to the impairing effects of alcohol, and the presence of the latter even selectively potentiated THC effects on measures of divided attention.

Keywords THC · Alcohol · Tolerance · Impulsivity · Cognition · Performance

Introduction

Cannabis use is largely concentrated among young people, aged 15–34 years. Population data suggest that, on average, 31% of young Europeans have ever used cannabis, while 12.5% have used the drug in the last year (EMCCDA 2009). In the USA, lifetime prevalence of cannabis use among young adults and last year prevalence are 49% and 21%, respectively (DHHS/SAMHSA 2007). Prospective studies have demonstrated that despite spontaneous cessation of cannabis use in the majority of cannabis users, a substantial proportion of users develop stable use patterns characterized by continuous use of cannabis (Chen and Kandel 1995; Perkonig et al. 2008; Perkonig et al. 1999). It has been estimated that over 1% of all European adults, about 4 million, are using cannabis daily or almost daily.

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Homburg, Germany

Most of these are aged 15–34 years, representing about 2.5% of Europeans in this age group (EMCCDA 2009).

Previous research has demonstrated that daily cannabis users are less sensitive to the impairing effects of Δ^9 -tetrahydrocannabinol (THC) intoxication on cognitive and psychomotor functions (D'Souza et al. 2008; Hart et al. 2001; Jones et al. 1981; Ramaekers et al. 2009) that have often been demonstrated in occasional cannabis smokers (Curran et al. 2002; Hart et al. 2002; Heishman et al. 1989; Lamers and Ramaekers 2001; Ramaekers et al. 2004; Ramaekers et al. 2006a), even when THC concentrations and levels of subjective high are similar (Ramaekers et al. 2009). This loss of sensitivity or tolerance to the behavioral effects of THC after prolonged use is believed to result from a change in pharmacodynamic response as evinced by CB1 receptor downregulation in large parts of the brain (Gonzalez et al. 2005). Alternatively, it has also been suggested that heavy cannabis users recruit alternative neural networks as a compensatory mechanism during task performance. Eldreth et al. (2004) and Kanayama et al. (2004) showed that compared with controls, cannabis users utilized additional brain regions to perform cognitive tasks, i.e., they compensated by working harder and recruiting compensatory networks.

Animal research has also suggested that pharmacological tolerance to the effects of THC may lead to cross-tolerance for actions of other drugs. Repeated cannabinoid administration decreased responsiveness of dopamine neurons in the mesoaccumbens in adolescent rats to an acute challenge with cannabinoid agonists but also to challenges with morphine, cocaine, and amphetamine (Pistis et al. 2004). The cannabinoid system has also been indicated in the development of tolerance to the effects of ethanol. Chronic ethanol exposure has been shown to produce downregulation of CB1 receptors and altered CB1 receptor gene expression (Hungund and Basavarajappa 2000; Ortiz et al. 2004). Rats made tolerant to the depressant effects of THC were also tolerant to the behavioral depressant effects of ethanol (Newman et al. 1972). Rats made tolerant to either ethanol or THC exhibited cross-tolerance to effects of the opposite compounds in learning and performance tasks (Siemens and Doyle 1979; Sprague and Craigmill 1976). These data strongly suggest the possibility of cross-tolerance between ethanol and THC.

Ethanol and THC share many similarities in their actions. Pharmacological and behavioral effects of ethanol, such as hypothermia, euphoria, analgesia, sedation, and cognitive and motor dysfunction have also been demonstrated for THC (Ameri 1999; Iversen 2003). Combined use of ethanol and THC in occasional cannabis users has repeatedly been shown to increase the magnitude of cognitive and motor impairments in an additive manner (Lamers and Ramaekers 2001; Liguori et al. 2002;

Ramaekers et al. 2004). It is unclear however if combined use of ethanol and cannabis would also lead to similar impairments in these performance domains in heavy cannabis users. Based on the animal literature, it might be expected that heavy users of cannabis may develop tolerance to the impairing effects of THC, ethanol, and their combination. However, there is only little research in humans to support this claim. A few studies have reported (Casswell and Marks 1973; Marks and MacAvoy 1989; Wright and Terry 2002) that regular cannabis users were less impaired in peripheral signal detection and tracking accuracy than controls while intoxicated by THC and/or ethanol. These findings suggest either the development of tolerance and cross-tolerance in regular cannabis users, or their ability to compensate for intoxication effects.

The present study was designed to assess the effects of THC and alcohol, alone, and in combination, on neurocognitive performance of heavy cannabis users in order to establish the presence of tolerance or cross-tolerance to the impairing effects of THC and ethanol. Neurocognitive tasks were selected from previous studies demonstrating their sensitivity to measure THC-induced impairments in occasional cannabis users (Ramaekers et al. 2009; Ramaekers et al. 2006b).

Methods

Subjects

Twenty-one heavy cannabis users (15 males, 6 females) entered the present study. A summary of their demographics and history of drug use is given in Table 1. Subjects were recruited through advertisements in coffee shops. Initial screening comprised of a questionnaire on medical history. Subjects were examined by the medical supervisor who checked vital signs and took blood and urine samples. Standard blood chemistry, hematology, and drug screen tests were conducted on these samples. General inclusion criteria were: free from psychotropic medication; good physical health as determined by medical examination and laboratory analysis; absence of any major medical, endocrine, and neurological condition; normal weight, body mass index (weight per square length) between 18 and 28 kg/m²; and written informed consent. Specific inclusion criteria were frequent use of cannabis (smoking on more than 4 days/week) during the previous year and presence of THC in serum on the day of screening. Exclusion criteria were: history of drug abuse (excluding marijuana) as assessed by drug urine screens and questionnaires; no experience with alcohol; non cigarette smokers; pregnancy or lactation or failure to use reliable contraceptives; color blindness, excessive drinking (>25 standard alcoholic

Table 1 Subject characteristics (mean, SD) and history of drug use for heavy cannabis users that completed the study ($N=19$)

Demographic variables	
Age (years)	23.2 (8.4)
Age range (years)	19–38
Frequency of cannabis use/number of times per year	373.7 (101.6)
Joints per occasion (number)	5.0 (3.9)
History of cannabis use (years)	9.0 (5.5)
Frequency of alcohol use/number of times per year	76.7 (50.6)
Drinks per occasion	8.4 (5.7)
History of alcohol use (years)	9.8 (3.1)
Occasional use of other drugs (number of subjects)	
MDMA	12
Amphetamine	6
Cocaine	10
LSD	1
Mushrooms	8
Salvia	1
Combined use of THC and alcohol (number of subjects)	18
Number of subjects attesting to driving under the influence of cannabis (DUIC)	15
Frequency of DUIC/year	139.5 (172.9)
Number of subjects attesting to driving under the influence of cannabis and alcohol (DUICA)	6
Frequency of DUICA/year	11.5 (9.2)

consumptions a week); hypertension (diastolic >100 ; systolic >170) or history of psychiatric disorders.

The study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Seoul (2008). All subjects were fully informed of study procedures, adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. A permit for obtaining, storing, and administering marijuana was obtained from the Dutch drug enforcement administration.

Design, doses, and administration

The study was conducted according to a double-blind, placebo-controlled, three-way design. Subjects underwent three alcohol-dosing conditions that were designed to achieve steady state blood alcohol concentration (BACs) of about 0, 0.5, and 0.7 mg/ml during a 5-h time window. The order of alcohol-dosing conditions was counterbalanced across subjects. In addition, subjects smoked a THC cigarette (400 $\mu\text{g}/\text{kg}$) at 3 h post-onset of alcohol dosing, in each alcohol condition. Alcohol dosing started at 10:30 hours in the morning with placebo alcohol, 0.5 or

0.7 g/kg alcohol. Additional alcohol booster doses of about 0.1 g/kg or alcohol placebo were given on an as needed basis at approximately every half hour up until 4.5 h after onset of alcohol dosing in order to keep BAC at the desired level. On average, subjects received 5.4 additional booster doses containing alcohol. Alcohol was administered as “pure” ethanol (96%) mixed with orange juice to a volume of 300 ml for the initial dose. Total volumes of booster doses mixed with orange juice were approximately 80 ml. THC smoking started at 3 h post-onset of alcohol dosing and lasted for about 15 min. The cigarettes were prepared beforehand for each individual from stock provided by the Dutch Bureau for Medicinal Cannabis. Marijuana cigarettes were prepared from batches containing 11% THC, a standard potency for marijuana sold at Dutch pharmacies for medical use. The total amount of cannabis was weight calibrated for each individual subject and mixed with tobacco to achieve a standard cigarette size and weight. Subjects were instructed to smoke the cigarette according to a standardized procedure (Ramackers et al. 2006a) in order to minimize the subject's possibility of dose titration and to increase optimal absorption of THC: i.e., inhale for 4 s, hold breath for 10 s, and exhale/break for 15 s. This sequence was repeated until the cigarettes were smoked as completely as possible. Mean (SD) number of puffs smoked from the cigarette in the three alcohol/THC conditions were 17 (4.4), 17 (5.2), and 17 (2.9) respectively. A minimum wash-out of 4 days transpired between experimental treatments.

Procedures

Subjects were asked to refrain from drugs other than cannabis. Subjects were not allowed to use alcohol on the day prior to an experimental session and were requested to arrive at experimental sessions well rested. Subjects were allowed to continue their usual cannabis-smoking routine during the study period. Drug and alcohol screens were performed prior to experimental sessions upon arrival of the subject. Urine drug screens assessed for the presence of morphine, cocaine, marijuana, methamphetamine, and amphetamine. Alcohol/THC treatments were only administered if subjects tested positive for THC, but negative for other drugs and alcohol. Subjects always tested positive for THC on test days. Subjects received a standardized lunch prior to THC smoking. Performance tests were conducted at fixed intervals during 7 h post-onset of alcohol dosing. The critical tracking task was conducted at 1 h, 2 h, 3 h 20, 4 h 20 min, 5 h 20 min and 6 h 20 min post-onset of alcohol administration; a divided-attention task was conducted at 1 h 10 min, 3 h 30 min, 4 h 30 min and 5 h 30 min post-onset alcohol dosing; the stop-signal task was conducted at 1 h 30 min, 4 h and 6 h post-onset alcohol dosing; and a

Tower of London task was conducted at 1 h 40 min, 4 h 10 min and 6 h 10 min post-onset of alcohol dosing. Subjects received a training session prior to onset of the experimental sessions in order to familiarize them with the tests and procedures and minimize practice effects.

Neurocognitive assessments

The critical tracking test (CTT) measures the subject's ability to control a displayed error signal in a first-order compensatory tracking task. Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The subject's compensatory response increases in frequency with an increasing phase lag. Control is lost at the point where the compensatory response lags the cursor's last movement by 180°. The response frequency at this point is defined as the critical frequency or λ -c. The test includes five trials of which the lowest and the highest score are removed. The average of the remaining scores is taken as the final score (Jex et al. 1966)

The divided-attention task (DAT) measures the subject's ability to divide attention between two tasks performed simultaneously. The primary task consists of the tracking task as described above but at a constant level of difficulty set at 50% of the subject's maximum capacity. Tracking error is measured as the difference in millimeters between the position of the cursor and the midpoint of the scale. In the secondary task, the subject monitors a central display upon which single digits are presented at 1-s intervals. The occurrence of the digit "2" is a signal for the subject to remove the foot from a pedal as rapidly as possible. Inter stimulus interval varies between 1 and 2 s. Mean absolute tracking error (millimeters) and number of control losses are the main parameters of the primary task. Number of correct signal detections and reaction time to signals are the main performance measures in the secondary task (Moskowitz 1973).

The stop-signal task (SST) measures motor impulsivity, which is defined as the inability to inhibit an activated or pre-cued response leading to errors of commission. The current test is adapted from an earlier version of Fillmore et al. (Fillmore et al. 2002) and has been validated for showing stimulant and sedative drug effects (Ramaekers and Kuypers 2006). The task requires subjects to make quick key responses to visual go signals, i.e., the letters ABCD presented one at a time in the middle of the screen, and to inhibit their response if a subsequent visual stop signal, i.e., "*", appears in one of the four corners of the screen. The stop signal is presented at predefined delays of 50, 150, 250, and 350 msec. The main parameters are stop reaction time and commission errors during "no go" trials.

Stop reaction time represents the estimated mean time required to inhibit a response. Stop reaction time is calculated by subtracting the stop-signal delay from the reaction time on go-trials associated with n th percentile of the reaction time distribution. The n th percentile corresponds to the percentage of commission errors (Logan et al. 1984)

The Tower of London (TOL) is a decision-making task that measures executive function and planning (Shallice 1982). The original version of the Tower of London consists of three colored balls, which must be arranged on three sticks to match the target configuration on a picture while only one ball can be moved at a time. The present version consists of computer-generated images of begin- and end-arrangements of the balls. The subject decides as quickly as possible, whether the end-arrangement can be accomplished in 2, 3, 4, or 5 steps from the begin arrangement by pushing the corresponding coded button. Number of correct decisions and mean reaction time are the main outcome measures.

Subjective high and drunkenness

Subjects rated their subjective high and drunkenness on visual analogue scales (100 mm) as a percentage of the maximum "high" or "drunkenness" ever experienced. Subjective high and drunkenness were rated on nine consecutive time points throughout 8 h after onset alcohol dosing. In addition, subject rated which of the two drugs (ethanol or THC) produced the most dominant feeling at each of these time points.

Pharmacokinetic assessments

Blood samples (6 ml) were taken at baseline, 15, 30, 45, and 60 min during the first hour after onset of THC smoking (THC cigarette was smoked within 15 min) and subsequently at every 30 min between 1 and 4 h after smoking. Blood samples were centrifuged and serum was frozen at -20°C until analyses for pharmacokinetic assessments. THC concentrations and its main metabolites (THC-COOH, OH-THC) were determined using a validated and accredited routine method for the analysis of cannabinoids in forensic blood samples (Toennes et al. 2008). The procedure essentially consists of an automated solid phase extraction and gas chromatography with mass spectrometric detection with a limit of quantification of 0.6 ng/ml which has also been successfully used for the analysis of THC in oral fluid (Kauert et al. 2006; Toennes et al. 2010). Subjects' BAC was monitored using a Lion SD4 breath alcohol analyser at baseline and approximately every 30 min through 8 h after onset of alcohol dosing.

Statistics

All neurocognitive measures were analyzed with SPSS 13.0 using a GLM univariate analysis of variance with Alcohol (three levels) and THC over time (three to six levels, depending on the number of test repetitions) as fixed factors and Subjects as random factor. The univariate model tested for main effects of alcohol, THC over time, and alcohol \times THC over time. The factor alcohol compares performance between three alcohol doses across all test replications and gives an indication of the overall effect of alcohol on performance. The factor THC over time compares performance before and after THC smoking across all alcohol conditions and gives an indication of the overall THC effect on performance. The interaction alcohol \times THC indicates whether the effect of THC on performance changes as a function of alcohol dose. Subjective measures of high and drunkenness were analyzed according to the same statistical design but tested only for the main effects of THC over time (nine levels) and alcohol (three levels), respectively.

Results

Missing values

Two subjects dropped out of the study after the first treatment condition for reasons unrelated to the study. Incomplete data from the drop-out subject did not enter statistical analysis. One subject was unable to reliably perform the divided-attention task. His data were not included in the statistical analysis of this task.

BAC and THC concentrations

Mean (SE) BAC concentrations and THC concentrations during treatments are shown in Fig. 1 and Table 2, respectively. On average, BAC concentration achieved the desired peak levels of 0.5 and 0.7 mg/ml in the low and high alcohol dose conditions. BAC levels dipped around 2.5 h after onset of dosing during lunch when subjects did not receive a booster dose, but returned to peak levels after administration of subsequent booster doses. BACs during the alcohol placebo condition were always zero. Concentrations of THC and its main metabolites were comparable in every treatment condition. Seven subjects indicated that they had smoked a cannabis cigarette on test days prior to the test session. All other subjects experienced their last cannabis cigarette during the preceding day. The impact of routine cannabis smoking of subjects was negligible since average baseline THC levels were low (i.e., <10 ng/mL) as compared to THC levels after smoking the experimental THC cigarette.

Subjective high and drunkenness

Subjective high was significantly elevated by the factor THC ($F_{8,462}=64.7$; $p=0.000$). Subjective drunkenness was significantly elevated by alcohol ($F_{8,462}=86.6$; $p=0.000$). Subjects indicated that the feeling of drunkenness was dominant prior to THC smoking and that the feeling of high was dominant after smoking. Mean (SE) rating of subjective high, drunkenness, and dominance of drug are shown in Fig. 2.

Neurocognitive measures

Lambda- c in the critical tracking task significantly decreased after alcohol ($F_{2,303}=5.42$; $p=0.005$) but was not affected by THC or alcohol \times THC. Mean (SE) lambda- c in every treatment condition is shown in Fig. 3.

Alcohol also significantly increased tracking error, control losses, and reaction time ($F_{2,185}=6.68$, 9.51, and 16.91, respectively; $p<0.002$) and decreased the number of correct signal detections ($F_{2,185}=7.6$; $p=0.001$) in the divided-attention task. In addition, number of control losses, correct signal detections, and reaction time were also significantly affected by THC ($F_{3,185}=5.97$, 6.89, and 9.46, respectively; $p<0.001$). Control losses were also affected by the interaction of alcohol \times THC ($F_{6,185}=2.31$; $p=0.036$). Mean (SE) performance in the divided-attention task in every treatment condition is shown in Fig. 4.

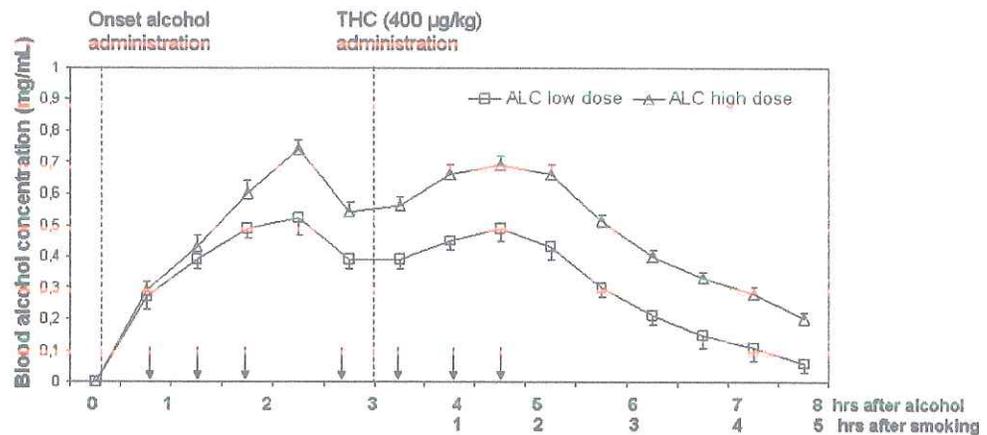
Stop reaction time ($F_{2,141}=4.03$; $p=.020$) and commission errors ($F_{2,141}=7.51$; $p=0.001$) in the stop-signal task significantly increased after alcohol, but were unaffected by THC or alcohol \times THC. Performance in the Tower of London task was not affected by any factor. Mean (SE) performance in the stop-signal task in every treatment condition is shown in Fig. 5.

Discussion

The present study was designed to assess tolerance and cross-tolerance to the neurocognitive effects of THC and alcohol in heavy cannabis users. Results demonstrated that alcohol detrimentally affected performance of heavy cannabis users. THC generally did not affect performance, confirming earlier reports on tolerance to performance impairing effects of THC. Performance in the divided-attention task however was affected by both THC and alcohol, and their combination.

Alcohol was given in a low- and high-dose condition with the general aim to achieve steady BAC concentrations around 0.5 and 0.7 mg/ml, respectively, during performance testing in a 5-h time window. After 5 h, BACs were allowed to decline over time. Steady BACs were achieved by administering booster alcohol doses almost every 30 min

Fig. 1 Mean (SE) BAC as a function of time after onset of alcohol drinking and onset of THC cigarette smoking in the low- and high-dose alcohol condition. Arrows indicate time points at which booster alcohol doses could be administered on an as needed basis to achieve steady BAC levels between 1 and 5 h after onset of drinking



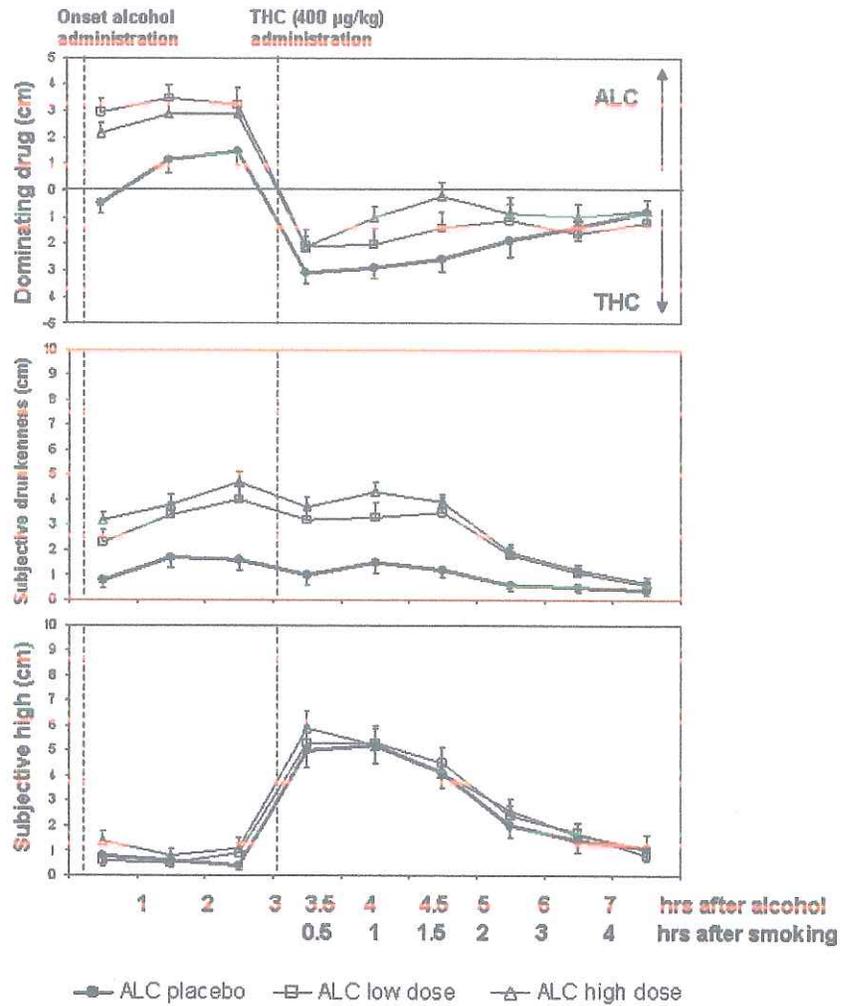
on an as needed basis. In general, repeated alcohol dosing produced the desired BAC concentrations during performance testing in the two alcohol conditions. Performance tests were basically scheduled in three separate time windows: i.e., between 1–2.5, 3.5–5.5, and 5.5–7 h after alcohol onset. Mean BAC concentrations in the low and high alcohol-dose condition fluctuated around 0.5 and 0.7 mg/ml, respectively, during performance testing in the first and second time window. Performance testing during

the third time window took place during the declining phase of BAC in both alcohol conditions. Subjective feelings of drunkenness during alcohol treatments were also comparable during the first and second time window, and gradually decreased with declining BACs in the third time window. BAC and subjective drunkenness data indicate that the levels of alcohol intoxication were comparable during performance testing in the first and second time window (i.e., prior and post-smoking THC),

Table 2 Mean (SD) serum concentrations of THC, THC-COOH, and OH-THC as a function of time after onset of smoking

		Time after smoking (h)										
		Baseline	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4
Alcohol placebo												
THC	Mean	8.6	112.1	49.3	32.0	24.7	20.7	13.4	10.1	8.8	8.6	7.9
	SD	10.3	47.5	21.9	12.2	8.9	6.7	6.4	4.4	4.1	4.5	6.2
THC-COOH	Mean	80.7	124.0	123.9	111.8	109.7	106.5	102.0	97.7	87.0	82.7	80.6
	SD	75.1	102.4	104.6	91.3	91.8	90.4	84.9	86.7	74.3	64.7	67.0
OH-THC	Mean	4.9	16.3	14.4	12.0	10.8	9.4	7.5	6.1	5.3	5.0	4.8
	SD	7.1	10.0	10.0	7.8	6.8	5.5	4.6	4.4	3.8	3.9	3.8
Low alcohol dose												
THC	Mean	9.0	98.3	47.7	31.2	23.1	19.5	14.4	10.7	7.8	8.6	8.0
	SD	11.8	50.0	28.0	19.1	13.2	12.2	9.2	7.4	5.1	6.3	6.0
THC-COOH	Mean	58.6	82.9	83.7	79.0	75.7	76.3	70.4	65.6	52.3	57.3	54.0
	SD	53.4	61.0	58.8	56.1	59.5	63.5	55.2	54.5	48.7	49.7	50.2
OH-THC	Mean	4.5	18.4	15.2	12.6	10.6	9.8	7.7	6.1	4.7	5.0	4.3
	SD	7.0	13.6	9.3	7.3	6.5	6.1	5.2	4.3	3.9	4.4	3.6
High alcohol dose												
THC	Mean	9.6	93.0	45.2	27.1	18.5	16.0	11.6	10.0	7.9	8.4	8.1
	SD	15.7	40.5	26.7	14.2	8.6	7.8	6.3	5.9	5.1	5.4	6.0
THC-COOH	Mean	70.3	87.9	96.7	94.2	85.8	73.1	71.0	68.8	62.9	60.1	62.3
	SD	61.7	62.9	75.3	76.6	72.5	63.2	62.6	62.2	56.4	49.6	50.2
OH-THC	Mean	5.8	17.8	16.1	12.8	10.8	8.8	7.3	6.5	5.2	5.2	4.8
	SD	9.5	10.0	9.4	7.7	7.3	5.8	5.2	4.8	4.1	4.0	3.9

Fig. 2 Mean (SE) subjective high (lower panel) and drunkenness (middle panel) as a function of time after alcohol and THC administration. The upper panel displays subjective dominance of alcohol or THC over time

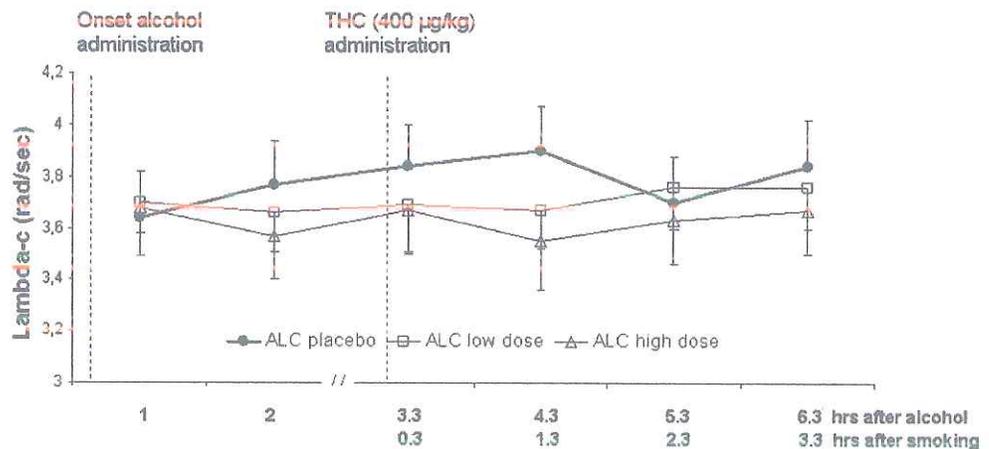


and declined at similar rates during performance assessments in the third time window.

The effects of alcohol in objective performance measures were consistent and straightforward. Alcohol significantly affected all performance measures in the critical tracking task, the divided-attention task, and the stop-signal task. In the critical tracking task, alcohol significantly decreased

tracking performance. In the divided-attention task, alcohol increased reaction time, number of control losses, and decreased number correct signal detections and tracking. Alcohol increased stop reaction time and commission errors in the stop-signal task. The neurocognitive effects of alcohol in heavy cannabis users are comparable to those that have been reported in infrequent drug

Fig. 3 Mean (SE) lambda-c in the CTT as a function of time after alcohol and THC administration in every treatment condition



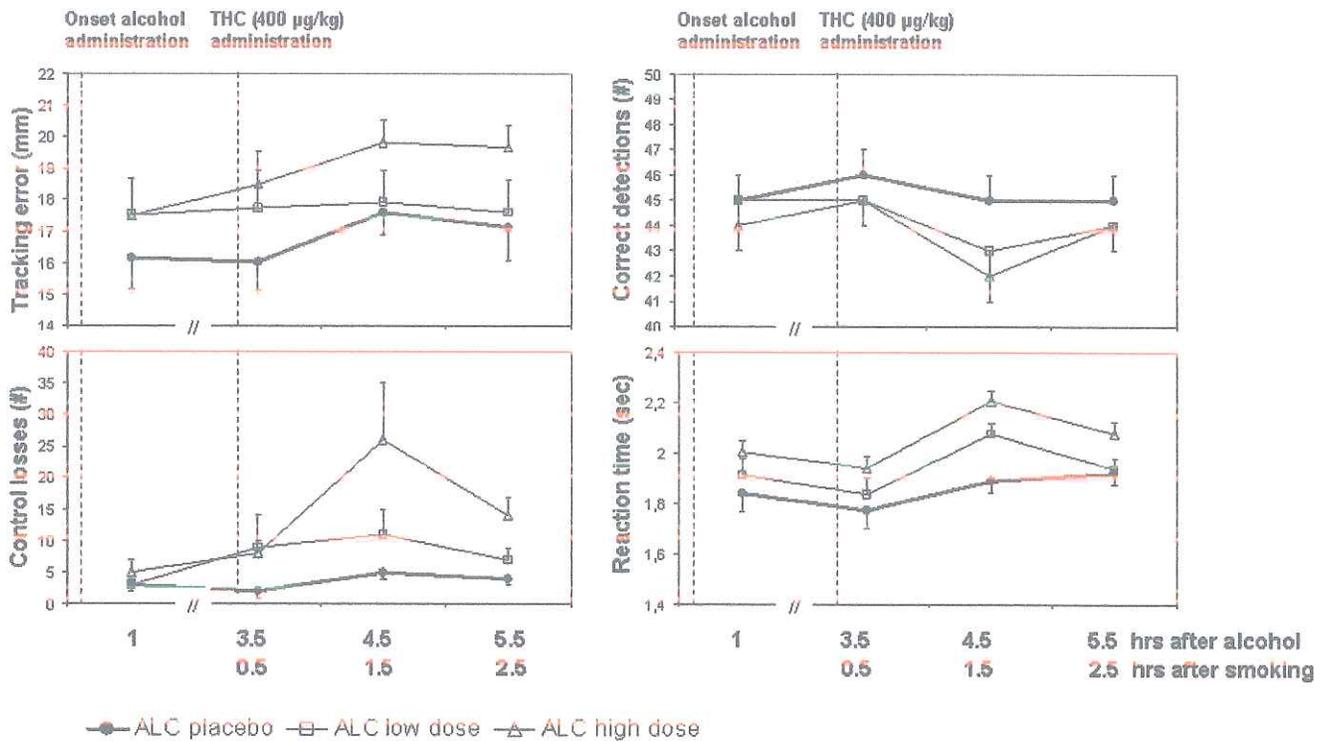


Fig. 4 Mean (SE) tracking error, control losses, correct detections, and reaction time during the DAT as a function of time after alcohol and THC administration in every treatment conditions

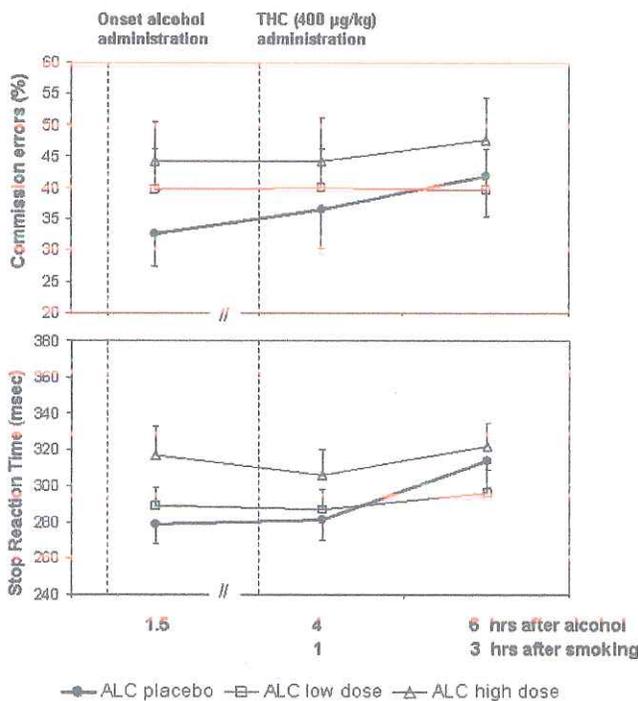


Fig. 5 Mean (SE) stop reaction time and commission errors in the SST as a function of time after alcohol and THC administration in every treatment condition

(including cannabis) users (Heishman et al. 1988; Kuypers et al. 2006; Liguori et al. 2002; Ramaekers and Kuypers 2006) and healthy volunteers (de Wit et al. 2000; Vermeeren et al. 2002). The present data strongly indicate that heavy cannabis use does not produce cross-tolerance to the impairing potential of alcohol.

Subjects smoked a cannabis cigarette every treatment condition at 3 h after onset of alcohol or alcohol placebo administrations. Subjective high was elevated to similar degrees after smoking cannabis in each treatment condition. THC concentrations were also comparable between treatments with peak THC concentrations ranging from 93 to 112 ng/ml. Together, these data suggest that THC administrations were very comparable in every treatment condition.

THC did not affect performance of heavy cannabis users in the critical tracking task, the stop-signal task, and the Tower of London. These tasks have previously been shown to be very sensitive to the impairing potential of THC when administered to infrequent cannabis (Ramaekers et al. 2006a). The lack of THC effects on any of these tasks basically confirms previous notions that heavy cannabis users can develop tolerance to behaviorally impairing effects of THC (D'Souza et al. 2008; Hart et al. 2001; Jones et al. 1981; Ramaekers et al. 2009). However it was interesting to note that tolerance was not apparent in all performance tasks. During divided-attention task performance, THC increased the number of control losses and reaction time and decreased the number of

correct signal detections. Number of times that subjects lost control over the primary task (tracking) during this dual task performance appeared particularly sensitive to the impairing effect of THC. During alcohol placebo, mean number of control losses were always low, independent of THC administration. During treatments with low and high ethanol doses, mean number of control losses increased by a factor two and five, respectively, after smoking a THC cigarette. Univariate analysis indeed revealed a significant alcohol \times THC interaction for this particular parameter, supporting the notion that the combination of alcohol and THC detrimentally affected the number of control losses in a synergistic manner.

THC effects on reaction time and signal detection in the divided-attention task may have also been related to concomitant alcohol use. The latter measures did not reveal an alcohol \times THC interaction, but an additive effect of alcohol and THC cannot be excluded. Previous studies demonstrated that the divided-attention task is very sensitive to the effects of THC and alcohol alone when given to occasional cannabis users or healthy volunteers (Moskowitz 1984; Ramaekers et al. 2009; Schulte et al. 2001). Other studies have demonstrated that low doses of THC and alcohol that do not affect psychomotor function when given alone may still impair performance when given in combination (Lamers and Ramaekers 2001). In other words, small THC impairments that would go unnoticed in isolation still might exceed the (statistical) threshold of detection when added to the impairment produced by concurrent alcohol. Likewise, it is conceivable that negligible THC effects on divided attention as previously demonstrated in heavy cannabis users (Ramaekers et al. 2009) may become more apparent when added to those of a social dose of alcohol. This might particularly be true for attention tasks that are known for their very high sensitivity to drug and alcohol effects (Moskowitz 1984).

Data from the present study confirmed that chronic cannabis users develop tolerance to the behaviorally impairing effects of THC. However, previous notions (Marks and MacAvoy 1989; Wright and Terry 2002) that chronic cannabis use would also develop cross-tolerance for the impairing effects of alcohol were not confirmed. It should be noted however that previous studies never demonstrated complete tolerance to the behaviorally impairing effects of alcohol in heavy cannabis users. Generally, they showed that heavy cannabis users were less impaired after an alcohol challenge than non-drug users or infrequent cannabis users. Moreover, such demonstrations of partial tolerance were always very selective for single performance parameters (e.g., tracking accuracy), whereas other task parameters (e.g., reaction time) did not reveal cross-tolerance. Previous demonstrations of cross-tolerance were obtained after administration of single doses of alcohol. Performance testing occurred during the

descending phase of the blood alcohol curve. Consequently, BACs were generally lower than those obtained in the present study after repeated alcohol dosing. For example, Wright and Terry (2002) tested tracking performance of heavy cannabis users within 30 min after drinking while mean BACs declined from 0.28 to 0.22 mg/ml. Mean BAC levels in the present study however were two to three times as high and experimentally controlled to achieve relatively steady state levels during 5 h of repeated performance testing. Repeated alcohol challenges and high BAC levels thus may have provoked more pronounced alcohol impairments than can be observed after single administration of a low alcohol dose. Consequently, cross-tolerance or behavioral adaptation may have been lacking or insufficient to compensate for prolonged alcohol impairments as observed in the present study.

The general lack of cross-tolerance for the impairing effects of alcohol as well as the potential of ethanol to potentiate the effects of THC in the divided-attention task may have important implications for heavy cannabis users who drive under the influence of both drugs. Heavy cannabis users usually operate their vehicle on day to day basis because they believe they developed resistance against the impairing effect of THC (Ramaekers et al. 2009). In the present study, most participants (79%) admitted to driving under the influence of cannabis and a substantial proportion (32%) also admitted to driving under the influence of cannabis and alcohol in combination. The present data however demonstrated that mean BAC concentrations up to 0.7 mg/ml produce significant performance impairment and that the presence of alcohol may potentiate detrimental effects of THC during dual task performances that are common during car driving. Additive and synergistic effects of alcohol and THC on driving performance have previously been shown in occasional cannabis users (O'Kane et al. 2002; Ramaekers et al. 2004; Sewell et al. 2009). The present study demonstrates that additive and synergistic effects of THC and alcohol on performance can pertain to heavy cannabis users as well.

In conclusion, the present study generally confirms that heavy cannabis users develop tolerance to the impairing effects of THC on neurocognitive task performance. Yet, heavy cannabis users did not develop cross-tolerance to the impairing effects of alcohol, and the presence of the latter even selectively potentiated THC effects on measures of divided attention.

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