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The "Next Day" Effects of Cannabis Use: A Systematic Review

Danielle McCartney,[1–3,*] Anastasia Suraev,[1–3] and Iain S. McGregor[1–3]

Abstract

Background: Δ^9-Tetrahydrocannabinol (THC), the main intoxicating component of cannabis, can cause cognitive and psychomotor impairment. Whether this impairment is still present many hours or even days after THC use requires clarification. Possible "next day" effects are of major significance in safety-sensitive workplaces. We therefore conducted a systematic review of studies investigating the "next day" effects of THC.

Methods: Studies that measured performance on safety-sensitive tasks (e.g., driving, flying) and/or neuropsychological tests >8 h after THC (or cannabis) use using interventional designs were identified by searching two online databases from inception until March 28, 2022. Risk of bias (RoB) was evaluated using the relevant Cochrane tools. Results were described in terms of whether THC had a significant effect on performance relative to the primary comparator (i.e., placebo or baseline, as appropriate).

Results: Twenty studies ($n=458$) involving 345 performance tests were reviewed. Most studies administered a single dose of THC (median [interquartile range]: 16 [11–26] mg) and assessed performance between >12 and 24 h post-treatment. $N=209/345$ tests conducted across 16 published studies showed no "next day" effects of THC. Nine of these 16 studies used randomized, double-blind, placebo-controlled designs. Half ($N=8$) had "some" RoB, and half ($N=8$) had a "high" RoB. Notably, $N=88$ of these 209 tests failed to demonstrate "acute" (i.e., <8 h post-treatment) THC-induced impairment. $N=12/345$ tests conducted across five published studies indicated negative (i.e., impairing) "next day" effects of THC. None of these five studies used randomized, double-blind, placebo-controlled designs and all were published >18 years ago (four, >30 years ago). Three had "some" RoB, and two had a "high" RoB. A further $N=121/345$ tests indicated "unclear" "next day" effects of THC with insufficient information provided to assess outcomes. The remaining $N=3/345$ tests indicated positive (i.e., enhancing) "next day" effects of THC.

Conclusions: Some lower quality studies have reported "next day" effects of THC on cognitive function and safety-sensitive tasks. However, most studies, including some of higher quality, have found no such effect. Overall, it appears that there is limited scientific evidence to support the assertion that cannabis use impairs "next day" performance. Further studies involving improved methodologies are required to better address this issue.

Keywords: cannabis; THC; cannabinoids; impairment; cognitive function; driving

Introduction

Two hundred million people use cannabis each year.[1] This includes those using cannabis for its euphorigenic effects (i.e., so-called "recreational" users) and, increasingly, those using it to treat medical conditions such as chronic pain, insomnia, and anxiety.[2]

The potential harms associated with cannabis use have been debated over many decades. One ongoing concern is that the major cannabis constituent, Δ^9-tetrahydrocannabinol (THC), can induce intoxication and impair cognitive and psychomotor performance (e.g., reaction time, working memory, divided attention),[3]

[1]Lambert Initiative for Cannabinoid Therapeutics and [2]Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia.
[3]School of Psychology, Faculty of Science, The University of Sydney, Sydney, New South Wales, Australia.

*Address correspondence to: Danielle McCartney, PhD, Lambert Initiative for Cannabinoid Therapeutics, Brain and Mind Centre, The University of Sydney, Camperdown, NSW 2050, Australia, E-mail: danielle.mccartney@sydney.edu.au

increasing the risk of error, accident, and injury when operating a motor vehicle or engaging in other safety-sensitive tasks.[4–6] Indeed, epidemiological studies suggest that "THC-positive" drivers are between ~1.1 and 1.4 times more likely to become crash-involved than other drivers.[7]

The duration of THC-induced impairment, or length of time an individual should wait following cannabis use before performing safety-sensitive tasks, is a critical issue. A recent meta-regression analysis[3] concluded that there was a "window of impairment" extending from ~3 to 10 h after THC use, with the exact duration dependent on the following: (1) *dose*: higher THC doses produced longer lasting impairment; (2) *route of administration*: oral THC produced longer lasting impairment than inhaled THC (e.g., smoked, vaporized), owing to the fact that gastrointestinal absorption is slower than pulmonary absorption[8,9]; and (3) *regularity of cannabis use*: occasional cannabis users became more impaired than regular cannabis users (who appear to be more tolerant to the impairing effects of THC[10]). This review did not, however, include performance tests conducted >12 h after THC use.

Some government agencies and experts in occupational safety caution that THC-induced impairment may persist for >24 h and recommend that individuals avoid performing safety-sensitive tasks for at least this long after cannabis use.[11,12] This can impact upon those who are reliant on driving for their work and/or family life, and upon individuals employed in safety-sensitive positions (e.g., transit and construction workers, defense personnel), who may use cannabis "off-duty" (e.g., in the evening, on the weekend) to treat conditions such as insomnia and chronic pain. However, such advice does not appear to have been informed by a comprehensive review of the scientific evidence.

We therefore conducted a systematic review to better understand the "next day" (i.e., >8 h) effects of THC use on cognitive function and safety-sensitive tasks.

Methods

The methods of this review were developed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 6.2, 2021).[13]

Literature search

Relevant studies were identified by searching the online databases Scopus and Web of Science (Thomas Reuters) from inception until March 28, 2022, using the Boolean expression in Supplementary File S1. Two investigators (D.M. and A.S.) independently screened all titles and abstracts against the following inclusion criteria: (1) English language; (2) full-length article; (3) original research; (4) interventional design; and (5) THC administration. Suitable records were then screened for eligibility by full text (see "Eligibility criteria" section). The final decision to include (or discard) a study was made between these two investigators; discrepancies were resolved in discussion with a third investigator (I.S.M.). One investigator (D.M.) also hand-searched the reference lists of the included publications and two previous reviews[3,14] to ensure all relevant articles were captured.

Eligibility criteria

Studies that measured performance on "safety-sensitive" tasks (e.g., simulated or on-road driving performance, simulated aeroplane flying) and/or discrete neuropsychological tests >8 h post (last)-THC (or cannabis) use using an interventional experimental design (any)[15] were eligible for inclusion. The >8-h interval was selected to represent a typical overnight "recovery" period[16] and to minimize overlap with a previous review investigating the shorter-term effects of THC (i.e., ≤12 h).[3] No "upper limit" was imposed. All participant populations (e.g., clinical, "healthy") and comparator conditions (e.g., placebo, baseline) were accepted. However, studies were excluded if THC was co-administered with another treatment (excluding placebo treatments, other cannabinoids or cannabis constituents, tobacco, or participants' usual medication) or if results were reported in another included article. Only full-length, English-language, original research articles published in scientific journals were accepted.

Note that if a study contained multiple "intervention arms," more than one of which was eligible for inclusion, the separate "arms" were treated as discrete "studies," termed trials, identifiable by the additional letters (e.g., a–d) in the citation.

Performance outcomes

All objective outcomes measured on safety-sensitive tasks and discrete neuropsychological tests >8 h post-THC administration were accepted. Outcomes measured ≤8 h post-THC administration (on eligible performance tests) were also included. Indeed, these data were used to determine whether the performance tests administered >8 h post-treatment were sensitive to the "acute" (i.e., <8 h post-treatment) effects of THC.

Quality assessment

Risk of bias (RoB) in included studies was evaluated by two independent assessors (D.M. and A.S.) using (1) the Revised Cochrane Risk of Bias tool (RoB 2.0)[17] and (2) the RoB 2.0 for crossover trials,[18] as appropriate. Both tools examine five potential sources of bias, that is, bias arising from (1) the randomization process; (2) deviations from the intended intervention; (3) missing outcome data; (4) measurement of the outcome; and (5) selective outcome reporting. The latter also examines bias arising from period or carryover effects. Both tools generate an overall "risk rating" (i.e., "low risk," "some concerns," "high risk").

Data extraction

The extracted data included the following: (1) study design; (2) participant characteristics (e.g., age, sex, body weight, health status, cannabis use behavior); (3) treatment characteristics (e.g., type, composition, route of administration, THC dose); (4) task characteristics (e.g., test, outcomes, number of assessments, length of time between THC administration and the performance test[s]); and (5) standardization procedures employed, that is, the methods used to control participants' pre-trial and "within-trial" (i.e., up until the >8 h post-treatment assessment) sleep behavior and cannabis, alcohol, caffeine, and other psychoactive drug use. The latter were considered important as they have been shown to influence cognitive and psychomotor performance.[3,19–21]

Data synthesis

The results of the included studies were synthesized qualitatively, that is, described in terms of whether THC was found to have a statistically significant effect (i.e., $p < 0.05$) on each performance test (i.e., any one of its outcome measures) relative to the primary comparator, taken as placebo in placebo-controlled trials and baseline (i.e., pre-treatment) elsewhere. If an outcome was analyzed within a complex model (e.g., including three or more treatments and[or] other factors, e.g., time) and no main effect of treatment or relevant interaction(s) was observed, the effect was assumed to be nonsignificant. If a main effect of treatment or relevant interaction was observed, statistical significance was ascertained on the basis of *post-hoc* comparisons.

The results of *post-hoc* comparisons on main effects of treatment that included a time parameter were generalized across all included time points unless the individual time points were compared by treatment or the comparison incorporated baseline (i.e., pre-treatment) data (in the latter case, the comparison was considered ambiguous). If *post-hoc* comparisons were not performed, or there was any ambiguity in the reported result, the statistical significance of the effect was not presented in this review. Meta-analysis was not performed as studies often failed to report (or graph) the information required to calculate an effect estimate (most studies [80%] were also published >10 years ago [65%, >20 years ago], making it difficult to retrieve the missing data).

Each neuropsychological test was reviewed and categorized into one of the following cognitive domains as previously demonstrated by McCartney et al[3] and shown in Supplementary Table S1: (1) divided attention; (2) executive function; (3) information processing; (4) tracking performance; (5) reaction time; (6) motor function; (7) sustained attention; (8) working memory; (9) perception; (10) learning and(or) memory; and (11) spatial reasoning.

The terms used to describe participants' cannabis use behavior (e.g., daily, weekly–daily, monthly, etc.) are also as per McCartney et al[3] and defined in Supplementary Table S2. These categories were further collapsed into two main groupings: *regular cannabis users* (which included populations of daily users, weekly users, weekly–daily users) and *other cannabis users* (all other populations) to aid in synthesizing the available literature.

Note that the length of time between THC administration and the beginning of the performance test was calculated from: (1) the last THC exposure if more than one dose was administered before the performance test; and (2) the beginning of the "battery" if multiple tests were administered in succession and their individual start times were not reported.

Results

Overview of included studies

Twenty studies ($n = 458$ participants; 79% male, excluding studies that did not report the sex of their participants) were included in this systematic review. These studies administered a total of 345 performance tests (i.e., across all trials and time points >8 h post-treatment). The study selection process is detailed in Supplementary File S1.

The characteristics of the included studies are summarized in Table 1. Briefly, most studies used randomized ($N = 11$) or "nonrandomized" (i.e., randomization was not reported; $N = 5$) double-blind, placebo-

Table 1. Characteristics of Included Studies

	Studies (*N*) or participants (*n*)	Citations
Study design		
Randomized, DB, PC	*N* = 11	23,25,26,28,29,31, 34–37,39
Nonrandomized,[a] DB, PC	*N* = 5	22,27,30,32,38
Nonrandomized, SB,[b] PC	*N* = 3	24,33,40
Pre-/post-trial	*N* = 1	41
Participant characteristics		
Male	*n* = 297	—
Female	*n* = 79	—
Sex not specified	*n* = 82 (*N* = 4)	31,32,40,41
Average age ≤ 30 years	*N* = 15	22–24,26,28–31, 34–39,41
Average age > 30 years	*N* = 4	25,31,32,40
Average age not specified	*N* = 2	27,33
"Regular" cannabis users[c]	*N* = 4	22,28,29,37
"Other" cannabis users[c]	*N* = 16	23–27,30–36,38–41
Healthy population	*N* = 20	22–41
Treatment characteristics		
Smoked cannabis or THC	*N* = 13	22–24,28–31,33, 35,37,38,40,41
Ingested cannabis or THC	*N* = 7	25–27,32,34,36,39
THC dose unknown	*N* = 5	22–24,30,35
THC dose (mg) (median [IQR])	16 [11–26][d]	—
Type of performance test[e]		
Divided attention	*N* = 6	22,25–27,30,33
Executive function	*N* = 4	23,30,34,35
Information processing	*N* = 11	22–28,30,33,34,36
Tracking performance	*N* = 1	33
Reaction time	*N* = 5	22,23,27,34,35
Motor function	*N* = 3	28,30,35
Sustained attention	*N* = 4	27,28,34,37
Working memory	*N* = 6	22,23,30,34–36
Perception	*N* = 3	22,24,30
Learning and(or) memory	*N* = 9	22–25,27,28,30,34,35
Spatial reasoning	*N* = 1	35
Driving performance	*N* = 4	29,37–39
Flying performance	*N* = 3	31,40,41
Unknown	*N* = 2	32,36
Time of performance test		
> 8 to 12 h Post-treatment	*N* = 7	22,24–27,33,37
> 12 to 24 h Post-treatment	*N* = 16	23,25,28–41
> 24 to 48 h Post-treatment	*N* = 8	23,26,28,29,31,34, 35,40
≤ 8 h Post-treatment	*N* = 18	23–26,28–41
"Recovery" conditions		
Supervised	*N* = 8	22–24,27,30,35, 36,39
Unsupervised	*N* = 10	26,28,29,31–34,38, 40,41
Unclear or not specified	*N* = 2	25,37

[a]Includes studies that did not indicate whether randomization was performed.
[b]Includes studies that did not indicate whether researchers were blinded.
[c]As defined in "Data synthesis" section.
[d]Across all trials where the THC dose is known.
[e]Includes those administered > 8 h post-treatment, only.
DB, double blind; IQR, interquartile range; PC, placebo controlled; SB, single blind; THC, Δ^9-tetrahydrocannabinol.

controlled designs; however, three were single blind and one used a "pre-/post-treatment" design. All included "healthy" participants, only (i.e., no studies of clinical populations were eligible for inclusion). Other (i.e., mostly occasional) cannabis users and populations with an average age ≤ 30 years were studied more often than regular (i.e., weekly, or more often) cannabis users and those with an average age > 30 years, respectively (Table 1). Most studies administered THC by smoking (*N* = 13); the remainder did so through oral ingestion (*N* = 7) (all, but three[22–24] gave a single dose of THC).

The median (interquartile range [IQR]) (last) THC dose was 16 [11–26] mg (where reported; *N* = 15). Two types of "safety-sensitive task" (simulated driving and flying) and a wide range of neuropsychological tests were administered. The number of tests conducted between > 8–12, > 12–24, and > 24–48 h post-treatment was 98, 158, and 89, respectively. Eight studies supervised their participants throughout the > 8 h "recovery" period; the remainder (*N* = 12) allowed them to leave the laboratory between assessments. All appeared to assess performance the day following THC administration (i.e., the "next day" or longer). (Note that only the 12-, 10-, and 10-h assessments conducted in Schoedel et al,[25] Ménétrey et al,[26] and Nicholson et al,[27] respectively, are presented in both the current and former[3] review).

Risk of bias

The results of the RoB assessment are detailed in Supplementary File S2 and summarized in Figure 1. None of the included studies demonstrated an overall "low risk" of bias, although two, Matheson et al[28] and Brands et al,[29] received "low risk" ratings on four out of the five RoB domains assessed. Nine studies were found to have "some concerns," and 11 had a "high risk" of bias. The most common problems were RoB arising from (1) missing outcome data; (2) selective outcome reporting; and (3) carryover effects—with studies often failing to indicate whether any participant discontinued in the trial, analyze their data in accordance with a pre-specified plan, and report the number of participants assigned to each treatment order. Only four studies justified their chosen sample size.

Standardization procedures

The "standardization procedures" employed, that is, methods used to control participants' pre-trial and

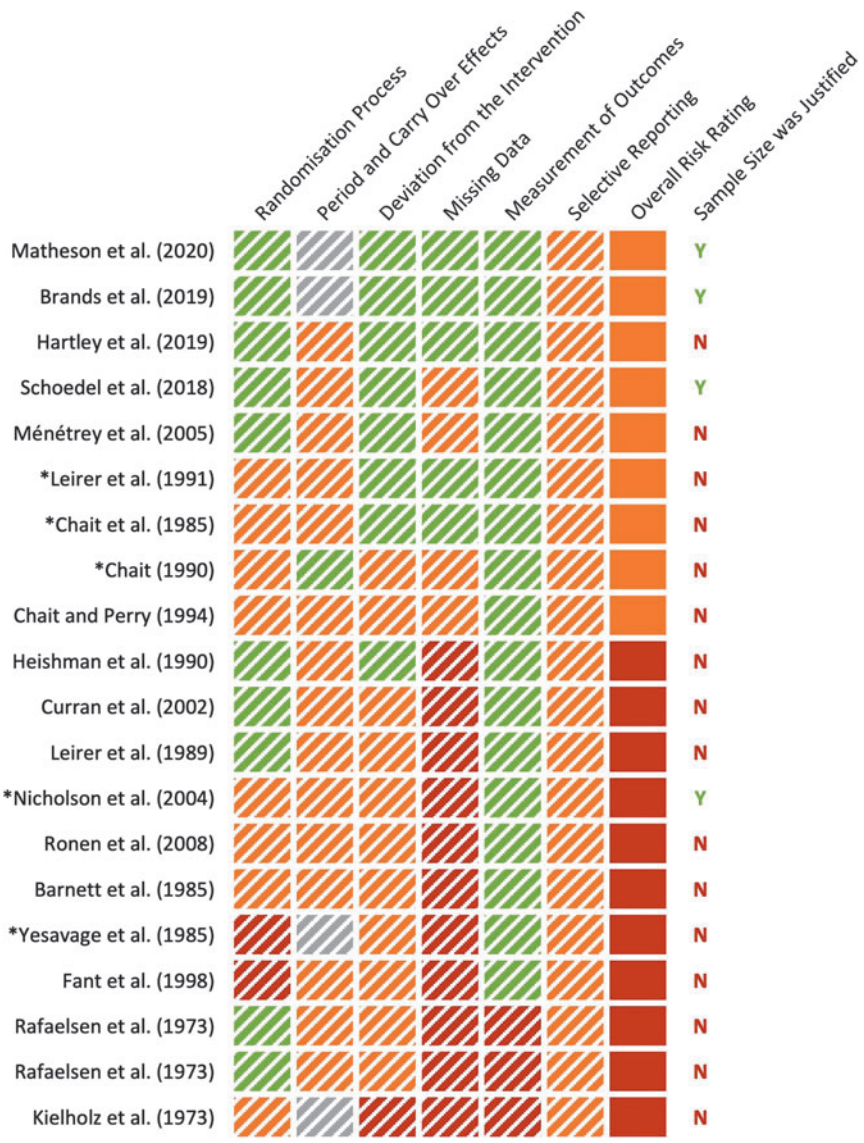


FIG. 1. Risk of bias as assessed using the Revised Cochrane Risk of Bias tool (RoB 2.0)[17] and the RoB 2.0 for crossover trials[18] (as appropriate). Green: low risk of bias; orange: some concerns; red: high risk of bias; gray: not applicable (not a crossover trial); N: No; Y: Yes. *Studies that detected significant detrimental effects of THC on "next day" performance (see Table 2). See Supplementary File S2 for full assessment.

"within-trial" (i.e., up until the >8 h post-treatment assessment) sleep behavior and cannabis, alcohol, caffeine, and other drug use, are summarized in Fig. 2. Studies that supervised their participants throughout the >8-h recovery period ($N=8$) achieved better within-trial standardization than those that did not ($N=12$). However, the latter tended to achieve better pre-trial standardization with most ($N=9$) controlling at least one pre-trial condition. Nicholson et al[27] and Chait and Perry[30] implemented the most robust standardization procedures; followed by Matheson et al[28] and Brands et al.[29] Three studies failed to report implementing any standardization procedure.[25,31,32]

"Next Day" effects of THC

The results of the included studies are described below and detailed in Table 2. Note that the studies that administered multiple performance tests can appear

	Pre-Session Standardisation				'Within-Session' Standardisation (Until >8-h Assessment)				
	Cannabis	Alcohol	Other Drugs	Caffeine	Cannabis	Alcohol	Other Drugs	Caffeine	Sleep
Studies in which 'Recovery' was Supervised:									
*Nicholson, et al.[27] (2004)	Withheld (Verified)	Withheld (Verified)	Withheld (Verified)	Withheld (Unverified)	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Controlled (Supervised)
Chait and Perry[30] (1994)	Withheld (Unverified)	Withheld (Verified)	Withheld (Unverified)	Continued	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Controlled (Supervised)
Heishman, et al.[23] (1990)	Withheld (Verified[a])	Not Specified[b]	Withheld (Unverified)	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Not Specified	Controlled (Supervised)
*Chait[22] (1990)	Withheld (Unverified)	Not Specified	Not Specified	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Controlled (Supervised)
Fant, et al.[35] (1998)	Not Specified[c]	Not Specified[c]	Not Specified[c]	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Not Specified	Controlled (Supervised)
*Chait, et al.[24] (1985)	Not Specified	Not Specified	Not Specified	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Not Specified	Controlled (Supervised)
Rafaelsen, et al.[39] (1973)	Not Specified	Not Specified	Not Specified	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Not Specified	Controlled (Supervised)
Rafaelsen, et al.[36] (1973)	Not Specified	Not Specified	Not Specified	Not Specified	Withheld (Supervised)	Withheld (Supervised)	Withheld (Supervised)	Not Specified	Controlled (Supervised)
Studies in which 'Recovery' was Unsupervised:									
Matheson, et al.[28] (2020)	Withheld (Unverified[d])	Withheld (Verified)	Withheld (Verified)	Continued	Withheld (Unverified)	Withheld (Verified)	Withheld (Verified)	Continued	Not Specified
Brands, et al.[29] (2019)	Withheld (Unverified[d])	Withheld (Verified)	Withheld (Verified)	Continued	Withheld (Unverified)	Withheld (Verified)	Withheld (Verified)	Continued	Not Specified
Ménétrey, et al.[26] (2005)	Withheld (Verified)	Withheld (Verified)	Withheld (Verified)	Not Specified	Withheld (Unverified)	Withheld (Unverified)	Withheld (Unverified)	Not Specified	Not Specified
Barnett, et al.[33] (1985)	Withheld (Verified)	Not Specified[b]	Withheld (Verified)	Withheld (Unverified)	Withheld (Unverified)	Not Specified[b]	Withheld[e]	Withheld (Unverified)	Not Specified
Hartley, et al.[37f] (2019)	Withheld (Unverified[d])	Withheld (Verified)	Withheld (Verified)	Not Specified[g]	Withheld (Unverified)	Not Specified	Not Specified	Not Specified[g]	Not Specified[h]
*Yesavage, et al.[41] (1985)	Withheld (Unverified)	Not Specified[b]	Withheld (Verified)	Not Specified	Withheld (Unverified)	Withheld (Unverified)	Withheld (Unverified)	Not Specified	Not Specified
Curran, et al.[34] (2002)	Withheld (Verified)	Not Specified[i]	Not Specified[i]	Continued	Withheld (Unverified)	Not Specified[i]	Not Specified[i]	Continued	Not Specified
*Leirer, et al.[40] (1991)	Withheld (Verified)	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified
Ronen, et al.[38] (2008)	Withheld (Unverified)	Withheld[k] (Unverified)	Not Specified	Not Specified	Withheld (Unverified)	Withheld[k] (Unverified)	Not Specified	Not Specified	Controlled (Unverified)
Leirer, et al.[31] (1989)	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified
Schoedel, et al.[25f] (2018)	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified
Kielholz, et al.[32] (1973)	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified

FIG. 2. Standardization procedures employed in included studies. A substance was considered "*withheld*" if participants were instructed to avoid using it for ≥24 h (12 h for caffeine) or if abstinence was "*verified*." Abstinence was considered "*verified*" if participants returned a negative "drug test"; that is, a breath test (alcohol), urine screen (other drugs), or blood test (caffeine). Pre-session cannabis abstinence was only "*verified*" if participants returned a negative blood or urine screen; furthermore, within-session cannabis abstinence was only "*verified*" if participants were supervised until the >8 h post-treatment assessment. Within-session alcohol and other drug use were also assumed to be "*verified*" if participants were supervised until this assessment (but could otherwise be demonstrated through a drug test). A substance was considered "*continued*" if participants were instructed to continue using it as usual. Sleep was considered "*controlled*" if participants were supervised until the >8 h post-treatment assessment or instructed to obtain sufficient sleep. Adherence to the latter was considered "*verified*" if an objective measure of sleep quality or duration was obtained. [a]Urine 11-COOH-THC concentrations were $<20\ ng \bullet mL^{-1}$. [b]Participants were instructed to avoid using "drugs"; however, it is unclear whether this included alcohol. [c]Participants were retained in the laboratory for 2 weeks; however, the pre-session one standardization procedures were not specified. [d]Short-term cannabis abstinence cannot be verified in a population of regular users. [e]It is unclear if this was verified. [f]"Recovery" was assumed to be unsupervised. [g]Individuals with high habitual caffeine intakes were excluded. [h]Individuals with sleep disorders were excluded. [i]Individuals with high habitual alcohol intakes were excluded. [j]Individuals who used psychedelic drugs were excluded. [k]Alcohol intake was restricted to one glass. *Studies that observed significant negative effects of THC on "next day" performance (see Table 2).

Table 2. Characteristics and Results of Included Trials (>8-h Treatment, only)

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Matheson et al[28]_a (2020)	Randomized; DB; PC (BSD)	*C*: 30 (21 M); 22 ± 2 years I: 31 (18 M); 22 ± 2 years	Weekly–daily	Smoked cannabis cigarettes (562 ± 170 mg; 12.5% THC) (< 0.5% CBD)	70.3 ± 21.3[a]	Grooved pegboard task	Time to complete (DH) Time to complete (non-DH)	24 & 48 h	No significant effect
						DSST	Number of completed trials Number of correct trials Reaction time	24 & 48 h	**THC ↑ number of correct trials at 48 h**
						CPT	Percent omission errors Percent commission errors Hit rate Hit rate variability Detectability	24 & 48 h	No significant effect
						HVLT-R	Immediate recall Total recall Learning score Delayed recall Percent retained True positives False positive Discrimination index	24 & 48 h	No significant effect
Matheson et al[28]_b (2020)	Randomized; DB; PC (BSD)	*C*: 30 (21 M); 22 ± 2 years I: 30 (26 M); 22 ± 2 years	Weekly–daily	Smoked cannabis cigarettes (752 ± 131 mg; 12.5% THC) (< 0.5% CBD)	94.0 ± 16.4[a]	Grooved pegboard task	Time to complete (DH) Time to complete (non-DH)	24 & 48 h	No significant effect
						DSST	Number of completed trials Number of correct trials Reaction time	24 & 48 h	**THC ↑ number of correct trials at 48 h.**
						CPT	Percent omission errors Percent commission errors Hit rate Hit rate variability Detectability	24 & 48 h	No significant effect
						HVLT-R	Immediate recall Total recall Learning score Delayed recall Percent retained True positives False positive Discrimination index	24 & 48 h	No significant effect
Brands et al[29]_a (2019)	Randomized; DB; PC (BSD)	*C*: 30 (21 M); 22 ± 2 years I: 31 (18 M); 22 ± 2 years	Weekly–daily	Smoked cannabis cigarettes (562 ± 170 mg; 12.5% THC) (< 0.5% CBD)	70.3 ± 21.3[a]	Simulated driving	SDLP Speed	24 & 48 h	No significant effect
						Simulated driving (dual task)	SDLP Speed	24 & 48 h	No significant effect

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Brands et al[29]_b (2019)	Randomized; DB; PC (BSD)	*C*: 30 (21 M); 22 ± 2 years I: 30 (26 M); 22 ± 2 years	Weekly–daily	Smoked cannabis cigarettes (752 ± 131 mg; 12.5% THC) (< 0.5% CBD)	94.0 ± 16.4[a]	Simulated driving Simulated driving (dual task)	SDLP Speed SDLP Speed	24 & 48 h 24 & 48 h	**THC ↓ SDLP at 48 h** No significant effect
Hartley et al[37]_a (2019)	Randomized; DB; PC (WSD)	15 M; 22 ± 3 years	Weekly	Smoked cannabis cigarettes (9.8% THC; 1 g tobacco) (< 0.1% CBD and CBN)	10	Simulated driving PVT	SDLP Reciprocal reaction time	12 & 24 h 12 & 24 h	No effect[b] No effect[b]
Hartley et al[37]_b (2019)	Randomized; DB; PC (WSD)	15 M; 22 ± 3 years	Weekly	Smoked cannabis cigarettes (9.8% THC; 1 g tobacco) (< 0.1% CBD and CBN)	30	Simulated driving PVT	SDLP Reciprocal reaction time	12 & 24 h 12 & 24 h	No effect[b] No effect[b]
Hartley et al[37]_c (2019)	Randomized; DB; PC (WSD)	15 M; 22 ± 3 years	Daily	Smoked cannabis cigarettes (9.8% THC; 1 g tobacco) (< 0.1% CBD and CBN)	10	Simulated driving PVT	SDLP Reciprocal reaction time	12 & 24 h 12 & 24 h	No effect[b] No effect[b]
Hartley et al[37]_d (2019)	Randomized; DB; PC (WSD)	15 M; 22 ± 3 years	Daily	Smoked cannabis cigarettes (9.8% THC; 1 g tobacco) (< 0.1% CBD and CBN)	30	Simulated driving PVT	SDLP Reciprocal reaction time	12 & 24 h 12 & 24 h	No effect[b] No effect[b]
Schoedel et al[25]_a (2018)	Randomized; DB; PC (WSD)[c]	43 (31 M)[d]; 38 ± 9 years	Infrequent–daily	THC capsules	10	Divided attention task HVLT-R DSST	Tracking accuracy Delayed recall Percent retained Number of completed trials Number of incorrect trials	12 & 24 h 12 & 24 h 12 & 24 h	No significant effect No relevant analysis[e] No relevant analysis[e]
Schoedel et al[25]_b (2018)	Randomized; DB; PC (WSD)[c]	43 (31 M)[d]; 38 ± 9 years	Infrequent–daily	THC capsules	30	Divided attention task HVLT-R DSST	Tracking accuracy Delayed recall Percent retained Number of completed trials Number of incorrect trials	12 & 24 h 12 & 24 h 12 & 24 h	No significant effect No relevant analysis[e] No relevant analysis[e]
Ronen et al[38] (2008)	DB; PC (WSD)	14 (10 M); 22 ± 2 years	Monthly–weekly	Smoked THC cigarettes	17	Simulated driving	RMS lane position RMS speed Speed RMS steering deviations Reaction time (dual task)	24 h	No significant effect[f]

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Ménétrey et al[26]_a (2005)	Randomized; DB; PC (WSD)	8 M[g]; range: 22–30 years	Unclear	Hemp milk decoction	16.5	Road sign test	Time to complete	10 & 25 h	Ambiguous[h]
						Divided attention task	Tracking accuracy Number of errors Reaction time	10 & 25 h	Ambiguous[h]
Ménétrey et al[26]_b (2005)	Randomized; DB; PC (WSD)	8 M[g]; range: 22–30 years	Unclear	Hemp milk decoction	45.7	Road sign test	Time to complete	10 & 25 h	Ambiguous[h]
						Divided attention task	Tracking accuracy Number of errors Reaction time	10 & 25 h	Ambiguous[h]
Ménétrey et al[26]_c (2005)	Randomized; DB; PC (WSD)	8 M[g]; range: 22–30 years	Unclear	THC capsules	20	Road sign test	Time to complete	10 & 25 h	Ambiguous[h]
						Divided attention task	Tracking accuracy Number of errors Reaction time	10 & 25 h	Ambiguous[h]
Nicholson et al[27]_a (2004)	DB; PC (WSD)	8 (4 M); range 21–34 years	Current nonusers	Oromucosal spray	15	Word memory recall	Immediate recall Delayed recall	10 h	**THC ↓ immediate and delayed recall at 10 h**
						Digit memory recall	Reaction time Number of errors	10 h	No significant effect
						6-Letter memory recall	Reaction time Number of errors	10 h	No significant effect
						DSST	Number of completed trials	10 h	No significant effect
						Multi-attribute task	System monitoring RT System monitoring RA Communications RT Communications RA Resource management RT Resource management RA Tracking accuracy	10 h	No significant effect
						Choice reaction time task	Reciprocal reaction time Number of errors	10 h	No significant effect
						Sustained attention task	Reaction time Number of errors	10 h	No significant effect
Nicholson et al[27]_b (2004)	DB; PC (WSD)	8 (4 M); range 21–34 years	Current nonusers	Oromucosal spray (5 mg CBD)	5	Word memory recall	Immediate recall Delayed recall	10 h	No significant effect
						Digit memory recall	Reaction time Number of errors	10 h	**THC ↑ reaction time at 10 h**
						6-Letter memory recall	Reaction time Number of errors	10 h	No significant effect
						DSST	Number of completed trials	10 h	No significant effect
						Multi-attribute task	System Monitoring RT System Monitoring RA Communications RT Communications RA Resource management RT Resource management RA Tracking accuracy	10 h	No significant effect

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
						Choice reaction time task	Reciprocal reaction time Number of errors	10 h	No significant effect
						Sustained attention task	Reaction time Number of errors	10 h	No significant effect
Nicholson et al[27]_c (2004)	DB; PC (WSD)	8 (4 M); range 21–34 years	Current nonusers	Oromucosal spray (15 mg CBD)	15	Word memory recall	Immediate recall Delayed recall	10 h	No significant effects
						Digit memory recall	Reaction time Number of errors	10 h	No significant effects
						6-Letter memory recall	Reaction time Number of errors	10 h	No significant effect
						DSST	Number of completed trials	10 h	No significant effect
						Multi-attribute task	System monitoring RT System monitoring RA Communications RT Communications RA Resource management RT Resource management RA Tracking accuracy	10 h	No significant effect
						Choice reaction time task	Reciprocal reaction time Number of errors	10 h	No significant effect
						Sustained attention task	Reaction time Number of errors	10 h	No significant effect
Curran et al[34]_a (2002)	Randomized; DB; PC (WSD)	15 M; 24±2 years	Unclear	THC capsules	7.5	Buschkel selective reminding task	Immediate recall Delayed recall	24 & 48 h	Ambiguous
						RVIPT	Proportion of hits Reaction time	24 & 48 h	No significant effect
						Baddeley reasoning task	Reaction time Number of errors	24 & 48 h	No significant effect
						Subtract serial sevens task	Reaction time Number of errors	24 & 48 h	No significant effect
						Choice reaction time task	Reaction time Number of errors	24 & 48 h	No significant effect
						Digit cancellation task	Time to complete (ST) Number of errors (ST) Time to complete (DT) Number of errors (DT)	24 & 48 h	No significant effects
						Simple reaction time task	Reaction time	24 & 48 h	No significant effect

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Curran et al[34]_b (2002)	Randomized; DB; PC (WSD)	15 M; 24±2 years	Unclear	THC capsules	15	Buschkel selective reminding task	Immediate recall Delayed recall	24 & 48 h	Ambiguous
						RVIPT	Proportion of hits Reaction time	24 & 48 h	No significant effect
						Baddeley reasoning task	Reaction time Number of errors	24 & 48 h	No significant effect
						Subtract serial sevens task	Reaction time Number of errors	24 & 48 h	No significant effect
						Choice reaction time task	Reaction time Number of errors	24 & 48 h	No significant effect
						Digit cancellation task	Time to complete (ST) Number of errors (ST) Time to complete (DT) Number of errors (DT)	24 & 48 h	No significant effect
						Simple reaction time task	Reaction time	24 & 48 h	No significant effect
Fant et al[35]_a (1998)	Randomized; DB; PC (WSD)	10 M; 27 years, range: 24–31 years	Monthly–weekly	Smoked cannabis cigarettes (1.8% THC)	"Eight Puffs" (dose unknown)	Smooth-pursuit eye movements	Central speed (fixed) Central speed (varied) Peripheral speed (fixed) Peripheral speed (varied)	23, 24 & 25 h	Ambiguous[i]
						Circular lights task	Number of correct responses	23, 24 & 25 h	No significant effect
						Serial addition and subtraction task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Digit recall task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Logical reasoning task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Mannequin task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Fant et al[35]_b (1998)	Randomized; DB; PC (WSD)	10 M; 27 years, range: 24–31 years	Monthly–weekly	Smoked cannabis cigarettes (3.6% THC)	"Eight Puffs" (dose unknown)	Smooth-pursuit eye movements	Central speed (fixed) Central speed (varied) Peripheral speed (fixed) Peripheral speed (varied)	23, 24 & 25 h	Ambiguous[i]
						Circular lights task	Number of correct responses	23, 24 & 25 h	No significant effect
						Serial addition and subtraction task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Digit recall task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Logical reasoning task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
						Mannequin task	Number of correct responses Percent correct responses Reaction time	23, 24 & 25 h	No significant effect
Chait and Perry[30] (1994)	DB; PC (WSD)	14 (10 M); 25 years, range: 21–34 years	Monthly–daily	Smoked cannabis cigarettes (3.6% THC)	"Eight Puffs" (dose unknown)	Time production task	Time interval (30 sec) Time interval (60 sec) Time interval (120 sec)	11 & 18 h	No significant effect
						Standing steadiness task	Standing time	11 & 18 h	No significant effect
						DSST	Number of trials attempted Number of correct trials Percent correct	11 & 18 h	No significant effect
						Backward digit span task	Digit span	11 & 18 h	No significant effect
						Logical reasoning task	NS	11 & 18 h	No significant effect
						Visual divided attention task	Hit rate Reaction time Secondary target errors Number of false alarms	11 & 18 h	No significant effect
						Free recall task	Immediate recall	11 & 18 h	No significant effect
Leirer et al[40] (1991)	"Blinded"[j]; PC (WSD)	9 (Sex NS); 31 years, range: 24–40 years	Unclear	Smoked cannabis cigarettes	20	Simulated flying	Performance score	24 & 48 h	**THC ↓ performance at 24 h**

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Chait[22] (1990)	DB; PC (WSD)	12 (9 M); 21 years, range: 18–26 years	Weekly–daily	Smoked cannabis cigarettes (800–900 mg; 2.1% THC)	"Eight Puffs"[k] (dose unknown)	Time production task	Time interval	12, 12 & 12 h[k]	**THC ↓ time interval (all days)**[l,m]
						Simple reaction time task	NS	12, 12 & 12 h[k]	No significant effect
						Forward digit span task	Digit span	12, 12 & 12 h[k]	No significant effect
						Visual divided attention task	Reaction time Number of misses Number of false alarms Reaction time variability	12, 12 & 12 h[k]	**THC ↑ reaction time (all days)**[l]
						Choice reaction time task	NS	12, 12 & 12 h[k]	No significant effect
						Backward digit span task	Digit span	12, 12 & 12 h[k]	**THC ↓ digit span on day 1**
						DSST	NS	12, 12 & 12 h[k]	No significant effect
						Buschkel selective Reminding task	NS	12, 12 & 12 h[k]	No significant effect
Heishman et al[23]_a (1990)	Randomized; DB; PC (WSD)	3 M; range 27–29 years	Unclear	Smoked cannabis cigarettes (2.57% THC)	"1 × Cigarette" (dose unknown)	Two letter search task	Number of trials attempted Number of correct trials Percent correct	23, 25, 27, 29 & 31 h	Results not adequately reported
						Logical reasoning task	Number of trials attempted Number of correct trials Percent correct	23, 25, 27, 29 & 31 h	Results not adequately reported
						Digit recall task	Number of trials attempted Number of correct trials Percent correct	23, 25, 27, 29 & 31 h	Results not adequately reported
						Serial addition and subtraction task	Number of trials attempted Number of correct trials Percent correct	23, 25, 27, 29 & 31 h	Results not adequately reported
						Circular lights task	Number of correct responses	23, 25, 27, 29 & 31 h	Results not adequately reported

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Heishman et al[23]_b (1990)	Randomized; DB; PC (WSD)	3 M; range 27–29 years	Unclear	Smoked cannabis cigarettes (2.57% THC)	"2×Cigarette" (dose unknown)[n]	Two letter search task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Logical reasoning task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Digit recall task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Serial addition and subtraction task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Circular lights task	Number of correct responses	19, 21, 23, 25 & 27 h	Results not adequately reported
Heishman et al[23]_c (1990)	Randomized; DB; PC (WSD)	2 M; range 27–29 years	Unclear	Smoked cannabis cigarettes (2.57% THC)	"4×Cigarette" (dose unknown)[o]	Two letter search task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Logical reasoning task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Digit recall task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Serial addition and subtraction task	Number of trials attempted Number of correct trials Percent correct	19, 21, 23, 25 & 27 h	Results not adequately reported
						Circular lights task	Number of correct responses	19, 21, 23, 25 & 27 h	Results not adequately reported.
Leirer et al[31]_a (1989)	Randomized; DB; PC (WSD)	9 (Sex NS); 26 years, range: 18–29 years	Unclear	Smoked cannabis cigarettes	10	Simulated flying	Performance score (calm) Performance score (turbulent)	24 & 48 h	No significant effect
Leirer et al[31]_b (1989)	Randomized; DB; PC (WSD)	9 (Sex NS); 26 years, range: 18–29 years	Unclear	Smoked cannabis cigarettes	20	Simulated flying	Performance score (calm) Performance score (turbulent)	24 & 48 h	No significant effect

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Leirer et al[31]_c (1989)	Randomized; DB; PC (WSD)	9 (Sex NS); 38 years, range: 30–48 years	Unclear	Smoked cannabis cigarettes	10	Simulated flying	Performance score (calm) Performance score (turbulent)	24 & 48 h	No significant effect
Leirer et al[31]_d (1989)	Randomized; DB; PC (WSD)	9 (Sex NS); 38 years, range: 30–48 years	Unclear	Smoked cannabis cigarettes	20	Simulated flying	Performance score (calm) Performance Score (turbulent)	24 & 48 h	No significant effect
Barnett et al[33]_a (1985)	"Blinded"[j]; PC (WSD)	8 M; range: 22–33 years	Unclear	Smoked cannabis cigarettes (700 mg; 1% THC)	100 $\mu g \cdot kg^{-1}$ (6.8–7.3 mg)	Visual search task	Reaction time	10, 12 & 23 h	No effect[b]
						Divided attention task	Reaction time Tracking accuracy	10, 12 & 23 h	No effect[b]
						Critical tracking task	Tracking accuracy	10, 12 & 23 h	No effect[b]
Barnett et al[33]_b (1985)	"Blinded"[j]; PC (WSD)	8 M; range: 22–33 years	Unclear	Smoked cannabis cigarettes (700 mg; 1% THC)	200 $\mu g \cdot kg^{-1}$ (14–15 mg)	Visual search task	Reaction time	10, 12 & 23 h	No effect[b]
						Divided attention task	Reaction time Tracking accuracy	10, 12 & 23 h	No effect[b]
						Critical tracking task	Tracking accuracy	10, 12 & 23 h	No effect[b]
Barnett et al[33]_c (1985)	"Blinded"[j]; PC (WSD)	8 M; range: 22–33 years	Unclear	Smoked cannabis cigarettes (700 mg; 1% THC)	250 $\mu g \cdot kg^{-1}$ (17–18 mg)	Visual search task	Reaction Time	10, 12 & 23 h	No effect[b]
						Divided attention task	Reaction time Tracking accuracy	10, 12 & 23 h	No effect[b]
						Critical tracking task	Tracking accuracy	10, 12 & 23 h	No effect[b]
Chait et al[24]_a (1985)	"Blinded"[j]; PC (WSD)	13 M; 25 years, range: 21–35 years	Infrequent–daily	Smoked cannabis cigarettes (1 g; 2.9% THC)	"Ten Puffs" (dose unknown)	Card sorting task	Time to complete (simple) Time to complete (suit)	9.5 h	No significant effect
						Free recall task	Immediate recall	9.5 h	No significant effect
						DSST	Number of correct trials	9.5 h	No significant effect
						Time production task	Time interval (10 sec) Time interval (30 sec)	9.5 h	**THC ↑ time interval (10 & 30 sec) at 9.5 h compared to target**
Chait et al[24]_b (1985)	"Blinded"[j]; PC (WSD)	6 M; age NS	Unclear	Smoked cannabis cigarettes (1 g; 2.9% THC)	"Five Puffs" (dose unknown)	Card sorting task	Time to complete (simple) Time to complete (suit)	9.5 h	Results not reported
						Free recall task	Immediate recall	9.5 h	Results not reported
						DSST	Number of correct trials	9.5 h	Results not reported
						Time production task	Time interval (10 sec) Time interval (30 sec)	9.5 h	Results not reported

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Yesavage et al[41] (1985)	Pre-/post-trial	10 (Sex NS); 29 years	Unclear	Smoked cannabis cigarettes	19	Simulated flying	Distance off-center on landing Lateral deviation Vertical deviation Aileron (number of changes) Aileron (mean size) Elevations (number of changes) Elevations (mean size) Number of throttle changes	24 h	**THC ↑ distance off-center on landing, lateral deviation, aileron (number of changes), aileron (mean size) and elevations (mean size) at 24 h compared to baseline**
Rafaelsen et al[39]_a (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	8	Simulated driving	Brake time Start time Number of gear changes Mean speed	~15 h	No significant effect[p]
Rafaelsen et al[39]_b (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	12	Simulated driving	Brake time Start time Number of gear changes Mean speed	~15 h	No significant effect[p]
Rafaelsen et al[39]_c (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	12	Simulated driving	Brake time Start time Number of gear changes Mean speed	~15 h	No significant effect[p]
Rafaelsen et al[39]_d (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	16	Simulated driving	Brake time Start time Number of gear changes Mean speed	~15 h	No significant effect[p]
Rafaelsen et al[36]_a (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	8	Digit span task (direction NS) Addition test Subtract serial sevens task Finger labyrinths task Bourdon's cancellation test	Digit span Time to complete Number of errors Time to complete Number of errors Time to complete Number of errors Number of letters scanned Number of errors	~15 h ~15 h ~15 h ~15 h ~15 h	No significant effect[p] No significant effect[p] No significant effect[p] No significant effect[p] No significant effect[p]

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Rafaelsen et al[36]_b (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	12	Digit span task (direction NS)	Digit span	~15 h	No significant effect[p]
						Addition test	Time to complete Number of errors	~15 h	No significant effect[p]
						Subtract serial sevens task	Time to complete Number of errors	~15 h	No significant effect[p]
						Finger labyrinths task	Time to complete Number of errors	~15 h	No significant effect[p]
						Bourdon's cancellation test	Number of letters scanned Number of errors	~15 h	No significant effect[p]
Rafaelsen et al[36]_c (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	12	Digit span task (direction NS)	Digit span	~15 h	No significant effect[p]
						Addition test	Time to complete Number of errors	~15 h	No significant effect[p]
						Subtract serial sevens task	Time to complete Number of errors	~15 h	No significant effect[p]
						Finger labyrinths task	Time to complete Number of errors	~15 h	No significant effect[p]
						Bourdon's cancellation test	Number of letters scanned Number of errors	~15 h	No significant effect[p]
Rafaelsen et al[36]_d (1973)	Randomized; DB; PC (WSD)	8 M; range: 21–29 years	Unclear	Oral cannabis (baked into cake)	16	Digit span task (direction NS)	Digit span	~15 h	No significant effect[p]
						Addition test	Time to complete Number of errors	~15 h	No significant effect[p]
						Subtract serial sevens task	Time to complete Number of errors	~15 h	No significant effect[p]
						Finger labyrinths task	Time to complete Number of errors	~15 h	No significant effect[p]
						Bourdon's cancellation test	Number of letters scanned Number of errors	~15 h	No significant effect[p]
Kielholz et al[32]_a (1973)	DB; PC (BSD)	54[q] (Sex NS); 34 years	Unclear	THC capsules	350 $\mu g \cdot kg^{-1}$ (~24.5 mg)[r]	Tapping task	Taps (comfortable) (right) Taps (comfortable) (left) Taps (fast) (right) Taps (fast) (left)	17.5 h	Results not adequately reported
						Spiral rotor task	NS	17.5 h	Results not adequately reported
						The compensation apparatus	NS	17.5 h	Results not adequately reported
						The tracking apparatus	Reaction time Frequency of pedal pressure	17.5 h	Results not adequately reported

(*continued*)

Table 2. Continued

Citation	Study design	Participants	Usual cannabis use behavior	Treatment	THC dose (mg)	Performance test	Outcomes	Time since last THC use	Effect of THC (compared to placebo unless otherwise stated)
Kielholz et al[32]_b (1973)	DB; PC (BSD)	54[q] (Sex NS); 34 years	Unclear	THC capsules	400 $\mu g \cdot kg^{-1}$ ($\sim$28 mg)[r]	Tapping task	Taps (comfortable) (R) Taps (comfortable) (L) Taps (fast) (R) Taps (fast) (L)	17.5 h	Results not adequately reported
						Spiral rotor task	NS	17.5 h	Results not adequately reported
						The compensation apparatus	NS	17.5 h	Results not adequately reported
						The tracking apparatus	Reaction time Frequency of pedal pressure	17.5 h	Results not adequately reported
Kielholz et al[32]_c (1973)	DB; PC (BSD)	54[q] (Sex NS); 34 years	Unclear	THC capsules	450 $\mu g \cdot kg^{-1}$ ($\sim$31.5 mg)[r]	Tapping task	Taps (comfortable) (right) Taps (comfortable) (left) Taps (fast) (right) Taps (fast) (left)	17.5 h	Results not adequately reported
						Spiral rotor task	NS	17.5 h	Results not adequately reported
						The compensation apparatus	NS	17.5 h	Results not adequately reported
						The tracking apparatus	Reaction time Frequency of pedal pressure	17.5 h	Results not adequately reported

All "Effects of THC" are in comparison to placebo unless otherwise stated; comparisons to baseline are only reported when those to placebo were not conducted or not reported. Significant effects are in **bold text**.

[a]Cigarettes were smoked *ad libitum*.

[b]The authors modeled the "behavioral pharmacokinetics" of THC rather than investigating its effect at specific times post-treatment; however, their modeling still suggests impairment resolves within 8 h.

[c]Although "double blinded," participants had to demonstrate a capacity to distinguish between THC and placebo (in a "Quantification Phase") to be eligible for inclusion.

[d]Only 35 of these participants were included in the analyses investigating THC's effects on cognitive function.

[e]Only the "minimum" and "maximum" performance scores were presented and subjected to statistical analysis.

[f]Compared to "20 minutes post-placebo" (as performance was not assessed 24 h post-placebo).

[g]It is unclear whether six or eight participants completed the cognitive function tests.

[h]It is unclear how the time parameter was handled in these statistical analyses (see also ' "Next Day" effects of THC' section).

[i]The authors indicate that THC decreased pursuit speeds at 1.75 h, but do not clearly describe its effects at the other time points.

[j]The authors do not state whether a single- or double-blind design was used.

[k]Participants completed a total of five smoking periods involving "eight puffs" each: (1) 9 PM Friday; (2) 3 PM Saturday; (3) 9 PM Saturday; (4) 3 PM Sunday; and (5) 9 PM Sunday; cognitive function was assessed 12 h after each evening (9 PM) smoking period.

[l]Main effect of treatment across all 3 days.

[m]This effect is described as "negative" in this article (since any change in time production could indicate "impairment"); however, it is worth noting that participants were closer to the target time on THC than placebo.

[n]The first cigarette was administered 4 h before the second.

[o]The first two cigarettes were administered 4 h before the second two.

[p]We presume these comparisons are against placebo.

[q]Total number across all four treatment groups.

[r]Value estimated at a body weight of 70 kg.

BSD, between-subject design; C, control group; CBD, cannabidiol; CBN, cannabinol; CPT, continuous performance test; DB, double blind; DH, dominant hand; DSST, digit symbol substitution test; DT, double target; HVLT-R, Hopkins Verbal Learning Test Revised; I, intervention group; L, left; M, male participants; NS, not specified; PC, placebo controlled; PVT, psychomotor vigilance task; R, right; *R*, correlation coefficient; RA, response accuracy; RT, reaction time; RVIPT, rapid visual information processing task; SB, single blind; SDLP, standard deviation of lane position; ST, single target; WSD, within subject design.

in multiple "subsections" (e.g., if they observed negative "next day" effects on some tests, but not others).

No "Next Day" effects. A total of 180 neuropsychological tests and 29 safety-sensitive tasks showed no "next day" effect of THC ($N=18$ divided attention[25,27,30,33]; $N=12$ executive function[30,34,35]; $N=32$ information processing[22,24,27,28,30,33,34,36]; $N=6$ tracking performance[33]; $N=23$ reaction time[22,27,34,35]; $N=6$ motor function[28,30]; $N=19$ sustained attention[27,28,34,37]; $N=22$ working memory[22,30,34–36]; $N=2$ perception[30]; $N=26$ learning and(or) memory[22,24,27,28,30,35]; $N=6$ spatial reasoning[35]; $N=8$ unknown[36]; $N=20$ simulated driving[29,37–39]; and $N=9$ simulated flying[31,40]). Seventy, 82, and 28 of these 180 neuropsychological tests and 4, 17, and 8 of these 29 safety-sensitive tasks were conducted between >8–12, >12–24, and >24–48 h post-treatment, respectively.

No "next day" effect was observed across a total of 16 published studies.[22,24,25,27–31,33–40] Most of these 16 studies ($N=9$) used randomized double-blind, placebo-controlled designs[25,28,29,31,34–37,39] ($N=4$ nonrandomized double blind[22,27,30,38] and $N=3$ nonrandomized single blind[24,33,40]), involved other cannabis users ($N=12$),[24,25,27,30,31,33–36,38–40] and administered THC by smoking ($N=11$).[22,24,28–31,33,35,37,38,40] The median [IQR] THC dose was 15 [10–20] mg (where reported; $N=12$[25,27–29,31,33,34,36–40]).

With respect to RoB, half of these 16 studies were rated as having "some concerns" ($N=8$),[22,24,25,28–30,37,40] and the other half had a "high risk" of bias ($N=8$).[27,31,33–36,38,39] Of those with "some concerns," two received "low risk" ratings on four of the five RoB domains assessed[28,29] and three employed "robust" standardization procedures.[28–30]

Negative "Next Day" effects. A total of 10 neuropsychological tests conducted between >8 and 12 h post-treatment and two safety-sensitive tasks conducted 24 h post-treatment indicated negative (i.e., impairing) "next day" effects of THC ($N=2$ learning and[or] memory[27]; $N=4$ perception[22,24]; $N=1$ working memory[22]; $N=3$ divided attention[22]; and $N=2$ simulated flying[40,41]).

These negative "next day" effects were observed across a total of five published studies.[22,24,27,40,41] None of these studies used randomized double-blind, placebo-controlled designs ($N=2$ nonrandomized double-blind[22,27]; $N=2$ nonrandomized single-blind[24,40]; and $N=1$ pre-/post-treatment design[41]). Most involved other cannabis users ($N=4$)[24,27,40,41] and administered THC by smoking ($N=4$).[22,24,40,41] THC doses were 5, 15, 19, and 20 mg (where reported; $N=3$[27,40,41]).

With respect to RoB, three of these five studies were rated as having "some concerns,"[22,24,40] and two had a "high risk" of bias.[27,41] Of those with "some concerns," none employed "robust" standardization procedures.

Positive "Next Day" effects. Two neuropsychological tests and one safety-sensitive task, all administered 48 h post-treatment, indicated positive (i.e., enhancing) "next day" effects of THC ($N=2$ information processing[28] and $N=1$ simulated driving[29]).

These positive "next day" effects were observed across two published studies[28,29] conducted in the same investigation: a randomized double-blind, placebo-controlled trial. Participants were regular cannabis users and smoked either 70.3 ± 21.3 or 94.0 ± 16.4 mg THC *ad libitum*.

With respect to RoB, both studies were rated as having "some concerns"—but received "low risk" ratings on four of the five domains assessed.[28,29] Both also employed "robust" standardization procedures.

Unclear "Next Day" effects. A total of 121 performance tests indicated "unclear" or ambiguous "next day" effects of THC (i.e., insufficient information was provided to accurately determine the result) (Table 2). These unclear "next day" effects were observed across a total of seven published studies,[23–26,32,34,35] three of which reported all of their relevant results ($N=99$ performance tests) in a manner that was of limited use to the current review. First, Ménétrey et al[26] reported using a Kruskal-Wallis test to compare cognitive function data across four different treatments. This is problematic as these data were collected at seven different time points (plus baseline) and the authors do not explain how the time parameter was handled in their analyses.

Second, Heishman et al[23] were unable to perform statistical analyses as only three participants completed their trial (and only two completed treatment arm "c"). Third, the results of Kielholz et al[32] were poorly described and could not be reliably interpreted. These studies and tests were retained for completeness, but will not be discussed further.

"Acute Effects" of THC

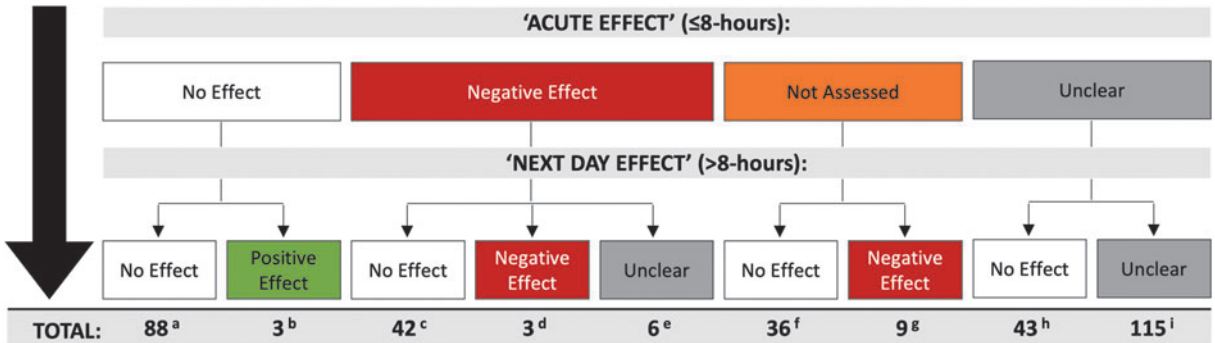
It is important to consider whether the 345 performance tests administered >8 h post-treatment also

demonstrated "acute" (i.e., <8 h post-treatment) effects of THC. Indeed, a lack of impairment at, say, 24 h is a more definitive illustration of no "next day" effects on a performance test if impairment had been evident on that same test at shorter durations following THC (i.e., <8 h post-treatment). The relevant results are detailed in Supplementary File S1 and summarized in Figure 3. We note the following: only 20% ($N=42$) of the tests that showed no "next day" effects of THC also demonstrated "acute" effects (i.e., initial impairment). Most did not (42%; $N=88$). The remainder either did not assess (17%; $N=36$) or adequately describe (21%; $N=43$) the acute effects of THC.

Discussion

This systematic review found little by way of high-quality scientific evidence to support the assertion that cannabis use impairs "next day" performance. Indeed, of the 345 performance tests reviewed, only 12 indicated negative (i.e., impairing) "next day" effects of THC. Notably, the five studies that observed these effects were all published >18 years ago (four, >30 years ago) and found to have significant methodological limitations.

Only two investigations: the flight simulator studies of Leirer et al[40] and Yesavage et al[41] provided any evidence of THC-induced impairment persisting beyond 12 h. Both studies administered ~20 mg THC to a poorly characterized participant population (i.e., their cannabis use behavior and sex were not reported) by smoking (cannabis) and reported impairment 24 h post-treatment. However, they also employed suboptimal designs (i.e., "pre-/post-treatment" and non-randomized, single blind, placebo controlled) and



TOTAL:	88 [a]	3 [b]	42 [c]	3 [d]	6 [e]	36 [f]	9 [g]	43 [h]	115 [i]
>8–12 h:	6	0	6	1	4	36	9	26	10
>12–24 h:	57	0	25	2	2	0	0	17	55
>24–48 h:	25	3	11	0	0	0	0	0	50

a: Matheson et al. (2020)_a, b; Brands et al. (2019)_a, b; Schoedel et al. (2018)_a; Curran et al. (2002)_a, b; Fant et al. (1998)_a, b; Chait & Perry (1994); Leirer et al. (1989)_a, c; Chait et al. (1985)_a; Rafaelsen et al. (1973a)_a, b; Rafaelsen et al. (1973b)_a, b, c, d.
b: Matheson et al. (2020)_a, b; Brands et al. (2019)_b.
c: Matheson et al. (2020)_b; Schoedel et al. (2018)_b; Ronen et al. (2008); Curran et al. (2002)_a, b; Chait & Perry (1994); Leirer et al. (1991); Leirer et al. (1989)_b, d; Chait et al. (1985)_a; Rafaelsen et al. (1973a)_c, d; Rafaelsen et al. (1973b)_b, c, d.
d: Leirer et al. (1991); Yesavage et al. (1985); Chait et al. (1985)_a
e: Fant et al. (1998)_a, b
f: Nicholson et al. (2004)_a, b, c; Chait (1990)
g: Nicholson et al. (2004)_a, b; Chait (1990)
h: Hartley et al. (2019)_a, b, c, d; Barnett et al. (1985)_a, b, c.
i: Schoedel et al. (2018)_a, b; Ménétrey et al. (2005)_a, b, c; Curran et al. (2002)_a, b; Heishman et al. (1990)_a, b, c; Chait et al. (1985)_b; Kielholz et al. (1973)_a, b, c.

FIG. 3. A total of 345 performance tests were administered >8 h post-treatment. This figure shows the number demonstrating "no effect," a "positive effect," a "negative effect," and an "unclear effect" of THC (i.e., on any one of its outcome measures) >8–12, >12–24, and >24–48 h post-treatment. Counts are further subcategorized based on whether the performance test also demonstrated "no effect," a "negative effect," or an "unclear effect" "acutely" (i.e., anytime ≤8 h post-treatment) (or if acute effects were not assessed). Unused subgroupings were omitted from this figure. Note: reductions in driving speed ≤8 h post-treatment were not considered either "positive" or "negative" and were therefore omitted from this analysis. See Table 2 and Supplementary Table S3 for full results. THC, Δ^9-tetrahydrocannabinol.

inadequate standardization procedures (Fig. 2), one indicating a "high risk" of bias (due to missing outcome data and the randomization process employed).[41] It can further be assumed that flight simulator technology was very rudimentary at this stage in history (i.e., ~1990) and noted that these "next day" effects were not replicated in a third flight simulator study (employing a superior randomized, double-blind, placebo-controlled design) conducted by the same group of authors.[31]

Three additional investigations Nicholson et al,[27] Chait et al,[24] and Chait[22] reported impaired cognitive performance between >8 and 12 h after THC use. Again, however, each of these studies employed suboptimal designs (Table 2) and had either a "high risk" of bias (due to missing outcome data)[27] or inadequate standardization procedures[22,24] (Fig. 2); two also involved an unknown dose of THC.[22,24] Of further note is the fact that many of the effects observed across these three studies ($N=4$ out of 10)—and the only effect observed in Chait et al[24]—were on "time production" tests (i.e., during which participants estimate when a given amount of time has elapsed, e.g., 120 sec). These tests may be of limited relevance to driving and workplace safety. In addition, time estimations were often closer to the target on THC than placebo (i.e., arguably enhanced).[22]

The remaining "negative" effects could be due, in part, to certain methodological factors. For example, the oromucosal THC (5 and 15 mg) preparation used in Nicholson et al[27] would be expected to elicit longer lasting impairment than inhaled THC.[3,42] Chait[22] also utilized an unusually demanding treatment protocol in which participants completed five separate "smoking sessions" over a 48-h period. Overall, however, these "next day" effects did not appear to be associated with a specific methodological factor (e.g., dose, route of administration or whether regular or occasional users were assessed) and should be interpreted with caution.

The "next day" effects of alcohol use have also received some scientific attention. Indeed, a recent meta-analysis showed that "alcohol hangover" had a small to moderate detrimental effect on cognitive performance (e.g., sustained attention, psychomotor speed, short-/long-term memory).[43] The "next day" effects of THC use could not be quantified in this review as studies often failed to report the information required to calculate an effect estimate. However, the small number of significant effects observed would suggest that a THC "hangover" is unlikely to be more impairing than an alcohol hangover, which is generally tolerated among drivers and individuals employed in safety-sensitive positions.

A total of 209 performance tests conducted across 16 published studies showed no "next day" effects of THC.[22,24,25,27–31,33–40] Most of these 16 studies used randomized double-blind, placebo-controlled designs ($N=9$),[25,28,29,31,34–37,39] but still had methodological limitations. Indeed, half had a "high risk" of bias (often due to missing outcome data)[27,31,33–36,38,39] and most used inadequate standardization procedures[22,24,25,27,31,33–40] (Fig. 2). In addition, only three justified their chosen sample sizes (Fig. 1) (and none used noninferiority analysis to test the specific hypothesis that THC *does not* impair "next day" performance[44]).

One additional concern is that 42% of the tests showing no "next day" effects of THC also failed to demonstrate "acute" (i.e., <8 h post-treatment) THC-induced impairment (Fig. 3). This is important as "next day" effects seem unlikely to occur in the absence of initial impairment, which could reflect the use of lower THC doses and/or tests or cognitive domains that are relatively insensitive to the effects of THC. The collective results of these 16 studies should therefore be interpreted with some degree of caution.

Nevertheless, two recent studies, both finding no "next day" effects of THC, were identified as having employed good-quality research methods: Matheson et al[28] and Brands et al.[29] These studies were conducted within the same investigation: a randomized double-blind, placebo-controlled trial in which participants (weekly–daily cannabis users) smoked either 70.3 ± 21.3 or 94.0 ± 16.4 mg THC (cannabis) *ad libitum*. Both studies had "some" RoB—but received "low risk" ratings on four of the five domains assessed (Fig. 1).

They also justified their chosen sample size ($n=91$) (Fig. 1) and employed relatively robust standardization procedures (Fig. 2). Motor function, learning and(or) memory, information processing, sustained attention, and simulated driving performance were not impaired 24 or 48 h post-treatment in these investigations. Some positive (i.e., enhancing) effects were unexpectedly observed 48 h post-treatment. In addition, only learning and(or) memory demonstrated "acute" (i.e., <8 h post-treatment) impairment. However, these findings provide some confirmation that high doses of inhaled THC are unlikely to impair "next day" performance in regular cannabis users.

Further high-quality studies investigating the "next day" effects of THC in both occasional and medicinal cannabis uses are, of course, required, as are studies involving the administration of oral THC. Until the results of such studies become available, there remains some justification for a cautious regulatory approach. However, policy makers should bear in mind that the implementation of very conservative workplace regulations can have serious consequences (e.g., termination of employment with a positive drug test) and impact the quality of life of individuals who are required to abstain from medicinal cannabis use to treat conditions such as insomnia or chronic pain for fear of a positive workplace or roadside drug test.

The following factors might also be considered in future studies of this nature. First, while most of the studies conducted to date have administered a single dose of THC, many individuals (in particular, regular cannabis users) do not consume THC in this manner under real-world conditions. High-quality studies involving daily users of medical and nonmedical cannabis would therefore be valuable. Second, performance on safety-sensitive tasks (e.g., driving, flying) and neuropsychological tests may be susceptible to "practice" (learning) and "fatigue" (loss of motivation) effects over time, and these might be better controlled in future studies. Indeed, in addition to masking "acute" effects of THC, practice effects might be attenuated under the influence of THC such that "next day" effects appear to be present.

Conclusion

A small number of lower-quality studies have observed negative (i.e., impairing) 'next day' effects of THC on cognitive function and safety-sensitive tasks. However, higher-quality studies, and a large majority of performance tests, have not. Overall, it appears that there is limited scientific evidence to support the assertion that cannabis use impairs 'next day' performance. However, further research, in particular, studies involving both occasional and medicinal cannabis users and oral THC administration, is strongly recommended.

Authors' Contributions

All authors (D.M., A.S., and I.S.M.) contributed to the conception and design of the research project; D.M. and A.S. completed data acquisition; and all authors contributed to the interpretation of the research data, were involved in drafting and critically revising the article, and approved the final submitted version.

Author Disclosure Statement

ISM is a consultant to Kinoxis Therapeutics and Psylo Ltd and has received a speakers honorarium from Janssen and consultancy fees from the Medical Cannabis Industry Association. He holds a number of patents for cannabinoid and non-cannabinoid therapeutics. ISM also acts as an expert witness in legal cases where issues of cannabis-induced impairment may be relevant. AS has received consulting fees from the Medical Cannabis Industry Association and GlaxoSmithKline Consumer Healthcare Australia Pty Ltd trading as Haleon. DM has received consulting fees from the Medical Cannabis Industry Association.

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Supplementary Material

Supplementary File S1
Supplementary File S2
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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Abbreviations Used

IQR = interquartile range
RoB = risk of bias
THC = Δ^9-tetrahydrocannabinol