Pharmacology, Biochemistry and Behavior 97 (2011) 627–631

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers

Michael E. Ballard, Harriet de Wit *

Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, IL 60637, USA

ARTICLE INFO

Article history:
Received 2 August 2010
Received in revised form 12 October 2010
Accepted 17 November 2010
Available online 24 November 2010

Keywords:
Alcohol
THC
Cannabinoid
Cognition
Subjective
Humans

ABSTRACT

Rationale: Previous studies examining the combined effects of ethanol and cannabis, or its primary psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), have provided mixed results. Data from an *in vitro* study suggests that combined, sub-threshold doses of these drugs may interact to produce synergistic effects. Very low doses of the two drugs in combination have not been tested in humans.

Materials and methods: This study assessed whether combinations of acute, very low doses of ethanol and THC produce synergistic effects on subjective, cognitive, and physiological measures. Healthy volunteers (n = 11) received capsules containing placebo or THC (2.5 mg), and beverages containing placebo or ethanol (0.1 and 0.2 g/kg) alone, and in combination, across separate sessions, in a within-subjects, randomized, double-blind design. During each session, participants completed measures of working memory, psychomotor ability, and simple reaction time, and provided subjective mood and drug effect ratings. Cardiovascular measures were obtained at regular intervals.

Results: As intended, when administered alone, these very low doses of ethanol and THC had only moderate effects on isolated measures. The combined effects of these drugs were not synergistic, and in some cases appeared to be less-than-additive.

Conclusions: Our data provide no evidence for synergistic effects of acute combinations of very-low-dose ethanol and THC on subjective or physiologic response, or on cognitive performance.

1. Introduction

Alcohol and cannabis are two of the most commonly used psychoactive drugs, and are often used in combination. According to the 2008 National Survey on Drug Use and Health, roughly half (51.6%) of Americans over 12 years of age report current alcohol consumption, and 10.3% have used cannabis in the past year (SAMHSA, 2008). Their combined effects may be of particular concern because these drugs are frequently found together in blood sampled from drivers involved in crashes while under the influence (Bramness et al., 2010; Terhune and Fell, 1982). The effects may be additive, but they might also be synergistic, which could unexpectedly increase performance impairments or risky behaviors (Lane et al., 2004, 2005; Liguori et al., 2002; Ramaekers et al., 2004). Studying the combined behavioral effects of ethanol and Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is valuable for our understanding of these potential risks, and may additionally provide insight into the drugs' mechanisms of action.

Several previous studies have examined combinations of ethanol and cannabis in humans, with mixed results. An early epidemiological study concluded that alcohol and THC "interact synergistically to grossly impair driving performance" (Terhune and Fell, 1982), although a more recent epidemiological study concluded that their combined effects are, at most, only additive (Bramness et al., 2010). There are a few studies which provide evidence that ethanol and THC may produce synergistic effects on some measures. Perez-Reyes et al. (1988) reported that a moderate dose of ethanol (0.42 g/kg, 0.85 g/kg) and a low dose of smoked cannabis (2.4% THC) had additive, and perhaps synergistic, effects in a driving simulator, and Robbe (1998) reported that the combined effects of a low dose of ethanol (0.04% BAC) and smoked cannabis (0.1–0.3 mg/kg THC) on road-tracking and car-following were "at least additive". In one study, Macavoy and Marks (1975) reported synergistic effects between ethanol (0.05 and 0.1% BAC) and THC (2.6 and 5.2 mg) on attention in non-users of cannabis, but not in cannabis users; although, these findings were not replicated in a subsequent study (Marks and MacAvoy, 1989). Cheshire et al. (1976) reported possible synergism between moderate doses of ethanol (0.5 g/kg) and THC (10 mg/70 kg) on perceptual, cognitive, and motor functions. Finally, in rats, Dar (2000) found that ethanol potentiated THC-induced motor incoordination, a finding that was interpreted as behavioral synergism. Nonetheless, most of the controlled studies designed to assess cognitive and subjective mood measures after moderate doses of both drugs found

* Corresponding author. Department of Psychiatry and Behavioral Neuroscience, MC3077, The University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637, USA. Tel.: +1 773 702 1537; fax: +1 773 834 7698.
E-mail address: hdew@uchicago.edu (H. de Wit).

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.11.013

that their combined effects were, at most, only additive (Belgrave et al., 1979; Bramness et al., 2010; Chait and Perry, 1994; Chesher et al., 1977; Lamers and Ramaekers, 2001; Liguori et al., 2002; Lukas and Orozco, 2001; Manno et al., 1971; Perez-Reyes et al., 1988; Ramaekers et al., 2000). Thus, while a few studies provide evidence to suggest that moderate and high doses of ethanol and THC may combine to produce synergistic effects on some mood and performance measures, they appear to contrast with the majority of others, which found that their combined effects are not more-than-additive.

Drug interactions may be either pharmacokinetic or pharmacodynamic. In at least one study, ethanol increased plasma levels of THC after smoking cannabis (Lukas and Orozco, 2001), providing some evidence for a pharmacokinetic interaction. Additionally, two studies found that smoking cannabis increased blood alcohol concentrations (BACs) (Adams et al., 1978; Chesher et al., 1976), although other studies did not see this effect (Belgrave et al., 1979; Bird et al., 1980; Chait and Perry, 1994; Hansteen et al., 1976; Manno et al., 1971; Perez-Reyes et al., 1988). Pharmacodynamically, ethanol and THC act on some of the same neurotransmitter systems, such as the mesolimbic dopamine pathway (Boileau et al., 2003; Di Chiara and Imperato, 1988; Diana et al., 1998; Gessa et al., 1998; Tanda et al., 1997; Weiss et al., 1993). As well, the endocannabinoid system appears to play an important role in ethanol's effects. Perra et al. (2005) showed that pharmacological blockade of CB1 receptors with an inverse agonist abolished ethanol-induced stimulation of dopamine neurons in the ventral tegmental area, and inhibition of neuronal excitability in the nucleus accumbens. Furthermore, mice that were chronically exposed to ethanol exhibited decreased central CB1 receptor density (Basavarajappa et al., 1998) and receptor functionality (Basavarajappa and Hungund, 1999). There is also some indication that ethanol and THC may have synergistic effects on downstream signaling cascades, at very low doses. Results from an *in vitro* study suggested that sub-threshold doses of ethanol and cannabinoid receptor agonists synergistically increase protein kinase A (PKA) signaling (Yao et al., 2003), an enzymatic pathway implicated in addictive behaviors (Lee and Messing, 2008; Nestler, 2001). Thus, there may be both pharmacokinetic and pharmacodynamic interactions between ethanol and THC, which may combine to synergistically affect behavior.

Based on the Yao et al. (2003) observation, the present study investigated the interactive effects of combined very low doses of ethanol and THC in healthy volunteers. We selected marginally active doses of both ethanol and THC, and hypothesized that the combination of the drugs would produce synergistic behavioral effects.

2. Materials and methods

2.1. Subjects

Healthy human volunteers (n = 11) aged 21–35 were recruited from the community through newspaper advertisements, poster and words of mouth referrals. Telephone and in-person screening ensured that candidates met the following inclusion criteria: native English speakers; a high school diploma or the equivalent; cannabis use between 2 and 10 times in the lifetime but not more than 4 times in the last month; no diagnosis of cannabis or alcohol dependence; and no contraindicated medical issues by physical exam by a study physician.

Candidates were excluded if they had a current or prior diagnosis of a Major Axis I DSM-IV disorder including substance abuse or dependence, history of adverse responses to cannabis or alcohol, or if they smoked more than 5 tobacco cigarettes a week. Qualifying participants signed a consent form that detailed the study procedures. Participants were told to abstain from any drugs other than their usual amounts of caffeine or tobacco within 24 h of scheduled sessions, and not to smoke cannabis within the week preceding the session. The study was approved by the local institutional review board and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Study design

The study used a within-subject cross-over design consisting of six sessions conducted from 1 pm–5 pm at least 1 week apart. On each session, participants received a capsule containing placebo or THC (2.5 mg), and a beverage containing 0, 0.1, or 0.2 g/kg ethanol, in randomized order. The six conditions were: (a) placebo capsule/placebo beverage, (b) 2.5 mg THC/placebo beverage, (c) placebo capsule/low ethanol (0.1 g/kg) beverage, (d) 2.5mgTHC/low ethanol (0.1 g/kg) beverage, (e) placebo capsule/moderate ethanol (0.2 g/kg) beverage, and (f) 2.5mgTHC/moderate ethanol (0.2 g/kg) beverage. At the end of the study, the participants were debriefed about the study aims and received payment ($200).

2.3. Experimental procedure

After screening, participants attended an orientation session to explain the procedures, schedule the sessions, and familiarize participants with tasks and self-report questionnaires. Drug administration sessions were conducted in comfortably furnished rooms with a television/VCR, magazines, and a computer for administering questionnaires.

On arrival at the laboratory at 1 pm for each of the six sessions, participants provided breath and urine samples to test for recent drug and alcohol use. Thereafter, they completed pre-drug questionnaires, psychomotor performance, working memory, and risk taking tasks, and measures of blood pressure and heart rate were obtained. Participants then consumed a capsule that contained either placebo or 2.5 mg THC (1:30 pm), and 10 min later completed further subjective and physiological measures. Thirty minutes after ingesting the capsule, participants completed behavioral tasks, and then 60 min after the capsule consumed a beverage containing either 0.1 or 0.2 g/kg ethanol or placebo (2:30 pm). Ten minutes after consuming the beverage, they completed subjective ratings and physiological measures. Subjective ratings and physiological measures were also completed at 40 and 70 min after the beverage, along with behavioral measures. Between measurements, participants were allowed to watch television, movies, or read.

2.4. Dependent measures

2.4.1. Subjective and physiological measures

Subjective effects of drugs were assessed using the Drug Effects Questionnaire (DEQ; (Fischman and Foltin, 1991)), Visual Analog Scale (VAS; (Folstein and Luria, 1973)), Profile of Mood States (POMS; (McNair et al., 1971)), Addiction Research Center Inventory (ARCI; (Martin et al., 1971) including marijuana scale (Chait et al., 1985)), Biphasic Alcohol Effects Scale (BAES; (Martin et al., 1993)), and an end-of-session questionnaire (ESQ). On the DEQ, participants rate the extent to which they are experiencing certain, drug-specific effects (i.e. feel, like, dislike, high, and want more). On the VAS, they rate the extent to which they are feeling specific subjective effects (i.e. sleepy, hungry, stimulated, anxious, sedated, elated, and nauseated). On the POMS, participants rate the extent to which 72 mood adjectives apply to them at the moment. These adjectives form scales (i.e. friendliness, anxiety, depression, elation, anger, depression, fatigue, vigor, arousal, and confusion). The ARCI is a standardized measure of drug effects and consists of six empirically derived scales, which measure drug-induced euphoria (morphine–benzedrine group; MBG), stimulant like effects (amphetamine; A), intellectual efficiency and energy (benzedrine group; BG), sedation (pentobarbital–chlorpromazine alcohol group; PCAG), dysphoria and somatic effects (lysergic acid; LSD), and cannabis effects (M). The BAES is a 14-item adjective rating scale that consists of

"stimulation" and "sedation" subscales. Each adjective item is scored on an 11-point scale from 0 (not at all) to 10 (extremely), where higher scores indicate greater levels of stimulation and sedation.

Heart rate and blood pressure were measured at repeated intervals using a digital monitor (Dinamap 1846SX, Critikon, Tampa, Florida). Blood alcohol concentration (BAC) measurements were obtained with an alco-sensor III hand-held device (Intoximeters, Inc., Saint Louis, Missouri).

2.4.2. Behavioral measures

Digital Symbol Substitution Test (DSST; (Wechsler, 1958)) was used to assess non-specific drug-induced impairment. Participants were shown a code table with pairs of digits and symbols, and rows of double boxes with a digit in the top box and nothing in the bottom box. The task was to use the code table to find the symbol associated with each digit in the box, and write in order as many symbols as possible in the empty boxes below each digit in 30 s. The digit span (Wechsler, 1958) was used to measure working memory performance. In this task, participants are read progressively longer series of numbers ranging from two to nine digits and then asked to repeat the series, forward and backward. Finally, a simple reaction time task from the Automated Neuropsychological Assessment Metrics (ANAM; (Reeves et al., 1993)) was used. In this task the participant is instructed to press a button as quickly as possible each time a "*" symbol appears on the computer monitor.

2.5. Drugs

THC (Marinol® [dronabinol]; Solvay Pharmaceuticals, Marietta, Georgia) capsules were placed in opaque size 00 capsules in doses of 2.5 mg, with dextrose filler. Placebo capsules contained only dextrose. Ethanol was administered at the dose of 0.1 or 0.2 g/kg, with 95% ethanol, diluted with cranberry juice. The placebo beverage contained cranberry juice with 1 ml of 95% ethanol floating at the top to mask the taste.

2.6. Data analyses

Three-way repeated measures ANOVAs were undertaken, with ethanol (0, 0.1 g/kg, 0.2 g/kg), THC (0, 2.5 mg), and time as within-subjects variables. Change from baseline scores from time points following administration of both drugs were used for subjective and physiological, and the majority of cognitive, measures. ANAM measures were only taken once during sessions; hence raw scores were used for this analysis. Significance was set at $p \leq 0.05$, and significant main and interaction effects were examined further by paired t-tests with Bonferroni correction for individual drug doses compared to placebo scores, or at individual time points as necessary. Due to a computer malfunction, data from a few subjective measures from one participant at a single condition (i.e., THC + EtOH 0.2 g/kg) were lost — accounting for <2% of data for the affected scales. In order to retain use of this participant's data from the 5 other treatment conditions for analysis, mean group change from baseline scores were substituted for the missing values. We additionally verified that exclusion of this participant from analysis of affected measures had no effect on significance outcome.

3. Results

A total of 11 participants (5 female) with a mean age (±S.D.) of 25.3 (±3.1) years took part in this study. Seven were White, 2 were Black or African-American, and 2 were Asian. Participants reported smoking cannabis a mean of 4.6 ± 2.6 times in their lifetime, and only one participant reported using cannabis in the month prior to participation. Other lifetime drug use was light — three participants reported any lifetime recreational use of stimulants and/or ecstasy, one had used hallucinogens such as psilocybin, and one reported use of inhalants. In the 30 days prior to participation, four participants reported smoking cigarettes at least weekly and all but one had consumed alcohol at least weekly (Table 1).

Table 1
Participant demographics and summary of drug use.

Demographic characteristics	
Ethnicity (White/Black/Asian)	7/2/2
Age (mean years ± SEM)	25.3 ± 3.1
Gender (male/female)	6/5
Education (mean years ± SEM)	16.5 ± 2.3
Current drug use	
Alcohol use (mean drinks/week ± SEM)	5.8 ± 3.8
Tobacco cigarette use (N smoking>1 cigarette/week)	4
Caffeine use (mean cups/week ± SEM)	6.9 ± 6.5
Lifetime recreational drug use	
Cannabis (mean times used, ever ± SEM)	4.6 ± 2.6
Stimulants (# ever used/total)	3/11
Sedatives or opiates (# ever used/total)	0/11
Hallucinogens (# ever used/total)	1/11
Inhalants (# ever used/total)	1/11

3.1. Ethanol effects

When given alone, 0.1 and 0.2 g/kg ethanol produced only modest effects on subjective ratings and measures of cognitive performance. Interestingly, participants reported liking the effects of the moderate dose of ethanol (0.2 g/kg), and wanting more of this dose (Table 2), but neither dose of ethanol significantly affected DEQ ratings of drug "feel" compared to placebo. Despite a significant main effect of ethanol on feelings of euphoria as measured by the ARCI MBG scale (Table 2), neither dose of ethanol differed significantly from placebo on *post hoc* tests. Ethanol did not impair digit span performance overall, although visual inspection and a follow-up *post hoc* test indicated that 0.1 g/kg ethanol impaired total performance at 70 min post-ethanol (Table 2). Ethanol significantly increased BACs, with doses of 0.1 and 0.2 g/kg resulting in BACs of 0.02 and 0.04%, respectively, at 10 min post-ethanol, and these dropped to 0.01 and 0.02% at 40 min (Table 2). No other significant effects were seen on behavioral or physiological measures.

3.2. THC effects

When given alone, 2.5 mg THC produced modest effects on subjective ratings, measures of cognitive performance, and physiological measures. Although participants did not report feeling any drug effects, THC significantly reduced POMS 'vigor' scale scores (Table 3) and increased sedation as measured by the ARCI PCAG scale. THC altered POMS 'friendliness' scale scores (THC × time: $F[2,9] = 4.99$; $p = 0.035$) but none of the individual time points differed

Table 2
Effects of ethanol. Mean change from pre-drug baseline ± SEM scores for placebo, 0.1, and 0.2 g/kg EtOH averaged across all post-beverage time points (DEQ, ARCI and BAC). Values for digit span task are mean change from baseline performance at 70 min post-beverage.

Measure	Placebo	EtOH 0.1 g/kg	EtOH 0.2 g/kg	F[2,9] (p-value)
DEQ — like	0.06 ± 0.04	0.15 ± 0.03	0.20 ± 0.06*	9.88 (0.005)
DEQ — want more	0.09 ± 0.05	0.16 ± 0.05	0.20 ± 0.07*	8.54 (0.008)
ARCI — MBG	0.03 ± 0.12	0.27 ± 0.46	1.00 ± 0.35	6.32 (0.019)
Digit span Total	1.00 ± 0.69	−2.55 ± 0.84*	−0.09 ± 0.81	4.48 (0.045)
BAC (%)	0.00 ± 0.00	0.01 ± 0.00	0.02 ± 0.00	32.20 (<0.001)

*$p \leq 0.05$ compared to placebo; Bonferroni pairwise comparisons.

Table 3
Effects of THC. Mean change from pre-drug baseline ± SEM scores for placebo and 2.5 mg THC averaged across all post-capsule time points (POMS, ARCI, and diastolic BP). Values for DSST are mean change from baseline performance at 100 min post-capsule.

Measure	Placebo	THC	F[1,10] (p-value)
POMS — Vigor	−2.18 ± 0.69	−4.76 ± 0.84*	5.58 (0.040)
ARCI — PCAG	1.55 ± 0.68	3.73 ± 0.83*	9.02 (0.013)
DSST	1.45 ± 1.32	−3.64 ± 1.75*	5.27 (0.045)
Diastolic BP	2.86 ± 1.85	−3.14 ± 1.52*	5.25 (0.045)

*$p \leq 0.05$ compared to placebo; Bonferroni pairwise comparisons.

significantly in *post hoc* tests. Additionally, THC slightly impaired performance on the DSST overall ($F[1,10] = 4.60$; $p = 0.058$), and visual inspection and a follow-up *post hoc* test indicated that THC significantly impaired performance on this task at 100 min (Table 3). THC also significantly reduced diastolic blood pressure overall (Table 3). No other significant effects were seen on behavioral or physiological measures.

3.3. THC × ethanol interaction effects

The only interaction observed between ethanol and THC was on DEQ ratings of "want more" (Fig. 1; THC × ethanol: $F[2,9] = 4.11$; $p = 0.054$). Whereas THC alone did not affect ratings of "want more", THC attenuated the increased ratings seen after administration of ethanol (0.2 g/kg).

4. Discussion

The aim of this study was to evaluate the subjective, cognitive, and physiological effects of very low doses of ethanol and THC in combination in healthy volunteers. Based on preclinical evidence of synergistic effects at sub-threshold doses, we hypothesized that combined very low doses of these drugs might similarly produce synergistic effects on some of these measures. As intended, and consistent with other studies (Chait and Perry, 1994; Koelega, 1995), these doses of ethanol and THC produced only modest subjective, cognitive, and physiologic effects when administered alone. However, contrary to our hypothesis, the combined effects of the two drugs were not additive or synergistic on any measure.

The only measure on which ethanol and THC interacted was on participants' ratings of desire to consume more of the drug they received. On this measure, THC, when given in combination with ethanol, appeared to reduce the increased ratings of wanting more ethanol after ethanol administration. While this finding was contrary to our hypothesis, it is consistent with a previous study in which participants consumed less ethanol when cannabis was concurrently available (Mendelson et al., 1986). This suggests that THC may either dampen the effects of ethanol, or replace the desire for more. However, our findings are apparently not consistent with some animal studies in which THC increased consumption of freely-available ethanol solutions

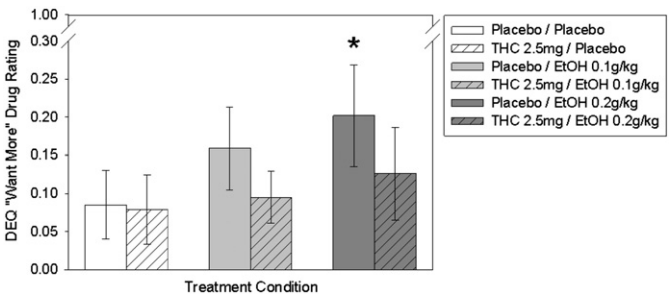

Fig. 1. Combined effects of THC and ethanol on DEQ ratings of "want more drug". Data are mean change from pre-drug baseline scores ± 1 SEM.*$p \leq 0.05$ compared to placebo/placebo condition; Bonferroni pairwise comparisons.

(Linsenbardt and Boehm, 2009; McMillan and Snodgrass, 1991). It is difficult to reconcile the animal and human findings because of the array of methodological differences.

In our study, there also was no evidence for a pharmacokinetic interaction. The ethanol doses of 0.1 and 0.2 g/kg produced peak BAC levels of 0.02 and 0.04% at 10 min, respectively, and this was not different in the conditions when participants were pretreated with THC. This lack of effect of THC on BAC is in agreement with several studies (Belgrave et al., 1979; Bird et al., 1980; Chait and Perry, 1994; Hansteen et al., 1976; Manno et al., 1971; Perez-Reyes et al., 1988) but not consistent with others which found that smoked cannabis can potentiate BAC (Adams et al., 1978; Chesher et al., 1976).

Our hypothesis was that very low doses of ethanol and THC in combination might produce synergistic effects in humans, even though this has not been observed at higher doses (Belgrave et al., 1979; Bramness et al., 2010; Chait and Perry, 1994; Chesher et al., 1977; Lamers and Ramaekers, 2001; Liguori et al., 2002; Lukas and Orozco, 2001; Manno et al., 1971; Perez-Reyes et al., 1988; Ramaekers et al., 2000). In our study, neither drug alone increased reports of feeling a drug effect. The moderate dose of ethanol (0.2 g/kg) produced small increases in ratings of drug liking and wanting more drug, and produced a small working memory impairment in the digit span task. THC alone produced small decreases in 'vigor' ratings on the POMS and increases in ARCI PCAG scale scores, and slightly impaired psychomotor performance on the DSST. Thus, the doses we used were threshold doses, and no synergistic effects were detected. It remains to be determined whether, consistent with the *in vitro* findings, the drugs interact under other conditions.

Our data suggest that, contrary to *in vitro* findings, combined very low doses of ethanol and oral THC do not produce synergistic effects in humans. These findings do not rule out the possibility that there may be interactions between ethanol and smoked whole plant cannabis, either through other chemical components in cannabis (Wachtel et al., 2002) or related to dose or time course. Although interactions between ethanol and whole plant cannabis may account for epidemiological reports of synergism, most laboratory studies using higher doses and smoked cannabis also found no synergistic effects. It additionally remains possible that synergism would be detected with a larger sample, or if there was greater control over plasma levels of THC. Future studies employing intravenous drug administration and careful monitoring of blood levels may reveal interactions at discrete dose combinations of these drugs. Notwithstanding these considerations, we failed to observe synergistic effects of very-low-dose ethanol and THC in humans. This disparity could be related to a multitude of discrepancies between the PKA signaling model used by Yao et al. (2003), and the behavioral measures used here. Whereas the *in vitro* findings provide insight into the molecular mechanisms of these two drugs at a neuronal level, their potential significance to explain behavior remains unclear.

In summary, we found no evidence of synergistic effects of low, threshold doses of ethanol and THC in healthy volunteers. Indeed, on at least one measure their combined effects were less-than-additive. Taken together, it does not appear that such low doses of ethanol and THC combine to produce a substantially greater risk of cognitive impairment than either drug taken alone.

Acknowledgments

This research was supported by DA02812. M.E.B. was supported by T32 DA007255. The authors acknowledge assistance of Jolan Terner-Rosenthal, Gillinder Bedi, and Vera Spagnolo.

References

Adams AJ, Brown B, Haegerstrom-Portnoy G, Flom MC, Jones RT. Marijuana, alcohol, and combined drug effects on the time course of glare recovery. Psychopharmacology (Berl) 1978;56:81–6.

Basavarajappa BS, Hungund BL. Chronic ethanol increases the cannabinoid receptor agonist anandamide and its precursor N-arachidonoylphosphatidylethanolamine in SK-N-SH cells. J Neurochem 1999;72:522–8.
Basavarajappa BS, Cooper TB, Hungund BL. Chronic ethanol administration down-regulates cannabinoid receptors in mouse brain synaptic plasma membrane. Brain Res 1998;793:212–8.
Belgrave BE, Bird KD, Chesher GB, Jackson DM, Lubbe KE, Starmer GA, et al. The effect of (−) trans-delta9-tetrahydrocannabinol, alone and in combination with ethanol, on human performance. Psychopharmacology (Berl) 1979;62:53–60.
Bird KD, Boleyn T, Chesher GB, Jackson DM, Starmer GA, Teo RK. Intercannabinoid and cannabinoid–ethanol interactions on human performance. Psychopharmacology (Berl) 1980;71:181–8.
Boileau I, Assaad JM, Pihl RO, Benkelfat C, Leyton M, Diksic M, et al. Alcohol promotes dopamine release in the human nucleus accumbens. Synapse 2003;49:226–31.
Bramness JG, Khiabani HZ, Morland J. Impairment due to cannabis and ethanol: clinical signs and additive effects. Addiction 2010;105:1080–7.
Chait LD, Perry JL. Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. Psychopharmacology (Berl) 1994;115: 340–9.
Chait LD, Fischman MW, Schuster CR. 'Hangover' effects the morning after marijuana smoking. Drug Alcohol Depend 1985;15:229–38.
Chesher GB, Franks HM, Hensley VR, Hensley WJ, Jackson DM, Starmer GA, et al. The interaction of ethanol and delta9-tetrahydrocannabinol in man: effects on perceptual, cognitive and motor functions. Med J Aust 1976;2:159–63.
Chesher GB, Franks HM, Jackson DM, Starmer GA, Teo RK. Ethanol and delta9-tetrahydrocannabinol interactive effects on human perceptual, cognitive and motor functions. II. Med J Aust 1977;1:478–81.
Dar MS. Cerebellar CB(1) receptor mediation of Delta(9)-THC-induced motor incoordination and its potentiation by ethanol and modulation by the cerebellar adenosinergic A(1) receptor in the mouse. Brain Res 2000;864:186–94.
Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 1988;85:5274–8.
Diana M, Melis M, Gessa GL. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur J Neurosci 1998;10:2825–30.
Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. Br J Addict 1991;86:1563–70.
Folstein MF, Luria R. Reliability, validity, and clinical application of the visual analog mood scale. Psychol Med 1973;3:8.
Gessa GL, Melis M, Muntoni AL, Diana M. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. Eur J Pharmacol 1998;341: 39–44.
Hansteen RW, Miller RD, Lonero L, Reid LD, Jones B. Effects of cannabis and alcohol on automobile driving and psychomotor tracking. Ann NY Acad Sci 1976;282:240–56.
Koelega HS. Alcohol and vigilance performance: a review. Psychopharmacology (Berl) 1995;118:233–49.
Lamers CT, Ramaekers JG. Visual search and urban driving under the influence of marijuana and alcohol. Hum Psychopharmacol 2001;16:393–401.
Lane SD, Cherek DR, Pietras CJ, Tcheremissine OV. Alcohol effects on human risk taking. Psychopharmacology (Berl) 2004;172:68–77.
Lane SD, Cherek DR, Tcheremissine OV, Lieving LM, Pietras CJ. Acute marijuana effects on human risk taking. Neuropsychopharmacology 2005;30:800–9.
Lee AM, Messing RO. Protein kinases and addiction. Ann NY Acad Sci 2008;1141:22–57.
Liguori A, Gatto CP, Jarrett DB. Separate and combined effects of marijuana and alcohol on mood, equilibrium and simulated driving. Psychopharmacology (Berl) 2002;163: 399–405.
Linsenbardt DN, Boehm II SL. Agonism of the endocannabinoid system modulates binge-like alcohol intake in male C57BL/6J mice: involvement of the posterior ventral tegmental area. Neuroscience 2009;164:424–34.
Lukas SE, Orozco S. Ethanol increases plasma delta(9)-tetrahydrocannabinol (THC) levels and subjective effects after marihuana smoking in human volunteers. Drug Alcohol Depend 2001;64:143–9.
Macavoy MG, Marks DF. Divided attention performance of cannabis users and non-users following cannabis and alcohol. Psychopharmacologia 1975;44:147–52.
Manno JE, Kiplinger GF, Scholz N, Forney RB. The influence of alcohol and marihuana on motor and mental performance. Clin Pharmacol Ther 1971;12:202–11.
Marks DF, MacAvoy MG. Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination. Psychopharmacology (Berl) 1989;99:397–401.
Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Ther 1971;12:245–58.
Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM. Development and validation of the Biphasic Alcohol Effects Scale. Alcohol Clin Exp Res 1993;17:140–6.
McMillan DE, Snodgrass SH. Effects of acute and chronic administration of delta 9-tetrahy-drocannabinol or cocaine on ethanol intake in a rat model. Drug Alcohol Depend 1991;27:263–74.
McNair D, Lorr M, Droppleman L. Profile of mood states. San Diego: Educational and Industrial Testing Service; 1971.
Mendelson JH, Mello NK, Lex BW. Alcohol and marijuana: concordance of use by men and women. NIDA Res Monogr 1986;68:117–41.
Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001;2:119–28.
Perez-Reyes M, Hicks RE, Bumberry J, Jeffcoat AR, Cook CE. Interaction between marihuana and ethanol: effects on psychomotor performance. Alcohol Clin Exp Res 1988;12:268–76.
Perra S, Pillolla G, Melis M, Muntoni AL, Gessa GL, Pistis M. Involvement of the endogenous cannabinoid system in the effects of alcohol in the mesolimbic reward circuit: electrophysiological evidence in vivo. Psychopharmacology (Berl) 2005;183:368–77.
Ramaekers JG, Robbe HW, O'Hanlon JF. Marijuana, alcohol and actual driving performance. Hum Psychopharmacol 2000;15:551–8.
Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 2004;73:109–19.
Reeves D, Bleiberg J, Spector J. Validation of the ANAM battery in multi-center head injury rehabilitation studies. Arch Clin Neuropsychol 1993;8:1.
Robbe H. Marijuana's impairing effects on driving are moderate when taken alone but severe when combined with alcohol. Hum Psychopharmacol 1998:13.
SAMHSA. National Survey on drug use and health. In: Studies, OoA, editor, 2008.
Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science 1997;276:2048–50.
Terhune KW, Fell JC. United States National Highway Traffic Safety Administration, Calspan Field Services. The role of alcohol, marijuana, and other drugs in the accidents of injured drivers NHTSA technical report. National Highway Traffic Safety Administration; 1982.
Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H. Comparison of the subjective effects of delta(9)-tetrahydrocannabinol and marijuana in humans. Psychopharmacology (Berl) 2002;161:331–9.
Wechsler D. The measurement and appraisal of adult intelligence. Baltimore: The Williams & Wilkins Company; 1958.
Weiss F, Lorang MT, Bloom FE, Koob GF. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. J Pharmacol Exp Ther 1993;267:250–8.
Yao L, Fan P, Jiang Z, Mailliard WS, Gordon AS, Diamond I. Addicting drugs utilize a synergistic molecular mechanism in common requiring adenosine and Gi-beta gamma dimers. Proc Natl Acad Sci U S A 2003;100:14379–84.