Published in final edited form as:
Clin Chem. 2013 March ; 59(3): . doi:10.1373/clinchem.2012.194381.

Cannabis Effects on Driving Skills

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Abstract

BACKGROUND—Cannabis is the most prevalent illicit drug identified in impaired drivers. The effects of cannabis on driving continue to be debated, making prosecution and legislation difficult. Historically, delays in sample collection, evaluating the inactive Δ^9-tetrahydrocannabinol (THC) metabolite 11-nor-9-carboxy-THC, and polydrug use have complicated epidemiologic evaluations of driver impairment after cannabis use.

CONTENT—We review and evaluate the current literature on cannabis' effects on driving, highlighting the epidemiologic and experimental data. Epidemiologic data show that the risk of involvement in a motor vehicle accident (MVA) increases approximately 2-fold after cannabis smoking. The adjusted risk of driver culpability also increases substantially, particularly with increased blood THC concentrations. Studies that have used urine as the biological matrix have not shown an association between cannabis and crash risk. Experimental data show that drivers attempt to compensate by driving more slowly after smoking cannabis, but control deteriorates with increasing task complexity. Cannabis smoking increases lane weaving and impaired cognitive function. Critical-tracking tests, reaction times, divided-attention tasks, and lane-position variability all show cannabis-induced impairment. Despite purported tolerance in frequent smokers, complex tasks still show impairment. Combining cannabis with alcohol enhances impairment, especially lane weaving.

SUMMARY—Differences in study designs frequently account for inconsistencies in results between studies. Participant-selection bias and confounding factors attenuate ostensible cannabis effects, but the association with MVA often retains significance. Evidence suggests recent

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Presented at the 2012 Society of Forensic Toxicologists Conference, Boston, MA. Received August 5, 2012; accepted September 21, 2012.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest*:
Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: Intramural Research Program, National Institute on Drug Abuse, NIH.
Expert Testimony: None declared.
Patents: None declared.

smoking and/or blood THC concentrations 2–5 ng/mL are associated with substantial driving impairment, particularly in occasional smokers. Future cannabis-and-driving research should emphasize challenging tasks, such as divided attention, and include occasional and chronic daily cannabis smokers.

Nearly two thirds of US trauma center admissions are due to motor vehicle accidents (MVAs),[3] with almost 60% of such patients testing positive for drugs or alcohol (1). In 2010, 11.4% of Americans 12 years or older drove under the influence of alcohol, and 10.6 million drove under the influence of illicit drugs (2). Despite real or perceived impairment, individuals report a willingness to drive if there is a good reason (3, 4) or if they believe they are tolerant (5). Alcohol and cannabis are the drugs most frequently detected (6).

Cannabis is the most widely consumed illicit substance worldwide (2). In 2009, 125–203 million individuals 15–64 years of age ingested cannabis in the previous year (7). In the US in 2010, 6.9% of individuals ≥12 years old had smoked cannabis in the previous month (2). The 2007 National Roadside Survey reported cannabis as the most common illicit drug quantified in drivers' blood or oral fluid (OF), with 8.6% of nighttime drivers testing positive for Δ^9-tetrahydrocannabinol (THC) (6, 8). Thus, driving under the influence of cannabis (DUIC) is a growing public health concern.

The acute psychological effects of cannabinoids include euphoria, dysphoria, sedation, and altered perception (9). The intensity of euphoria/dysphoria varies with dose, administration route, and vehicle; expectations of effects; and the cannabis smoker's environment and personality. Cannabis is associated with subjective physical discomfort and effort, as well as with lethargy (10). Acute cannabis intoxication produces dose-related impairment in cognitive and psychomotor functioning, and it can produce risk-taking behavior that can impair driving skills (11, 12). Dose refers to THC content in cannabis preparations in milligrams or micrograms per kilogram. Factors influencing dose include user experience, smoking topography, and cannabis THC concentration, all of which vary worldwide.

Cannabis effects include alterations in reaction time (RT), perception, short-term memory, attention, motor skills, tracking, and skilled activities (13, 14).

Objective and Search Methods

This review presents relevant published data and evaluates current knowledge of cannabis' effects on driving. The electronic databases PubMed, Scopus, Web of Science, and Embase were searched through February 20, 2012, for the key words "cannabis"; "marijuana"; "automobile driving"; "accidents, traffic"; and "motor vehicles." Additional articles were selected from references in identified sources.

DUIC: Epidemiologic Data

Early DUIC epidemiologic studies did not provide strong evidence of cannabis causality, because individuals with only nonpsychoactive 11-nor-9-carboxy-THC (THCCOOH) in the blood were included in cannabis-exposed groups (15). THCCOOH has a long window of detection in blood, well after the acute effects dissipate (16). In less-than-daily cannabis smokers, THCCOOH was detected up to 7 days after the smoking of 1 joint containing approximately 38 mg THC (cutoff, 0.5 ng/mL) (17). THC blood concentrations decrease

[3]Nonstandard abbreviations: MVA, motor vehicle accident; OF, oral fluid; THC, Δ^9-tetrahydrocannabinol; DUIC, driving under the influence of cannabis; RT, reaction time; THCCOOH, 11-nor-9-carboxy-THC; OR, odds ratio; BAC, blood alcohol content; FARS, Fatality Analysis Reporting System; CTI, clinical test for impairment; CT, critical tracking; DAT, divided-attention task; SDLP, SD of lateral position; DWI, driving while intoxicated.

rapidly after smoking (16, 18). Blood collection occurs about 90 min after arrest (19) and 3 to 4 h after an accident (20)—long enough that many samples have become cannabinoid negative, although the blood may have been positive at the time of the event. There also were few cannabis-only cases; multiple drugs with potential to contribute to impairment were usually found.

Cannabis smokers share demographic characteristics similar to those of other groups with a high crash risk, including youth (ages 18–25 years), male sex, risk taking, and high drunk-driving incidence (8, 20–23). Cannabis tolerance may develop in frequent smokers, with less impairment than for occasional smokers with similar THC concentrations (24). Statistically controlling for these potentially confounding variables sometimes makes results equivocal (25, 26).

Ten epidemiologic studies from 6 countries have investigated the relationship of MVA to cannabis intake (Tables 1 and 2). Various case control designs used self-reporting or objective biological measurements. Adjusting for confounders reduced the apparent effect sizes relative to crude values and sometimes caused a loss of statistical significance (21, 27–29). Six studies evaluated relationships between cannabis exposure and MVA by self-report (Table 1; see Table 1 in the Data Supplement that accompanies the online version of this review at http://www.clinchem.org/content/vol59/issue3). Examining cannabis consumption rather than DUIC has generally produced nonsignificant or lower odds ratios (ORs) than targeting DUIC. More frequent cannabis exposure (addiction patients; more than once a week, >4 days/week) was associated with a significantly increased MVA risk (risk ratio, 1.49; OR, 2.76 and 2.5, respectively) (27, 30, 31). A crude 11.4 OR for MVA injury within 3 h of cannabis smoking dropped to a nonsignificant OR of 0.8 after adjusting for confounders (28), whereas DUIC after smoking during the previous hour almost doubled crash risk [ORs, 1.84 (21) and 2.61 (27)], a finding that withstood adjustment for demographic characteristics (21, 27) and self-reported driving under the influence of alcohol (21). Driving within 1 h after smoking produced higher MVA ORs than driving within 2 h (32). Of 3 case control studies that included objective cannabis measurement (Table 2), two studies used urine samples and found no significantly increased ORs (33, 34), findings that are consistent with cannabis' extended urine-detection window. In the third study, 204 driver fatalities (blood THC ≥0.6 ng/mL) were compared with randomly selected control drivers (OF THC ≥5 ng/mL) (29). The crude OR for fatality was 13.9 for cannabis-positive drivers, and that result retained significance (OR, 8.6) after adjusting for demographics, time period, and season. Too few cannabis-only cases had accrued by then to establish a significant adjusted OR for THC alone. Two recent metaanalyses, each of which evaluated data from 9 epidemiologic studies (2 in common), documented a significantly increased MVA risk [OR, 2.66 (35) and 1.92 (36)], even after controlling for confounding variables.

Studies that presented culpability risk associated with cannabis use are summarized in Table 3 (see Table 2 in the online Data Supplement for additional details). Increased blood THC concentrations were associated with a higher culpability OR. In 2004, Drummer et al. (15) demonstrated a statistically significant increase in the adjusted OR for crash responsibility (2.7) for drivers with any measurable blood THC relative to drug-free drivers. When the blood THC concentration was ≥5 ng/mL, the OR increased to 6.6, a culpability comparable to that of a 0.15% blood alcohol concentration (BAC). Among alcohol-negative drivers who were positive for cannabinoids, the 1.39 unadjusted OR was significant for having at least 1 driver-related factor, which is defined as a potentially unsafe behavior or action contributing to the collision, in 10 years of Fatality Analysis Reporting System (FARS) data (22). After demographics and driving record were controlled, the OR remained significant (1.29). FARS drug test results are based on blood or urine; including urine data may contribute to low ORs, owing to the extended cannabinoid-detection windows. In France, drivers who had

detectable blood THC concentrations and were involved in fatal crashes had a 3.17 OR for crash responsibility (1.7 OR after adjustment for demographics, BAC, THC concentration, and crash time) (37). The driver-responsibility OR increased with increasing blood THC concentration. Crude (adjusted) ORs were 2.18 (1.57), 2.54 (1.54), 3.78 (2.13), and 4.72 (2.12) for <1, 1–2, 3–4, and ≥5 ng/mL, respectively. Although relatively few studies have evaluated the relationship of driver responsibility and cannabis intoxication, an increased blood THC concentration was strongly associated with driver MVA culpability.

The debate on cannabis' effects on driving continues despite these findings, creating challenges for implementing effective drugged-driving policies (15, 37, 38). To date, 17 states and the District of Columbia have enacted medical marijuana laws (39). Colorado, which legalized medical marijuana in 2000, has seen increased numbers of DUIC cases and is considering a 5- ng/mL blood THC per se law. This proposal generated strong debate, despite the evidence showing increased culpability (40). In Drummer's 58 cannabis-only culpable MVA cases (15), the median blood THC concentration was 12 ng/mL, with 84% of the cases having THC concentrations ≥5 ng/mL. Increasing blood THC concentrations predict increasing driving impairment. The median blood THC concentration for 456 Norwegian suspected drugged drivers (1997–1999) with blood samples positive for cannabis only was 2.2 ng/mL (range 0.3–45.3 ng/mL) (24). The physician who performed the clinical test for impairment (CTI) judged 54% of the individuals as impaired. Grouping drivers by concentration range and adjusting for sex, needle marks, and self-reported regular cannabis consumption produced impairment ORs of 2.4, 2.5, and 3.2 for blood THC concentrations of 3.0–4.8, 4.9–10.1, and >10.2 ng/mL, respectively. Although some investigators have described a strong linear relationship between serum and OF THC concentrations, linear relationships between performance impairment and serum and OF concentrations are weak (41), and the results for interindividual variation show that it is inaccurate to predict plasma concentrations from OF concentrations (42).

In Australia, it is illegal to drive with any detectable blood THC (43). Police randomly test blood or OF for THC. In the first year of testing, median THC OF and blood concentrations were 81 ng/mL (range, 5–6484 ng/mL) and 6 ng/mL (range, 3–19 ng/mL), respectively (44). One year later, the median OF THC concentration was 66.5 ng/mL (median for blood, 6 ng/mL) (43). Mean OF and blood concentrations were 274.3 and 7.6 ng/mL. In 2005, Switzerland imposed a punishable blood THC limit of 2.2 ng/mL (45). Of 1704 drivers confirmed to be THC positive (≥1.0 ng/mL), 1292 (76%) had THC concentrations >2.2 ng/mL. Mean, median, and maximum blood concentrations were 5.8, 3.8, and 62 ng/mL, respectively. In cannabis-only cases (57.7%), mean (8.1 ng/mL vs 5.9 ng/mL) and median (5.8 ng/mL vs 4.1 ng/mL) concentrations were significantly higher for single vs polydrug users, respectively. A 10-year study of driving under the influence of drugs in Sweden (8794 THC-positive cases) revealed mean and median blood THC concentrations of 2.1 ng/mL and 1.0 ng/mL, respectively (19). Drivers claiming regular cannabis consumption (177 of 456) were significantly less often (32% vs 55%) to be judged as impaired by CTI than occasional smokers, with no difference in the median blood THC concentration (24). A multiple regression model controlling for THC concentration revealed a 1.8 impairment OR for occasional vs regular cannabis smokers.

A 2007 international expert evaluation of epidemiologic and experimental evidence concluded that risk-based legal limits were unsupportable (38). The consensus proposal was a serum lower limit of 7–10 ng/mL, which was based on metaanalyses of experimental data, with a safety margin added for individual variability and laboratory error. In contrast, Jones et al. (19) advocated that zero tolerance based on THC limits of quantification is more pragmatic, because any nonzero science-based per se laws would allow many individuals to evade prosecution. The debate is complicated by the temporal dissociation of THC

concentrations from acute driving impairment. Karschner et al. (46) recently reported THC concentrations (≥0.25 ng/mL) in whole blood and plasma samples obtained from chronic daily cannabis smokers monitored continuously for abstinence for >7 days. Recently Bosker et al. (47) documented psychomotor impairment in chronic daily cannabis smokers relative to matched occasional drug users with respect to validated driving-impairment indicators [critical tracking (CT) and divided attention] through 21–23 days of abstinence. Residual cognitive impairment (48) and withdrawal effects, such as sleep disruption (49), were reported after chronic cannabis smoking. These effects may impair driving performance.

DUIC: Experimental Data

Experimental studies of driving performance under the influence of cannabis are the most rigorous way to evaluate impairment causality. Tables 4 and 5 summarize the results of laboratory studies on cannabis-induced neurocognitive function and driving (simulator and on-road). Study details—including THC dose, the participants' history of cannabis use, performance measures, and results—are presented in Tables 3 and 4 in the online Data Supplement. Past experimental studies often were inconclusive because outcome measures lacked sensitivity and had not been tailored to specific THC effects (50, 51). Cannabis drivers appeared to be aware of impairment and attempted to compensate by driving more slowly and taking fewer risks (4, 10, 52–55). Perceived driving effort increased under the influence of THC (4). Others reported that it was not possible to fully compensate because of a control cost (53). THC's impairing effects increase with task complexity, so a realistic driving task involves subtasks requiring simultaneous attention. Study participants performed worse (*a*) on divided-attention tasks (DATs) (≥2 subtasks performed simultaneously) (52, 53, 56); (*b*) during unexpected circumstances and choices; or (*c*) during long, monotonous drives. Cannabis-associated impairment may manifest as a failure to demonstrate expected practice effects, a result suggesting drivers lose some benefit afforded by prior experiences (55). An increased RT is among the most common cannabis-associated impairments (10, 12, 50, 53, 57, 58). Road tracking (maintaining the correct road position) is one of the most sensitive, dose-dependent measures (59). THC intake increases lane position variability (weave) or SD of lateral position (SDLP) (10, 53, 59, 60), as well as steering wheel variability (10, 53). A recent study demonstrated significant THC-induced cognitive performance decrements (immediate recall, attention, working memory, executive function) (61) in occasional smokers over a wide range of prior cannabis exposure (2–1000 lifetime episodes). One 3.95% THC cigarette produced a degree of body sway and brake latency similar to that observed for a 0.05% breath alcohol content (57).

Five controlled cannabis-administration studies examined smoked cannabis' effects on neurocognitive function (Table 4; see Table 3 in the online Data Supplement). THC doses of 13 mg and 17 mg did not produce time or distance perception effects in chronic daily cannabis smokers at approximately 1.25 h after smoking (62). Individuals who smoked cannabis one or more times per month underestimated 60- and 120-s intervals 1.25 h after smoking two 3.6% THC cigarettes (4 puffs/cigarette) administered 2 h apart (56). THC intake (13 and 17 mg) produced minor but significant dose-dependent impairment in a card-sorting task at approximately 0.75 h after smoking (62) and in a digit–symbol substitution test (56). At 1 hour after smoking, neither 13 mg nor 17 mg THC significantly affected decision-making speed in a gambling task (62), although the percentage of participants who chose least-likely outcomes was significantly higher after the higher dose than after ingesting placebo. RT in a Tower of London test (decision-making) after 400 and 500 μg/kg THC (approximately 28 mg and 35 mg, respectively) was not significantly affected in occasional (≤1 day/week) or frequent (>4 days/week) smokers (5, 63). The number of correct decisions in the Tower of London tests decreased significantly at 0.75–5.75 h after recreational smokers (≥5 times in the previous year) consumed 500 μg/kg THC (41), but

frequent smokers (>4 days/week) were not significantly affected after 1 h (5). Complex tasks requiring multiple neurocognitive and/or neuromotor skills were particularly sensitive to THC's impairing effects and displayed less tolerance. In a virtual maze, ingestion of 17 mg THC significantly increased wall collisions (5.5) relative to the placebo (2.9), and 13 mg THC also increased wall collisions (3.2) (62). Significant CT performance decrements were observed in occasional smokers 0.25–5.25 h after they smoked 250 μg/kg (approximately 17.5 mg) THC (41) and at 0.17–7.08 h after they smoked 500 μg/kg (5, 41). In these experiments, THC did not significantly affect CT in frequent smokers (>4 days/week) (5, 63), but DATs (5, 56, 63) and RTs (stop-signal task) (5, 41) reflected impairment in both frequent and occasional smokers.

The results of simulator and on-road studies are briefly summarized in Table 5 and are fully characterized in Table 4 in the online Data Supplement. Driving-simulator studies offer greater face validity than laboratory studies for measuring effects of THC on driving effects and are less risky for participants. Simulators also allow measurement of specific performance decrements in ways unachievable in actual road-driving experiments. Nine simulator experiments were examined. RT, road tracking, speed, and speed SD were the most commonly measured outcomes. THC ingestion dose-dependently increased RT in 4 of 6 studies (10, 53, 55, 57, 64, 65). Low THC doses (13 and 17 mg) produced significant and dose-dependent increases in RT in a DAT (10), suggesting a particular sensitivity of a DAT to THC effects. Only 1 simulator experiment included headway maintenance (53). Smoked THC (19 and 38 mg) significantly and dose-dependently increased the headway mean and SD relative to placebo. The most sensitive road-tracking measure was SDLP, results of which revealed THC-associated impairment in 2 of 4 studies. Relatively low-dose (13 and 17 mg) smoked THC increased SDLP relative to placebo in occasional smokers (1–4 times per month) (10), and 19 mg and 38 mg also produced significant increases (4 cm and 7 cm, respectively) (53). No significant increases in SDLP were reported after 13 mg in occasional smokers (1–4 times per month) (3) or after 22.9 mg in smokers who smoked 1–10 times per month (55). Other monitored road-tracking outcomes were the number of cones knocked over (57), the percentage of time in a lane (60), and "straddled line" variables (66). Significant THC-induced impairment was demonstrated 60–330 min (60) and 80 min (66) after 14–52 mg THC was smoked. At an earlier time point (30 min after smoking), results did not attain significance, but there were trends toward impairment in "straddling the solid line" (i.e., dividing different-direction lanes, $P = 0.09$) and "straddling the barrier line" (broken line dividing same-direction lanes, $P = 0.08$) (66).

The results of Standardized Field Sobriety Tests 55 and 105 min after smoking corresponded to those of 80-min simulator results in >65% of cases for 14- and 52-mg THC doses. Standardized Field Sobriety Tests classified several participants as "impaired" when driving performance suggested otherwise, but line straddling is a relatively insensitive impairment measure. Four of 5 studies detected compensatory decreases in mean speed after THC doses ≥13 mg (3, 10, 53, 55). When cannabis history was described, all participants were occasional smokers. No significant THC effect was observed (1.77% or 3.95% THC cigarettes) for participants who smoked at least weekly but not daily (57). Speed variability increased after THC smoking relative to placebo in 3 of 6 studies (10, 53, 64), suggesting that the drivers had less vehicular control. DATs were used in only 2 simulator studies. After smoking 22.9 mg THC, participants failed to demonstrate the practice effects that were observed with placebo on a paced auditory serial-addition test during an otherwise uneventful drive (55). During combined car-following and sign-detection tasks, smoking of 38 mg THC increased the headway mean and SD (53). In occasional smokers, 45.7 mg THC also decreased visual search and processing speed (60).

A series of on-road studies (4, 59, 67) conducted in the Netherlands evaluated the effects of smoked THC on actual driving performance (Table 5). In a 22-km road-tracking, closed-course test, 100, 200, and 300 μg/kg of smoked THC (approximately 7, 14, and 21 mg, respectively) increased SDLP relative to placebo with no significant differences in the speed mean or SD (4). The degree of SDLP impairment was the same at 40 min and 100 min after the start of smoking. In a highway experiment with an escalating dose (100, 200, and 300 μg/kg THC), 16 participants started driving 45 min after commencing smoking (59). The drive included a 16-km car-following task (approximately 15 min), a 64-km road-tracking task (approximately 50 min), and a second 16-km car-following task. THC smoking increased SDLP dose dependently: The lowest dose produced a slight and nonsignificant SDLP increase, the medium dose a significant but modest increase, and the highest dose a significant and substantial increase. The mean headway in the car-following test increased 8, 6, and 2 m for the 100-, 200-, and 300-μg/kg doses, respectively. The authors suggested the inverse headway–dose relationship was a practice effect due to decreasing driver caution with increasing experience with the task, rather than pharmacodynamic tolerance. THC smoking (100 and 200 μg/kg) impaired driving performance on 40-km car-following and road-tracking tasks (67). Drives were conducted 30 and 75 min after smoking. The headway SD and SDLP increased significantly relative to placebo after each active dose (headway SD, by 2.9 and 3.8 m for 100 and 200 μg/kg, respectively; SDLP, by 2.7 and 3.5 cm). The participants' SDLP values were higher in the second drive than in the first. The final on-road study administered placebo or 100 μg/kg smoked THC at 25 min before a 45-min drive through a city (4). Performance was evaluated with the Driving Proficiency Test. Smoking THC had no significant effect on total score, vehicle checks, handling, action in traffic, traffic observation, or turning.

Combined Alcohol and Cannabis Intake

Cannabis and alcohol share some cognitive and psychomotor effects (10, 41, 68). Both are central nervous system depressants, and alcohol activates the cannabinoid CB1 receptor pathway (69); however, different effects on driving behavior were noted at the THC doses evaluated. Alcohol consumption led to faster driving (3), whereas the cannabis doses typically studied reduced driving speed. Alcohol inflates self-confidence, causing underestimation of impairment (10). In contrast, cannabis-influenced drivers occasionally appear more cautious in experimental settings.

Alcohol and cannabis are commonly identified together in MVA victims. DUIC is more common among people who also drive drunk (70). Among 322 MVA victims, 30% of the THC-positive individuals had been drinking alcohol also (1). A larger French case control study found that >40% of 681 THC-positive drivers involved in fatal crashes had BACs above the 0.05% legal limit (37). Over a 90-day period, 30.6% of 108 drivers admitted to the University of Maryland Medical Center Shock Trauma Center tested positive for alcohol (93.5% with BAC values ≥0.07%); one third of the drivers also tested positive for cannabis (urinalysis, 50 ng/mL cutoff; analyte not specified) (23). Alcohol was detected with THC in nearly 20% of Swiss cases in which the THC concentration in blood exceeded the 2.2- ng/mL legal limit (45).

Among 727 French drivers involved in fatal accidents with blood THC concentrations ≥1 ng/mL, 40% of the drivers also had an illegal BAC, ≥0.05% (20). Drunk driving (with or without cannabis) produced a higher single-vehicle accident incidence (62%) than did DUIC (34%). Drivers whose blood contained only cannabis were 2.3 times more likely to be culpable than those without cannabis or alcohol. This responsibility index (the percentage responsible divided by the percentage not responsible) increased to 9.4 for those with only alcohol in their blood, and to 14.1 with both alcohol and cannabis. THC-positive drivers

with BAC values ≥0.05% had a culpability OR 2.9, relative to those with a BAC ≥0.05% alone (15), implying that THC enhanced alcohol's impairing effects. In a case-controlled logistic regression analysis, patients in Ontario, Canada, who sought treatment for combined alcohol and cannabis abuse had a significantly higher likelihood of a prior conviction for driving while intoxicated (DWI) (OR, 3.65) relative to randomly chosen driver controls matched by age and sex (71). Cannabis-only patients were not significantly different from controls for DWI convictions, whereas alcohol-only patients had a prior DWI conviction OR of 5.19. DWI convictions were not necessarily concurrent with consumption of drug(s) for which the individuals were subsequently treated. A significant risk ratio of 5.8 for a driving-related injury within an hour after cannabis exposure (case-crossover self-report study) nearly doubled, to a 10.9 risk ratio for alcohol and cannabis combined (32).

Four studies included laboratory data on alcohol and cannabis interactions (Table 4; see Table 5 in the online Data Supplement). In a time-estimation task, two 3.6% THC cigarettes (4 puffs each, 2 h apart) yielded underestimated time targets (56). Alcohol consumption [0.6 g/kg (male) and 0.5 g/kg (female)] produced overestimations. In combination, these effects canceled each other. Two of 3 studies showed a cannabis–alcohol interaction on DATs, suggesting this test was a sensitive measure. In occasional smokers (once to 4 times per month), some THC (13 mg) or alcohol (target BAC, 0.05%) impairment effects occurred 15–75 min after smoking (3). Although each substance increased false-alarm responses, the greatest effect occurred in combination. Performance impairment and subjective effects were generally strongest after consuming both drugs. Frequent smokers (≥4 days/week) showed increased control losses after 400 μg/kg THC and 0.05% and 0.07% BACs (63). Combinations produced the greatest effects, although whether alcohol and THC produced additive or synergistic effects was unclear. The percentage of drivers judged as impaired increased with increasing blood THC concentration and BAC (72). When neither alcohol (blood cutoff, 0.001%) nor THC (blood limit of detection, 0.2 ng/ mL) was detected, 14% of CTI observations showed impairment. Alcohol alone at BACs of 0.001%–0.05% (low) and >0.05% (high) was associated with 77% and 95% impairment, respectively. THC concentrations between 0.30 and 1.6 ng/mL were associated with 45%, 91%, and 97% impairment for 0, low, and high BACs, respectively. THC concentrations ≥1.6 ng/mL were associated with corresponding impairments of 53%, 93%, and 100%. These CTI data indicate progressive and increasing impairment with increasing alcohol and THC combinations.

One simulator study showed a cannabis–alcohol interaction (Table 5). In occasional smokers (once to 4 times per month), a 0.05% target BAC and 13 mg smoked THC increased the SDLP relative to either drug alone or placebo, which did not differ (3). Alcohol alone increased drive speed relative to that for THC; THC alone decreased speed. The combination produced a borderline-significant speed increase relative to THC alone. No significant effect was observed for the speed SD. Alcohol and THC consumption increased the total number of collisions (5 of 12) relative to either drug alone (2 of 12 and 3 of 12 for alcohol and THC, respectively).

The most straightforward cannabis–alcohol effect appeared in a study that administered 0, 100 μg/kg (approximately 7 mg), or 200 μg/kg (approximately 14 mg) THC and alcohol (target BACs, 0% or 0.04%) (Table 5) (59, 67). Alcohol plus the high THC dose increased the RT by 36%; this dosing condition was the only one that affected RT. Alcohol or the low THC dose alone slightly increased SDLP; the higher THC dose caused moderate impairment. Neither drug alone significantly increased the time out of lane. Combining either THC dose with alcohol severely increased SDLP and dose-dependently increased the time out of lane. Combining the 100- and 200-μg/kg doses with 0.04% BAC created a degree of impairment equivalent to that of 0.09% and 0.14% BAC, respectively. Visual

search for traffic at intersections was significantly decreased by 3% relative to placebo for a 0.04% BAC and after consumption of 100 μg/kg THC, an effect not observed with either drug alone (4).

Although several studies have reported additive or synergistic cannabis–alcohol effects, some studies reported no interactions. The inconsistencies were likely due to differences in procedures, outcome measures, and cannabis history for the study populations. After combining moderate drug doses in occasional smokers, no interaction effect was observed on free word recall, digit–symbol substitution, logical reasoning (56), standing steadiness, or equilibrium (56, 65). Frequent smokers did not show a cannabis–alcohol interaction in a Tower of London task, a stop-signal task, or CT after smoking 400 μg/kg (approximately 28 mg) THC and ingesting 0.05% or 0.07% BAC (63). A 3.3% (approximately 30 mg) THC cigarette decreased equilibrium scores, and 0.5 g/kg alcohol increased brake latency, with neither effect significantly altered with the combination (65). The authors speculated that the lack of interaction was an impairment-awareness artifact, coupled with the expectation of an "emergency." A recent 9-session simulator experiment that investigated 0, 19, and 38 mg THC and 0, 0.4, and 0.6 g/kg alcohol in all possible combinations demonstrated substantial impairment caused by THC alone (both active doses) (53). Both alcohol doses increased SDLP; the lower alcohol dose also increased the speed mean and SD. No interaction effects were observed, most likely because the alcohol doses were low. The mean achieved BACs were 0%, 0.02%, and 0.05% for placebo, low alcohol, and high alcohol conditions, respectively.

Preventing DUIC

One of the greatest challenges is dealing with public attitudes toward DUIC. One fourth (26.3%) of 320 drivers who smoked cannabis in the previous year indicated a >90% likelihood of future DUIC, even after having been shown data on increased crash risk (73). Only 7.5% reported they would be unlikely to drive (0%–10% likelihood). The majority indicated a >50% probability of future DUIC, even given the higher MVA risk. Regular smokers who had previously DUIC emphasized that publicity campaigns would not deter them from future DUIC (74). Past experience had convinced them that they could compensate for cannabis-associated performance decrements. Most believed cannabis caused minimal driving impairment; a few considered it to have no or even a positive effect on driving. A high likelihood of apprehension and punishment was a better deterrent. Given a hypothetical scenario with no chance of punishment, three quarters indicated a >50% chance for DUIC, and half indicated a >90% likelihood (73). In contrast, given a hypothetical scenario of a high degree of certainty of punishment, participants were significantly less willing to DUIC (OR, 0.2; $P < 0.001$). In a small study on DUIC attitudes, however, no one who reported having been stopped by police while DUIC indicated that they were deterred by this experience (none were charged) (74). Study findings suggested that random roadside testing (with arrest of those found cannabis positive) would be a better deterrent than advertising campaigns promoting the hazards of DUIC.

Conclusions/Discussion

Many epidemiology studies have involved selection bias. Some evaluated only specific populations, such as deceased drivers or those being treated for substance abuse or addiction. Case control studies are highly useful, but they may be biased by the selection of controls. Case and control populations may come from different time periods or include different cannabis-detection cutoffs or matrices (e.g., blood analysis for killed drivers vs OF for living drivers). The accuracy of self-reported information varies, depending on the data-collection methods. Self-reported prevalence estimates are often underestimated, owing to

the sensitivity of illicit drug-related information (27, 28). Even when objective measures of cannabis exposure were used, detection cutoffs were varied and not always reported. Urine testing has an extended cannabis-detection window and cannot establish a valid temporal association with crash risk.

Several studies have shown increased crash and culpability risks, even after adjusting for such confounders as age, sex, risky behaviors, and polypharmacy. Increased blood THC concentrations and driving within an hour after smoking were strongly associated with higher crash and culpability risks. Human laboratory-controlled drug-administration studies showed THC-induced driving-performance decrements within the first hour that lasted ≥2 h after smoking, results that are largely consistent with epidemiologic data. Laboratory-based impairment experiments identified DATs and executive-function tasks as the most sensitive to cannabis' effects. Investigations of actual driving performance have demonstrated dose-dependent THC impairment in road tracking, although only low to moderate THC doses were administered because of safety concerns. Simulator technology has improved since it was first used for impairment experiments, having progressed from rudimentary controls and a projected cyclorama (64) to full passenger cars, interactive screens with more complete fields of view, advanced driver monitoring via built-in cameras, realistic 3-dimensional audio output to enhance the simulated drive, and motion platforms that simulate physical driving sensations (10, 53, 55). Such advanced driving simulators are an ideal platform for future research because they combine realistic driving scenarios with highly controlled and measurable environments and provide a degree of safety not possible with on-road experiments. Driving simulators are particularly necessary when challenging drivers with difficult tasks (such as DATs and real-time decision-making processes) and when evaluating higher THC doses. Simulator studies from the last decade have demonstrated significant THC impairment of RT and the SDLP. THC smoking (22.9 and 38 mg) inhibited expected practice effects on DATs and produced deleterious performance effects, respectively (53, 55). Depending on the THC dose, driving speed may be reduced (3, 10, 53), particularly while multitasking (55), and headway may be increased (53). These results suggest impairment awareness and compensation but do not preclude control decrements.

Inconsistencies in findings are likely due to differences in study design; the population and setting (simulator vs road); the sophistication of the equipment; the sensitivity and specificity of the tasks (including drive length); THC dosage; and time after smoking. Differences in driver compensation while under observation may contribute to the variability in results. Future work should focus on extended segments of monotonous driving (which draw drivers into a state of complacency or sleepiness) followed by sudden changes requiring reaction, realistic situations presenting decision dilemmas, and DATs. These constructs appear the most sensitive to THC's impairing influence.

Combining alcohol with THC exacerbated the observed effects, especially with respect to RT and SDLP. Low (100 μg/kg) and moderate (200 μg/kg) THC doses, combined with a 0.04% BAC produced road-tracking impairment to a degree similar to BACs of 0.09% and 0.14% (59). Because consuming alcohol and cannabis together is common, fully evaluating their combined impact on driving performance is essential. The use of clinically relevant THC and alcohol doses in future studies is necessary to generate findings that can better inform public policy. In previous research, the administration of low THC and alcohol doses often accounted for a lack of observed effects, at least in part. Cannabis smokers typically self-titrate doses, and alcohol drinkers consume enough alcohol to attain BACs ≥0.05%. Most self-administered cannabis and alcohol doses are higher than the doses administered in many research studies.

Tolerance to acute impairment is an important consideration for future research and policy debates. DAT and tracking tasks have demonstrated impairment in chronic cannabis smokers, but other parameters have not (5, 63). The debate regarding per se and zero-tolerance drugged-driving laws is a prominent issue. Increased blood THC concentrations are strongly associated with increased crash risk, but there is no direct correlation between driving impairment and THC concentration.

DUIC is an important public health and safety concern that requires the development of an evidence-based policy and legislation targeted at drugs and driving. Impaired driving endangers individuals inside and outside the vehicle. Consuming cannabis before driving, with or without alcohol, is a common occurrence that produces substantial morbidity and mortality on the roadway. Research is needed to further define cannabis' effects on driving performance and to provide the scientific basis for laws to improve road safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

We thank A. White-Olson (NIH library) for assisting with the literature search and D.A. Gorelick, MD, PhD, for editorial assistance. We also acknowledge the Graduate Partnership Program, the NIH, and the University of Maryland Baltimore.

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Table 1

Self-reported risk of MVA while DUIC.

Location/country	Cases	Cases, n	Controls	Controls, n	CB[a] exposure time before driving	CB only	Parameter	OR or RR	95% CI or *P* value	Crude or adjusted (factors)	Reference
Atlantic Canada	10th- and 12th-grade students, DUIC	877	10th- and 12th-grade students, no CB	3178	≤1 h	—	MVA	4.14[b]	<0.001	C	Asbridge et al. (21)
Atlantic Canada	10th- and 12th-grade students, DUIC	877	10th- and 12th-grade students, no CB	3178	≤1 h	—	MVA	1.84[b]	<0.001	Demographics, DUIA	Asbridge et al. (21)
Ontario, Canada	Adults, drove within 1 h of CB intake in past year	70	Adult drivers	2606	≤1 h	—	MVA	3.89[b]	2.30–6.59	C	Mann et al. (27)
Ontario, Canada	Adults, drove within 1 h of CB intake in past year	70	Adult drivers	2606	≤1 h	—	MVA	2.61[b]	1.45–4.68	Demographics	Mann et al. (27)
Auckland, New Zealand	Drove within 3 h of CB intake	37	Did not drive within 3 h of CB intake	1102	≤3 h	—	MVA-I[c]	11.4[b]	3.6–35.4	C	Blows et al. (28)
Auckland, New Zealand	Drove within 3 h of CB intake	37	Did not drive within 3 h of CB intake	1102	≤3 h	—	MVA-I[c]	0.8[b]	0.2–3.3	Demographics, time of day, no. of passengers, risky behavior (BAC, speed, seatbelt use)	Blows et al. (28)
Spain	Regular cocaine users, driving within 1 h of CB intake	68	Same population, not driving within 1 h of CB intake[e]	68	≤1 h	—	NFDI, past year	7.0[d]	3.1–16	—	Pulido et al. (32)
Spain	Regular cocaine users, driving	68	Same population, not driving	68	≤2 h	—	NFDI, past year	2.2[d]	1.0–4.9	—	Pulido et al. (32)

Location/country	Cases	Cases, n	Controls	Controls, n	CB[a] exposure time before driving	CB only	Parameter	OR or RR	95% CI or *P* value	Crude or adjusted (factors)	Reference
	within 2 h of CB intake		within 2 h of CB intake[e]								
Spain	Regular cocaine users, driving within 1 h of CB intake	45	Same population, not driving within 1 h of CB intake[e]	45	≤1 h	CB only	NFDI, past year	5.8[d]	2.4–14	—	Pulido et al. (32)
Spain	Regular cocaine users, driving within 2 h of CB intake	45	Same population, not driving within 2 h of CB intake[e]	45	≤2 h	CB only	NFDI, past year	2.2[d]	0.9–5.2	—	Pulido et al. (32)
Spain	Regular cocaine users, driving within 1 h of CB intake and 2 h of alcohol	19	Same population, not DUID[e]	19	≤1 h	Plus alcohol in past 2 h	NFDI, past year	10.9[d]	1.3–88	—	Pulido et al. (32)

[a] CB, cannabis; RR, relative risk; C, crude; DUIA, driving under the influence of alcohol; MVA-I, MVA with injury; NFDI, nonfatal driver injury; DUID, driving under the influence of drugs.

[b] OR.

[c] Cars in MVA with ≥1 occupant hospitalized or killed.

[d] RR.

[e] Case-crossover design.

Table 2

Risk of MVA after analytical documentation of cannabis exposure.

Country	Drivers, N	Cases	Cases (THC+),[a] n	Controls	Controls (THC+), n	Analytical matrix	THC cutoff, ng/mL	CB Only	Parameter	OR	95% CI	Crude (C) or adjusted (factors)	Reference
The Netherlands	926	Injured drivers	110 (13)	Randomly selected drivers (roadside survey)	816 (49)	Urine and/or blood	Not given	—	MVA-DI	1.22	0.55–2.73	Demographics, drugs, time of day, season	Movig et al. (33)
Norway	10 744	Killed drivers	204 (<24)	Randomly selected drivers (roadside survey)	10 540 (≤53)	Blood (cases), OF (controls)	Blood, 0.6; OF, 5	—	MVA-DF	13.9	6.6–29.2	C	Gjerde et al. (29)
Norway	10 744	Killed drivers	204 (<24)	Randomly selected drivers (roadside survey)	10 540 (≤53)	Blood (cases), OF (controls)	Blood, 0.6; OF, 5	—	MVA-DF	8.6	3.9–19.3	Demographics, time period, season	Gjerde et al. (29)
Norway	10 744	Killed drivers	204 (<24)	Randomly selected drivers (roadside survey)	10 540 (≤53)	Blood (cases), OF (controls)	Blood, 0.6; OF, 5	CB only	MVA-DF	1.9	0.3–13.7	C	Gjerde et al. (29)
Norway	10 744	Killed drivers	204 (<24)	Randomly selected drivers (roadside survey)	10 540 (≤53)	Blood (cases), OF (controls)	Blood, 0.6; OF, 5	CB only	MVA-DF	0.9	0.1–7.3	Demographics, time period, season	Gjerde et al. (29)
Norway	10 608	Killed drivers in SVA	68 (<10)	Randomly selected drivers (roadside survey)	10 540 (≤53)	Blood (cases), OF (controls)	Blood, 0.6; OF, 5	No CB-only cases	SVA-DF	18.9	6.5–54.6	C	Gjerde et al. (29)
Norway	10 608	Killed drivers in SVA	68 (<10)	Randomly-selected drivers (roadside survey)	10540 (≤53)	Blood (cases); OF (controls)	Blood, 0.6; OF, 5	No CB-only cases	SVA-DF	9.0	2.7–30.3	Demographics, time period, season	Gjerde et al. (29)
Thailand	1049	Injured drivers[b]	200 (4)	Drivers with no traffic injury history in past 6 months	849 (20)	Urine	50	—	RTI	0.78	0.25–2.40	C	Woratanarat et al. (34)
Multiple	9 Studies	Metaanalysis: epidemiologic studies							MVA	2.66	2.07–3.41		Li et al. (35)
Multiple	9 Studies	Metaanalysis: epidemiologic studies							MVA	1.92	1.35–2.73		Asbridge et al. (36)
Multiple	3 Studies	Metaanalysis: case control studies							MVA	2.79	1.23–6.33		Asbridge et al. (36)
Multiple	6 Studies	Metaanalysis: culpability studies							MVA	1.65	1.11–2.46		Asbridge et al. (36)
Multiple	5 Studies	Metaanalysis: studies with fatal collisions							MVA	2.10	1.31–3.36		Asbridge et al. (36)
Multiple	4 Studies	Metaanalysis: studies with nonfatal collisions							MVA	1.74	0.88–3.46		Asbridge et al. (36)

[a] THC+, THC positive; CB, cannabis; C, crude; MVA-DI, MVA with driver injury; MVA-DF, MVA with driver fatality; SVA, single-vehicle accident; SVA-DF, SVA with DF; RTI, road traffic injury.

[b] Admitted to hospital within 24 h.

Table 3

Risk of driver culpability or responsibility in MVAs after cannabis exposure.[a]

Location/country	Cases	Cases, n	Controls	Controls, n	Analytical matrix	THC cutoff, ng/mL	CB[a] only	Parameter	OR	95% CI	Crude (C) or adjusted (factors)	Reference
Victoria, NSW, and WA, Australia	Fatally injured drivers, THC+	58	Fatally injured drivers, THC−	1704	Blood	Not given	CB only	MVA-DC	2.7	1.02–7.0	Demographics, crash type, BAC, year, year × crash type	Drummer et al. (15)
Victoria, NSW, and WA, Australia	Fatally injured drivers, THC ≥5 ng/mL	49	Fatally injured drivers, THC−	1704	Blood	5	CB only	MVA-DC	6.6	1.5–28	Demographics, crash type, BAC, year, year × crash type	Drummer et al. (15)
France	Drivers in fatal crashes, THC+ (1–2 ng/mL)	298	Drivers in fatal crashes, THC−	9013	Blood	1	—	MVA-DC	2.54	1.86–3.48	C	Laumon et al. (37)
France	Drivers in fatal crashes, THC+ (1–2 ng/mL)	298	Drivers in fatal crashes, THC−	9013	Blood	1	—	MVA-DC	1.54	1.09–2.18	Demographics, BAC, blood THC concentration, time of crash	Laumon et al. (37)
France	Drivers in fatal crashes, THC+ (≥5 ng/mL)	240	Drivers in fatal crashes, THC−	9013	Blood	5	—	MVA-DC	4.72	3.04–7.33	C	Laumon et al. (37)
France	Drivers in fatal crashes, THC+ (≥5 ng/mL)	240	Drivers in fatal crashes, THC−	9013	Blood	5	—	MVA-DC	2.12	1.32–3.38	Demographics, BAC, blood THC concentration, time of crash	Laumon et al. (37)
US	Drivers in fatal crashes, THC+	1647	Drivers in fatal crashes, THC−	30 896	Blood or urine	Not given	0% BAC	MVA-DRF	1.39	1.21–1.59	C	Bédard et al. (22)
US	Drivers in fatal crashes, THC+	1647	Drivers in fatal crashes, THC−	30 896	Blood or urine	Not given	0% BAC	MVA-DRF	1.29	1.11–1.50	Demographics, driving record	Bédard et al. (22)

[a] See Table B in the online Data Supplement for complete table further stratified by THC concentration.

[b] CB, cannabis; C, crude; NSW, New South Wales; WA, Western Australia; THC+, THC positive; THC−, THC negative; MVA-DC, MVA with driver judged culpable; MVA-DRF, MVA with ≥1 driver–related factor (potentially unsafe driving action) contributing to crash.

Table 4

Summarized effects of cannabis and alcohol on neurocognitive function: laboratory studies.

Task/outcome measure[a]	Cannabis intake history[b]	Studies showing THC impairment	Studies not showing THC impairment	Studies showing cannabis–alcohol interaction	Studies not showing cannabis–alcohol interaction
Free recall	NS	—	Chait et al. (56)	—	Chait et al. (56)
Time/distance perception	F	—	Weinstein et al. (62)	—	—
	NS	Chait et al. (56)	—	Chait et al. (56)	—
RT	O	Ramaekers et al. (5)	—	—	—
	F	Ramaekers et al. (5)	Ramaekers et al. (63)	—	Ramaekers et al. (63)
	NS	Ramaekers et al. (41)	—	—	—
Standing steadiness/equilibrium	NS	Liguori et al. (65)	Chait et al. (56)	—	Chait et al. (56), Liguori et al. (65)
Wisconsin Card Sorting Task	F	Weinstein et al. (62)	—	—	—
Digit–symbol substitution test	NS	Chait et al. (56)	—	—	Chait et al. (56)
Backward digit span	NS	—	Chait et al. (56)	—	—
Logical reasoning	NS	—	Chait et al. (56)	—	Chait et al. (56)
Gambling task[c]	F	Weinstein et al. (62)	—	—	—
Tower of London	O	—	Ramaekers et al. (5)	—	—
	F	—	Ramaekers et al. (5), Ramaekers et al. (63)	—	Ramaekers et al. (63)
	NS	Ramaekers et al. (41)	—	—	—
Virtual maze	F	Weinstein et al. (62)	—	—	—
CT task	O	Ramaekers et al. (5)	—	—	—
	F	—	Ramaekers et al. (5), Ramaekers et al. (63)	—	Ramaekers et al. (63)
	NS	Ramaekers et al. (41)	—	—	—
DAT	O	Ronen et al. (3), Ramaekers et al. (5)	—	Ronen et al. (3)	—
	F	Ronen et al. (63)	Ramaekers et al. (5)	Ramaekers et al. (63)	—
	NS	Chait et al. (56)	—	—	Chait et al. (56)

[a]See Tables C (cannabis only) and E (cannabis and alcohol) in the online Data Supplement for specific outcome measures, THC doses, study details, and results.

[b] NS (not specified) denotes history not given, or various (see Tables C and E in the online Data Supplement for specific cannabis history). F (frequent) denotes ≥3 times per week or ≥12 times per month. O (occasional) denotes <12 times per month.

[c] THC effect on the percentage of choosing less-likely outcomes.

Table 5

Summarized effects of cannabis and alcohol on simulated and on-road driving.

Outcome measure[a]	Cannabis intake history[b]	Simulator studies showing THC impairment	Simulator studies not showing THC impairment	On-road studies showing THC impairment	On-road studies not showing THC impairment	Studies showing cannabis–alcohol interaction	Studies not showing cannabis–alcohol interaction
RT	O	Ronen et al. (10), Rafaelsen et al. (64)	Anderson et al. (55)	—	—	—	—
	NS	Lenné et al. (53), Liguori et al. (57)	Liguori et al. (65)	—	Robbe (59)	Robbe (59), Ramaekers et al. (67)	Lenné et al. (53), Liguori et al. (65)
Headway maintenance	NS	Lenné et al. (53)	—	—	Robbe (59)	—	Lenné et al. (53), Robbe (59), Ramaekers et al. (67)
Headway variability	NS	Lenné et al. (53)	—	Robbe (59), Ramaekers et al. (67)	—	Robbe (59), Ramaekers et al. (67)	Lenné et al. (53)
Road tracking, SDLP	O	Ronen et al. (10)	Ronen et al. (3), Anderson et al. (55)	—	—	Ronen et al. (3)	—
	NS	Lenné et al. (53)	—	Robbe (59), Ramaekers et al. (67)	—	Robbe (59), Ramaekers et al. (67)	Lenné et al. (53)
Road tracking, Other	O	Ménétrey et al. (60)	—	—	—	—	—
	NS	Papafotiou et al. (66)	Liguori et al. (57)	—	Robbe (59), Ramaekers et al. (67)	Robbe (59), Ramaekers et al. (67)	—
Speed	O	Ronen et al. (3), Ronen et al. (10), Anderson et al. (55)	Liguori et al. (57)	—	—	Ronen et al. (3)	—
	NS	Lenné et al. (53)	—	—	Robbe (59)	—	Lenné et al. (53)
Speed variability	O	Ronen et al. (10), Rafaelsen et al. (64)	Ronen et al. (3), Anderson et al. (55)	—	—	—	Ronen et al. (3)
	NS	Lenné et al. (53)	Liguori et al. (57)	—	Robbe (59)	—	Lenné et al. (53)
Divided attention	O	Anderson et al. (55)	—	—	—	—	—
	NS	Lenné et al. (53)	—	—	—	—	Lenné et al. (53)
Visual search/processing speed/short-term memory	O	Ménétrey et al. (60)	—	—	Lamers et al. (4)	Lamers et al. (4)	—

Outcome measure[a]	Cannabis intake history[b]	Simulator studies showing THC impairment	Simulator studies not showing THC impairment	On-road studies showing THC impairment	On-road studies not showing THC impairment	Studies showing cannabis–alcohol interaction	Studies not showing cannabis–alcohol interaction
Collisions[c]	O	Ronen et al. (3), Ronen et al. (10)	—	—	—	Ronen et al. (3)	—

[a] See Table D in the online Data Supplement for specific outcome measures, THC doses, study details, and results.

[b] O (occasional) denotes <12 times per month. NS (not specified) denotes history not given, or various (see Table D in the online Data Supplement for specific cannabis history).

[c] Collisions in the studies were too few for statistical analysis; data are reported as studywide number of collisions.