Clinical pharmacology of cannabinoids in early phase drug development

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2 Biomarkers for the effects of cannabis and THC in healthy volunteers

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Abstract

Background: An increasing number of novel therapeutic agents is targeted at cannabinoid receptors. Drug development programs of new cannabinoid drugs may be facilitated by the identification of useful biomarkers.
Aim: This systematic literature review aims to assess the usefulness of direct biomarkers for the effects of cannabis and THC in healthy volunteers.
Methods: 165 useful articles were found that investigated the acute effects of cannabis or THC on the central nervous system (CNS) and heart rate in healthy volunteers. 318 tests (or test variants) were grouped in test clusters and functional domains, to allow their evaluation as a useful biomarker and to study their dose response effects.
Results: THC/cannabis affected a wide range of CNS domains. In addition to heart rate, subjective effects were the most reliable biomarkers, showing significant responses to cannabis in almost all studies. Some CNS domains showed indications of stimulation at higher doses.
Summary: Subjective effects and heart rate are currently the most reliable biomarkers to study the effect of cannabis. Cannabis affects most CNS domains, but too many different CNS tests are used to reliably quantify the drug-response relationships.

Introduction

The discovery of cannabinoid receptors and endocannabinoids has pointed to the physiological and possibly pathophysiological relevance of cannabinoids in humans. This has stimulated the development of synthetic cannabinoids, which have been used in pre-clinical research to further investigate the role of the endocannabinoid system in health and disease. However, the clinical development of cannabinoids as medicines is only just beginning. Although a large number of studies have been performed with cannabis and THC (a CB1/CB2 agonist) in healthy volunteers, it is not clear which biomarkers are useful in early cannabinoid drug development, and how cannabis affects different central nervous system (CNS) functions. A biomarker is a characteristic that is measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1] A validated biomarker in early phase I studies that provides useful information on the potential therapeutic effects of the investigational drug could support the drug development programme of the new compound. In general, a useful biomarker for activity of a drug class should meet the following criteria: 1) a clear, consistent response across studies (from different research groups) and drugs from the same class; 2) a clear response of the biomarker to therapeutic doses; 3) a dose (concentration)-response relationship; 4) a plausible relationship between

the biomarker, the pharmacology of the drug class and / or the pathogenesis of the therapeutic area. Previously, these criteria were used to evaluate the literature for the usefulness of biomarkers for the effects in healthy volunteers of antipsychotic drugs[2], benzodiazepines[3], selective serotonin reuptake inhibitors[4] and 3,4-methylene-dioxy-methamphetamine (MDMA, ecstasy)[5]. In the current review, the effects of cannabis and THC in healthy volunteers were systematically evaluated using the same methodology.

Methods

STRUCTURED LITERATURE EVALUATION

A literature search was performed up to 15 November 2007 using MedLine, Web of Science and Embase. The following keywords were used: marijuana, marihuana, cannabis, THC, tetrahydrocannabinol and delta-9-tetrahydrocannabinol. The searches were limited to healthy adults and papers in English. The resulting studies were subject to several selection criteria.

This review aimed to assess the usefulness of direct CNS biomarkers and heart rate for studies of cannabinoids in healthy volunteers. Reviews, studies in experimental animals or patients, and studies of interactions of cannabis use with personality features, behavioural characteristics, metabolic variations, other drugs, pain models or environmental factors (including secondary or subgroup analyses) were excluded from this review.

Studies with fewer than 10 subjects were not included in this review. Study participants were divided into non-users and users. No distinction was made according to the levels of previous or current usage, which ranged from occasional to chronic frequent use. Frequent and infrequent users were grouped as users. The review was restricted to the effects of acute cannabis exposure. Hence, abstinence effects, 'morning after effects' (including sleep effects after dosing on the preceding day), long-term effects in chronic users or effects of repeated dosing were not incorporated in this review.

The study characteristics and each individual test result of all articles that complied with the criteria were put into a database (Microsoft Excel). The following items were recorded: number of subjects, sex (male; female), age, past cannabis use (users; non-users; unknown), abstinence period (yes; no; unknown), blinding (double blind; single blind; open; unknown), design (cross-over; partial cross-over; parallel; unknown), drug name (cannabis, including hashish and marijuana; THC (dronabinol)), dose, route of administration (oral; intrapulmonary; intravenous; unknown), THC equivalence (<7 mg; 7-18 mg; >18 mg), test name, test effect, test cluster and functional domain. Most studies used different tests on different doses of cannabis, which were all regarded as independent measures of the canna-

bis effect. Thus, the total number of evaluated tests (cases) was a product of the numbers of articles, drugs, doses and tests (including secondary outcomes).

Individual test results

Based on previous reviews, it was anticipated that in most cases no consistent quantitative results could be recorded for individual tests, because of the large diversity of methods, parameters and treatments. Therefore, the ability of a test to show a statistically significant difference from placebo or baseline was scored as + (improvement/increase), = (no significant effect) or - (impairment/decrease). Subjective assessments with a desirable effect (e.g. increase of a high scale) were scored as an improvement/increase, and unwanted effects (e.g. increase of sedation) as an impairment/decrease. Heart rate was expected to be an easily quantifiable exception, but for this parameter a concentration-effect-relationship has recently been described.[6] Since it would be redundant to repeat this effort cross-sectionally based on the literature, heart rate effects were scored quantitatively, similar to other tests in this review. In this way, heart rate served as an internal control of the methodological approach of this systematic review.

Some studies explicitly reported the use of several different tests in the methods section, without presentation of the results for no apparent reason. In these cases, it was assumed that these tests had not shown any significant effects. In some studies with different drug doses, overall significances were reported for drug effects, without (post hoc) quantifications of the statistical significance levels for each individual dose. In these cases, efforts were made to estimate the individual dose effects from graphs or tables provided in the article. If this was impossible, only the effect of the highest dose was assumed to be significant (in case of overall statistical significance) and lower doses were considered non-significant.

Grouping of individual test results

Because of an apparent lack of standardisation between the studies even for the same tests, a structured procedure described previously[2-5] was adopted in order to obtain an overview. This approach allowed the preservation of individual study data in early stages, followed by a progressive condensation of results into logical test clusters and functional domains. For the subjective assessments, visual analogue scales can for example be grouped under scales of feeling high, craving, alertness, general drug effect etc. A compendium of neuropsychological tests from Strauss *et al*.[7] was primarily consulted to group functional tests into clusters of related tests or test variants. If necessary, the compendium of Lezak was consulted.[8] Sometimes, these compendia did not mention the test. In these cases, the author's clas-

sification was followed or if necessary the test was looked up in other literature and classified by consensus. Tests and clusters were grouped further into domains that represent higher aggregates of integration of subjective, neuropsychological, neuroendocrine, neurophysiological or autonomic functions. For each test (cluster), the compendia and other literature were used to determine which function was principally assessed by the test. Neuropsychological domains consisted of executive functions, memory, attention, motor functions, language and perception. Some tests provided provided different parameters with information on more than one functional domain. The results of the effects of a single test on different domains were scored separately, and the secondary effects were marked.

Results from tests that were used only occasionally or tests used only by a single research group could not be generalised. Therefore, these were not analysed individually, but grouped with other comparable tests. This step started with the grouping of tests that could be regarded as variants of a basic form (e.g. individual scores that are also part of more comprehensive tools like Profiles of Mood States (POMS), Addiction Research Center Inventory (ARCI) or Bond and Lader Visual Analogue Scales (VAS)[9]). Subscales of such inventories were grouped if they fell in the same cluster. Within such clusters, all scales showing a significant effect were grouped, whereas all scales showing no effect were grouped separately. In this way, scales within the same cluster that showed mixed results were scored equivocally. Comprehensive scoring instruments like Waskow's Drug Effect Questionnaire can often be subdivided into different subjective clusters (e.g. drug effect, high effect, etc.), but these subscales were not always reported separately. In these cases, the results were presented as part of the overall Scale Drug Effect cluster. In a few articles, a couple of composite scores of different CNS functions were presented, which could not be grouped according to the clusters or domains used in this review. These tests were not included in the analysis.

All effect scores and subdivisions of the tests were initially performed by two of the authors (EM and AEI), and subsequently checked and discussed by the other authors (LZ, AEI and JVG).

DOSE-EFFECT RELATIONSHIPS

The chance that a test will detect a difference from placebo is expected to increase with dose. For each test that was used ten times or more and for all clusters, potential dose response relationships were determined. Dose-related increases or decreases of the average percentages of tests or clusters were reported without formal statistical analyses. Since the review yielded no immediately quantitative test effects, dose-relationships were represented by the proportions of statistically significant results for a given test or cluster. Similarly, since THC doses were not reported uniformly, THC/

cannabis dosages were pooled into 'lower', 'medium' and 'higher' dosages. The 'lower' dose was chosen to be a dose lower than 7 mg (roughly corresponding to half a cigarette), the 'medium' dose lay between 7 mg and 18 mg (approximately corresponding to one to one-and-a-half cigarette), and the 'higher' doses were all dosages above 18 mg (comparable with two cigarettes or more).[6,10,11]

Cigarette smoking was the predominant administration form. In many articles the exact THC content of a cigarette was mentioned. However, some articles mentioned the THC contents in percentage without the weight of the cigarette. In these cases a cigarette weight of 700 mg was assumed since most cigarettes weight between 500 and 900 mg. In other articles the number of puffs taken was documented. In these instances the dose was calculated as eight puffs corresponding with one marijuana cigarette.[11] Some studies provided weight-adjusted doses, without specifying the (average) body weight. In these cases, the 70 kg adult general population body weight was used to calculate the average administered dose.

To be able to compare the test results obtained for oral and intravenous administration with the results obtained for smoking, all doses were normalized to smoking. After smoking, roughly 50% of the THC contents of a cigarette is delivered into the smoke[12] and another 50% of the inhaled smoke is exhaled again[13]. In addition, the bioavailability after oral administration was assumed to be around 10%.[14,15] Therefore, all oral doses were divided by 2.5 to calculate the equivalent intrapulmonary THC doses. The THC plasma concentrations after smoking a 19 mg marijuana cigarette are equal to intravenous administration of 5 mg THC.[16] Therefore, all intravenous dosages were multiplied by four for dose normalization. In this way all routes of administration could be compared.

Results

STUDY DESIGN

The literature search yielded 165 different studies on cannabis and THC that met all criteria, published between 1966 and November 15th, 2007. The numbers of participants ranged from 10 to 161, where 115 studies (70%) included 10-20 subjects and 6 studies included more than 75 subjects (9%). Ages ranged from 18 to 59, but the vast majority were young adults between 18 and 35 years of age. In 57% of the studies only healthy males were included in the study and 2% of the studies included only females. Thirty-three percent of the studies included males and females while the sex of the subjects was not mentioned in 8%.

Most studies (80%) included subjects that were familiar with the effects of cannabis. In contrast, non-users were included in only 3%. Eleven percent of the studies reported inclusion of both cannabis users and non-

users. Previous cannabis use was not mentioned in 6% of the studies. A small majority of the studies (53%) described an abstinence period or the use of a THC drug screen. Four percent of the studies reported the lack of an abstinence period, while 44% did not mention this topic.

Fifty-seven percent of the reviewed studies had a double-blind design; 26% was single-blinded; 7% had an open design and for 10% the blinding was unknown. In addition, a small majority of the studies had a cross-over design (60%); 3% had a partial cross-over design; 33% had a parallel design and from 4% of the studies the study design was not mentioned in the article.

STUDY DRUG AND DOSING

Cannabis is also known as marijuana, and dronabinol is an analogue of THC, the predominant psychoactive component of cannabis. Cannabis was used in 63% of the studies and THC in 34% of the studies. Intrapulmonary administration was the preferred route of administration in 71% of the studies. Oral administration of the drug was mentioned in 25% of the studies and intravenous administration was only used in 3%. Three percent of the studies did not describe which form of cannabis was used and 1% did not mention the route of administration. In these cases it could be inferred from the doses and the design that cannabis was smoked.

TESTS, CLUSTERS AND DOMAINS

In total 318 different tests were used. Table 1 presents the frequency distribution of the different tests, and Table 2 presents the frequency of the test used ten times or more. This distribution shows that only a couple of tests were used frequently enough to allow individual analysis. The majority of the tests (196 tests, 61.6%) were only used once, and only heart rate (0.3%) was used over 50 times (in 92 articles). VAS scale high/stoned was studied in 30 articles, while the subjective effect rating scale high/stoned/euphoria was assessed in 28 articles. Taken together, the subjective high phenomenon was measured in more than 50 (35.2%) articles as well. The Digit Symbol Substitution Test (DSST) or variants like the Symbol Digit Substitution Tests was the most frequently used neuropsychological test (22 times). The Addiction Research Center Inventory (ARCI) was used in 18 articles.

Although many different tests and test variants were used to evaluate the effects of cannabis, most actually measured a limited number of core features. Therefore, tests were grouped further into clusters and subsequently in domains. Table 3a-d is a progressive condensation of all reported tests; from test to cluster to domain. This table includes the overall calculated significant drug effects on each cluster (impairment/decrease, no change or improvement/increase).

Table 3a-d shows that most drug-sensitive clusters cause a consistent functional impairment, and some an enhancement (heart rate, scale high). A few clusters show both impairments and improvements (e.g., time estimation, EEG alpha and evoked potential measurements, and scales for calmness, craving, mood and performance). Only a few frequently (>10 times) used test clusters showed significant responses to THC/cannabis in more than 80% of studies, notably heart rate (n = 85/92), scale high (n = 67/70) and scale psychotomimetic (n = 14/18). Most other clusters only reported significant drug effects in about 30-50 percent of the studies (Table 3a-d). All tests that were used five times or more showed a significant THC effect in at least one case; except EEG delta, which never responded in any study.

DOSE-RESPONSE RELATIONSHIPS

Tests and clusters that were used in more than 10 articles were inspected for potential dose-response relationships (Table 4). Heart rate showed a statistically significant increase in 78% of measurements in the THC equivalence dose group <7 mg, which increased to 99% and 98% after the use of 7-18 mg and >18 mg THC, respectively. The subjective high feeling included many different scoring methods, varying from observer rating scales to individual VAS scores, either in isolation or as a part of multidimensional inventories (Table 2d). Despite this variability, the cluster scale high showed very consistent effects for all dose groups. The lowest dose group of <7 mg THC already showed a response of 94%, and the middle (7-18 mg) and highest dose group (>18 mg) scored close to 100%. The related subjective cluster scale psychotomimetic also showed a consistent increase with THC/cannabis of 76-83% without a clear dose-response relationship. A small increase with dose (from 56% to 78%) was observed for the cluster scale drug effect.

The relationship between memory and doses of THC/cannabis were more complex. The impairment increased with dose for auditory/verbal delayed recall (from 23% with the lowest doses to 78% with the highest dose range), but the effects were less clear for immediate recall (Table 4). Auditory/verbal delayed recognition also deteriorated with dose (from 17% to 50%), but this was assessed in only 11 studies. Working memory impairment on the other hand seemed to decrease with dose, from 52% impairments in the lowest dose group to 9% in the highest (Table 4). Other clusters that also appeared to show an inverse dose response association were the DSST-like cluster, focused selective attention and tests of motor and visuomotor control (Table 4). The proportion of significant effects of THC/cannabis within the cluster scale aggression increased slightly with dose (from 20 to 40%). No clear dose-response relationships were observed for inhibition, reasoning/association and reaction time, and for most subjective scales (Table 4). For studies with different doses, we scored significance

for the highest dose only, if significance was merely reported for the overall group effect. Although in such cases we could have artificially induced a dose-response relationship, this was only observed in 3% of all test scores.

Discussion

This review aimed to systematically evaluate the usefulness of tests for the effects of cannabis and THC in healthy volunteers. The results were quite comparable to those of similar reviews of biomarkers of different CNS-active drugs in healthy volunteers.[2-5] A striking number of 318 different tests or test variants were described, and 61.6% of these were used only once. Grouping of tests in clusters and domains was required to evaluate the general usefulness of functional measurements, but this inevitably led to a loss of information. Even clustering tests with the same name and/or description could have bypassed differences among research groups or tests variants. In addition, this review investigated biomarkers for the effects of cannabis and THC in healthy volunteers, i.e. often with relatively small subject numbers; 70% of the studies had no more than 20 participants. It is possible that some tests will be useful biomarkers in patient studies or studies with large numbers of subjects. The observed variability in test results may have been enhanced by differences in prior cannabis use (non-users, occasional and frequent users). In this review these differences where not taken into consideration. A small majority of articles mentioned an abstinence period, but it is likely that this was also included in many other studies, without being mentioned. Chronic and occasional cannabis users show similar drug effects, although chronic users generally require higher doses and thus seem to be less sensitive.[17] The neglect of prior use intensity or abstinence duration may have confounded the detection of dose-response relationships, which was only roughly possible anyhow because of the many different doses and administration forms.

USEFUL CANNABINOID BIOMARKERS

The effects of cannabis were observed on all clusters and all domains and in almost all individual tests, which might be due to the wide distribution of cannabinoid receptors in the brain.[18] An increase in heart rate was the most consistent result (Table 1, 2, 3a), and almost all studies with heart rate measurements showed statistically significant effects. This was expected, since heart rate shows a sharp increase and rapid decline after intrapulmonary THC administration that is clearly concentration related.[6,19] Feeling high has previously also been shown to be closely related to THC plasma concentrations.[19] The high phenomenon was measured in many different ways, but despite this variability almost all studies showed statistically significant

subjective drug effects. The predicted and highly consistent effects of THC/cannabis on the most clearly concentration-related effects (heart rate and feeling high)[6,19] in this review also support the methodological approach that was adopted, to integrate the widely variable study designs, drug forms and doses, and tests reported in the literature. Feeling high seems to be the most sensitive CNS biomarker for the effects of cannabis, irrespective of how it is measured. The scales psychotomimetic and drug effect are not quite as sensitive, but they address subjective changes that are less specific for THC/cannabis. This is clearly illustrated by the only negative scores on the drug effect cluster, which are all due to the negative scores on the benzedrine scale (BG scale) of the Addiction Research Center Inventory (ARCI). Most other clusters show a low to medium sensitivity for the effects of THC/cannabis, with significant drug effects in roughly 30-60% of cases (Table 2a-d). These findings are comparable for other drug classes, which show very comparable sensitivities of neurophysiological, neuropsychological, and subjective tests of 30-60% with benzodiazepines[3] and neuroleptics[2]. In these reviews, saccadic peak velocity (SPV) was highly sensitive to benzodiazepines in 100%[3], and prolactin release to neuroleptics in 96%[2]. These parameters were not particularly responsive to THC/cannabis in the current review, where heart rate and subjective high feeling scored 92-96%. This illustrates the differential effect profiles of different pharmacological groups, even among drug classes that are generally considered to be 'CNS depressant'. Such variability should be considered when methods are selected to study the CNS effects of neuropsychiatric agents.

DOSE-RESPONSE RELATIONSHIPS

A useful biomarker should show a dose response relationship starting at a low therapeutic dose. In this review, doses could be grouped only roughly, and effects could only be scored as either statistically significant or not. Moreover, hardly any test was measured frequently and quantified consistently enough for a meaningful analysis of dose response associations. Perhaps due to these limitations, dose response relationships were found for only a few clusters (Table 4). THC doses were categorized in a low (<7 mg, roughly half a cannabis cigarette), medium (7-18 mg, approximately one to one-and-a-half cigarette) and high (>18 mg, two cigarettes or more) dose. This pragmatic division was not based on well-established relations between doses, plasma concentrations and CNS effects. Nonetheless, it led to roughly similar numbers of tests at the three different dose-levels (623-852 in each dose group), and thus reflects the practical dose-selection in the literature. This practice could however be based on the habit of subjects to smoke enough cannabis to elicit a desirable subjective state that does not cause unpleasant effects. It is not illogical to assume that this is reflected in the dose of one cigarette, and that a 'standard dose' is near the maximum-

tolerated dose for most subjects. In this review, lower doses (<7 mg) were only used in about 30% of the cases, and even this dose range caused subjective high feeling in 94% of cases. In a recent pharmacokinetic/pharmacodynamic (PK/PD) study, heart rate, VAS high and alertness, and postural stability were already sensitive to levels as low as 2 mg of intrapulmonary THC, and PK/PD effect relationships showed that near-maximum effects are reached with THC doses corresponding to roughly 10 mg of cannabis.[6,19] It seems that most doses studied in the literature may have been too high to show clear dose-response-relationships.

The memory effects of cannabis showed some dose response relationships but this differed for the various types of memory tests. Impairments increased with dose for auditory/verbal delayed recall and to a lesser extent for immediate recall and auditory/verbal delayed recognition (Table 4). Working memory on the other hand seemed to improve (i.e. normalize) with dose, with 52% impairments in the lowest dose group to 9% in the highest (Table 4). The clusters of focused selective attention and of motor and visuomotor control also appeared to show an inverse dose response association (Table 4). All these functions are highly influenced by attention and concentration.[7] Decreases in subjective alertness were noted in 43% with the lowest doses and 35% with the highest. This may have been accompanied by some agitation. Significant decreases in subjective calmness were found in 10% of cases with <7 mg and 26% with >18 mg (Table 4). At the same time, dose-related increases in (subjective) aggression (which increased with dose from 20% to 40%) and anxiety (from 11% to 33%) were observed. All this suggests that lower doses of THC/cannabis generally cause pleasant effects of relaxation and reduced attention, whereas with high doses CNS depression is partly overcome by more stimulatory effects. A survey of clusters like judgment and driving or subjective performance suggested that executive functions also tend to diminish at high doses, although these tests were not performed frequently enough for a reliable population dose-response relationship.

SUMMARY

Biomarkers are useful tools to study drug effects since they can provide information on the potential pharmacological effects of the investigational drug in early phase drug development. However, the number of tests and test variants that is used in studies of THC and cannabis seems excessively large. This abundance thwarts a good assessment of the physiological, neuropsychological and subjective effects of this drug class, and there is a dire need for test standardisation in these areas. In general, the doses studied in the literature reflect the patterns of recreational use, and are often too high to accurately determine pharmacological dose-response relationships. THC/cannabis has an effect on a wide range of central nervous

system domains. At lower doses, THC/cannabis seems to be relaxant and to reduce attention, which is accompanied by an impaired performance on other CNS tests that require active participation. At high doses, the drug seems to be more stimulatory. Subjective effects are the most reliable biomarkers to study the effects of cannabis, in addition to heart rate increases that reflect peripheral cannabinoid activation. This review may facilitate a rational selection of CNS tests in future studies of THC/cannabis and other cannabinoid agonists.

Table 1 Frequency distribution of the different tests used.

Test frequency	Number of tests	Frequency (%)
1	196	61.6%
2-5	87	27.4%
6-10	14	4.4%
11-25	18	5.7%
26-50	2	0.6%
>50	1	0.3%

Table 2 Frequency of tests used ten times or more.

Test name	Frequency
Heart Rate	92
Visual Analogue Scale (VAS) (scales high/stoned)	30
Subjective Effect Rating Scale (scales high/stoned/euphoria)	28
Digit Symbol Substitution Test (DSST)	22
Addiction Research Center Inventory (ARCI) (scale drug effect)	18
Profiles of Mood States (POMS) (scales anger/friendliness/hostility)	18
POMS (scales confusion/clear headedness/energy/confused-bewildered/vigour/stimulation)	18
VAS (scales sedation/stimulation-alertness/attentiveness/interest/clear headed/confused/energetic/ sluggish/ sleepiness/drowsy/concentration/forgetfulness)	18
POMS (scales anxiety-tension/tension/arousal)	17
Subjective Effect Rating Scale (scales intoxication/drunk/drug effect/placebo-THC/feel marijuana effect)	16
POMS (scales anxiety-tension/anxiety)	15
POMS (scales composure/depression/depression-dejection/elation/(positive)mood)	15
POMS (scale fatigue)	14
Potency Rating Scale	14
VAS (scales (good/bad) drug effect/feel drug/intoxication/drunk/comparison to usual smoke)	14
Time Estimation Task	13
VAS (scale anxiety/anxious/panic)	13
Pleasantness Rating Scale	12
VAS (scales content/down/mood/withdrawn/sociability feelings)	11
VAS (scales feelings of tranquility/calm/relaxed/mellow/arousal)	11
VAS (scales hungry/hunger)	11
Drug Effect Questionnaire (DEQ) (scales good/bad/strong/feel effect)	10
Pursuit Meter/Motor/Rotor Task	10

Table 3a Progressive condensation of all reported tests, into their corresponding clusters and domains. The overall cluster effects are reported together with the articles in which they are reported.

Domain Cluster	Tests	Effects (%) (-)	 (=)	 (+)	Article (fequency; n)
(Neuro)Endocrine					
Cortisol	Cortisol	0	0	100	20 (n=1)
Prolactin	Prolactin	0	100	0	20 (n=1)
Autonomic					
Heart rate	Heart Rate	1	7	92	17, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111 (n=92)
Pupil size	Pupil Size	24	59	18	21, 22, 29, 44, 68, 112, 113 (n=7)
Temperature	Temperature	12	88	0	21, 68, 101, 105 (n=4)
Neurophysiologic					
EEG	EEG	29	43	29	17, 43, 114 (n=3)
EEG alpha	EEG alpha	17	22	61	17, 22, 84, 85, 88, 93, 115, 116, 117 (n=9)
EEG beta	EEG beta	59	35	6	17, 22, 84, 88, 93, 115, 117 (n=7)
EEG delta	EEG delta	0	100	0	17, 22, 84, 115, 117 (n=5)
EEG theta	EEG theta	6	88	6	17, 22, 84, 93, 115, 117 (n=6)
Evoked potential	Auditory Evoked Potentials, Contingent Negative Variation (CNV), Evoked Potentials, Visually Evoked Potentials	20	45	35	22, 43, 93, 115, 118, 119, 120, 121, 122 (n=9)
Eye movements - nystagmus	Electro-nystagmographic Recordings, Electro-oculographic Recordings	0	100	0	69, 123 (n=2)
Eye movements - pursuit	Electro-oculographic Recordings, Eye Performance System (EPS-100), Eye-Point of Regard System, Tracking Task	38	63	0	21, 69, 123, 124 (n=4)
Eye movements - saccadic	Electro-oculographic Recordings, Eye-Point of Regard System, Saccadic Eye Movement	0	80	20	123, 124, 125, 126 (n=4)

Table 3b Progressive condensation of all reported tests, into their corresponding clusters and domains. The overall cluster effects are reported together with the articles in which they are reported. * Indicates that the test was also used as a secondary parameter.

Domain Cluster	Tests	Effects (%) (-)	 (=)	 (+)	Article (fequency; n)
Memory					
Auditory/verbal memory: delayed recall	Babcock Story Recall Test, Buschke Selective Reminding Test, Color-Number Matching Task, Digit Recall Task, Free Recall of Story Test, Hopkins Verbal Learning Test, Memory assessment of POMS scores, Orienting Word Task, Prose Recall Task, Randt Memory Battery, Recognition Task, Semantic Memory Retrieval Task, Text Learning Task, Verbal Recognition & Recall Task, Word List, Word Recall Task	53	47	0	20, 23, 51, 52, 53, 55, 64, 66, 91, 94, 107, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136 (n=21)
Auditory/verbal memory: delayed recognition	Cued Recall of Story Test, Delayed Story Recognition Task, Hopkins Verbal Learning Test, Name and Address Recognition Task, Verbal Recognition & Recall Task, Word List, Word Recognition Task	27	73	0	20, 23, 52, 53, 55, 56, 94, 107, 131, 135 (n=10)
Auditory/verbal memory: immediate recall	Babcock Story Recall Test, Benton Sentence Repetition Task, Buschke Selective Reminding Test, Color-Number Matching Task, Digit Recall Task, Free Recall of Story Test, Free Recall Test, Hopkins Verbal Learning Test, List Learning Task, Orienting Word Task, Prose Recall Task, Randt Memory Battery, Seashore Tonal Memory Task, Syllable List Learning Task, Text Learning Task, Word Anagram Solution Task, Word List, Word Recall Task	60	40	0	20, 23, 25, 30, 32, 50, 51, 52, 53, 55, 57, 64, 66, 91, 107, 127, 128, 129, 130, 132, 135, 136, 137, 138, 139, 140 (n=26)
Implicit memory	Common Facts Recall Task, Detailed Recall Task, Perceptual Priming Task, Remote Memory Task, Word List	0	100	0	64, 128, 131, 141 (n=4)
Learning	Artificial Conditioned Speech Connections, Colour/Word Presentation Task*, Driving Task, Hopkins Verbal Learning Test*, Intelligence Structure Test, Memory for Designs Test*, Method of Artificial Conditioned Speech Connections, Paired Associate Learning Task, Randt Memory Battery, Repeated Acquisition Task, Tactual Performance Test, Word List*	38	62	0	20, 25, 28, 45, 54, 66, 75, 91, 93, 129, 132, 138, 139, 142, 143, 144 (n=16)
Visual/spatial memory: delayed recognition	Benton Visual Retention Test	0	100	0	28 (n=1)
Visual/spatial memory: immediate recall	Memory for Designs Test, Peterson Visual Memory Test, Picture Recall Test	100	0	0	32, 54, 138 (n=3)

Executive					
Driving	Driving Task, Flight Simulator Task	62	38	0	24, 45, 79, 97, 145, 146, 147, 148 (n=8)
Inhibition	Central and Peripheral Light Flashes Task*, Colour/Word Presentation Task*, Decision Making Task, Delay Discounting Task, Digit Span Test with Signal Detection Task*, Divided Attention Task (DAT)*, Go/No-Go Task, Hopkins Verbal Learning Test*, Memory for Designs Test*, Monetary Stimulation Task, Randt Memory Battery*, Ratings of Narrative Quality, Stop Task, Stroop Color and Word Test, Temporally Controlled Operant Task, Thematic Apperception Test (TAT), Verbal Fluency Task, Word List*, Word Recall Task*	52	48	0	20, 23, 25, 30, 34, 41, 52, 53, 54, 66, 85, 86, 93, 107, 137, 140, 149, 150, 151, 152, 153 (n=21)
Judgement	Flexibility and Closure Test, Iowa Gambling Task, Scores of Willingness to Drive	25	75	0	105, 110, 146 (n=3)
Planning	Goal-Directed Serial Alternation Task, Thematic Apperception Test (TAT)	67	33	0	152, 154 (n=2)
Reasoning/association	Alternate Use Task, Analogy Task, Association IV, Associative Processing Test, Baddeley Reasoning Task, Categorization Task, Concept Formation Task, Contingent Categorization Task, Free and Constrained Associations Test, Halstead Category Test, Hidden Word Test, Iowa Test of Educational Development, Letter Series Test, Logical Reasoning Task, Numerical Reasoning Task, Object Description Test, Object-Match Task, Picture Arrangement Test, Production and Recall of Free Associations Test, Ratings of Narrative Quality, Thematic Apperception Test (TAT), Water-Jar Test, Word Grouping Test	37	63	0	21, 30, 33, 85, 128, 129, 130, 131, 134, 135, 138, 150, 151, 152, 153, 155, 156, 157, 158, 159 (n=20)
Set shifting	Delayed Auditory Feedback Device (DAF), Object-Match Task*, Trail Making Test*	20	80	0	37, 100, 131, 137, 160 (n=5)
Time estimation	Time Estimation Task	18	33	48	23, 29, 30, 42, 50, 64, 82, 83, 88, 102, 151, 154, 161 (n=13)
Working memory	Alphabet Task, Boggle Word Construction Test, Colour/Word Presentation Task, Conceptual Clustering Memory Test, Cued Recall of Story Test, Delayed Auditory Feedback Device (DAF), Digit Recall Task, Digit Span (Backward), Goal-Directed Serial Alternation Task, Matching to Sample Task, Mental Calculation Task, Picture Recognition Test, Rapid Information Task, Rapid Visual Information Processing Task, Repeated Acquisition Task, Running Memory Span, Serial Addition/Subtraction Task, Spatial N-Back Task, Sternberg Memory Scanning Task, Story Recognition Task, Word Anagram Solution Task, Word List*, Word Recognition Task	40	60	0	12, 20, 21, 23, 26, 30, 33, 37, 52, 55, 58, 66, 70, 85, 93, 100, 107, 116, 121, 127, 128, 131, 132, 138, 139, 154, 156, 160, 161, 162 (n=30)
Motor					
Motor control	Card Sorting Task, Choice Reaction Time Task, Compensation Apparatus, Finger Tapping Test, Finger Tremor Test, Foot Tapping Test, Klove Grooved Steadiness Task, Klove Static Steadiness Task, Manual Dexterity Test, Minnesota Rate of Manipulation - Block Turning, Pegboard Test, Tapping Task, Toe Tapping Test, Vienna Determination Apparatus (VDA)	47	53	0	26, 50, 97, 103, 130, 138, 157, 158, 160, 163, 164, 165 (n=12)
Postural stability	Body Sway, EquiTest, Finger Tapping Test*, Foot Tapping Test*, Klove Grooved Steadiness Task, Klove Static Steadiness Task, Standing Steadiness Task, Wobble Board	54	46	0	24, 26, 30, 31, 70, 97, 100, 103, 138, 157, 158, 160 (n=12)
Visuo-Motor control	Bender-Gestalt Test, Circulair Lights Task, Compensation Apparatus, Efficiency Test System, Gibson Spiral Maze, Groove Pegboard Task, Hand Maze Task, Hand Steadiness Task, Horizontal Groove Task, Klove Maze Coordination Task, One-Hole Test, Pursuit Meter/Motor/Rotor Task, Rod and Frame Deviation Task, Spiral Rotor Task, Star Tracing Task, Tracking Task, Trail Making Test A and B, Trail Making Test A, Vertical Groove Task, Vienna Determination Apparatus (VDA)	51	49	0	21, 26, 28, 29, 31, 37, 40, 88, 94, 100, 103, 116, 128, 130, 137, 138, 151, 157, 160, 161, 163, 164, 165, 166, 167 (n=25)

Table 3c Progressive condensation of all reported tests, into their corresponding clusters and domains. The overall cluster effects are reported together with the articles in which they are reported. * Indicates that the test was also used as a secondary parameter.

Domain Cluster	Tests	Effects (%) (-)	 (=)	 (+)	Article (fequency; n)
Attention					
Divided attention	Dichotic Listening Task, Digit Span Test with Signal Detection Task, Distraction Task, Divided Attention Task (DAT), Landolt C-Rings Test, Matching to Sample Task, Trail Making Test B	37	59	4	30, 33, 36, 41, 58, 70, 91, 111, 124, 130, 131, 132, 137, 160 (n=14)
DSST-like	Barrage de Signe, Digit Symbol Substitution Test (DSST), Digit Symbol Substitution with Memory Test	42	58	0	12, 23, 29, 30, 31, 38, 46, 50, 58, 70, 71, 72, 73, 83, 88, 91, 109, 126, 131, 132, 139, 151, 161 (n=23)
Flicker discrimination	Critical Flicker Fusion Test, Critical Stimulus Duration Task	33	56	11	89, 97, 129, 130, 168, 169 (n=6)
Focused/selective attention	3x3 Block Matrix Task, Arbeit und Konzentrationstest Geräte, Arithmetic Task, Auditory Reaction Time Task*, Choice Reaction Time Task*, Continuous Performance Task*, D2 Attention Test, Digit Span (Forward), Digit Span Test with Signal Detection Task*, Double Target Digit Cancellation Task, Number Facility Test, Paced Auditory Serial Addition Test, P-Deletion Test, Single Target Digit Cancellation Task, Stroop Color and Word Test	35	65	0	20, 23, 26, 41, 58, 66, 70, 85, 105, 111, 126, 128, 131, 136, 137, 158, 161 (n=17)
Reaction time	Alerting Task, Auditory Reaction Time Task, Central and Peripheral Light Flashes Task, Choice Reaction Time Task, Complex Reaction Time Task, Contingent Categorization Task*, Contingent Negative Variation (CNV)*, Dichotic Listening Task*, Discrimination Reaction Time Task, Driving Task*, Iowa Gambling Task*, Letter Matching Task, Matching to Sample Task*, Perceptual Speed Task, Peripheral Visual Detection Task*, Rapid Information Task, Reaction Time Task, Simple Auditory Reaction Time Task, Simple Reaction Time Task, Simple Visual Reaction Time Task, Spatial N-Back Task*, Stroop Color and Word Test*, Visual Reaction Time Task, Word Recognition Task*	48	51	1	12, 26, 31, 33, 34, 40, 66, 84, 85, 91, 93, 94, 97, 103, 110, 111, 118, 121, 126, 128, 129, 130, 131, 132, 139, 145, 157, 158, 160, 170, 171, 172 (n=32)
Sustained attention (Vigilance)	Continuous Performance Task, Mackworth Clock-Vigilance Task, Pursuit Meter/Motor/Rotor Task*, Visual Search Task	14	86	0	12, 20, 29, 31, 35, 83, 124, 160 (n=8)
Language					
Comprehension	Text Learning Task	100	0	0	129 (n=1)
Production	Cloze Method, Controlled Oral Word Association Test (COWAT), Object Description Test, Spontaneous Speech, Thematic Apperception Test (TAT), Verbal Fluency Task, Word Recall Task*	23	69	8	20, 39, 66, 128, 140, 150, 152, 159 (n=8)
Semantics	Iowa Test of Educational Development, Orienting Word Task	0	100	0	51, 129 (n=2)
Perception					
Auditory perception	Auditory Rhythm Test, Auditory Threshold Test	17	83	0	130, 173 (n=2)
Tactile perception	Tactual Performance Test, Vibratory Sense Appreciation Test	33	50	17	116, 130, 138 (n=3)
Visual/spatial perception	Archimedian Spiral After Effect, Binocular Depth Inversion Test, Block Design Test, Clock Faces Task, Closure Speed Test, Dot Tests, Driving Task, Glare Recovery Task, Group Embedded Figures Test, Hidden Figures Task, Mannequin Task, Peripheral Visual Detection Task, Size-Weight Illusion Test, Visual Acuity Task, Visual Autokinetic Motion Task, Visual Brightness Test, Visual Information Processing Task, Visual Recognition Task	27	73	0	21, 27, 40, 54, 97, 113, 130, 131, 135, 151, 156, 165, 172, 173, 174, 175, 176 (n=17)

Table 3d Progressive condensation of all reported tests, into their corresponding clusters and domains. The overall cluster effects are reported together with the articles in which they are reported.

Domain Cluster	Tests	Effects (%) (-)	 (=)	 (+)	Article (fequency; n)
Subjective Experience					
Scale aggression	Brief Psychiatric Rating Scale (Scale Hostility), Clyde Mood Scale (Scales Friendly/Aggressive), Gottschalk-Gleser Content Analysis (Scales Social Alienation/Hostility), Jackson Personality Research Form (Scale Autonomy), Jackson Personality Research Form (Scale Dominance), POMS (Scales Anger/Friendliness/Hostility), Primary Affect Scale (PAS) (Scale Anger), Ratings of Narrative Quality, Thematic Apperception Test (TAT), VAS (Scales Friendly/Social)	27	68	5	23, 30, 38, 49, 50, 60, 61, 62, 63, 67, 71, 91, 96, 97, 98, 105, 108, 133, 139, 150, 152, 153, 157, 165, 175, 177 (n=26)
Scale alertness	Addiction Research Center Inventory (ARCI) (Scale Stimulated), Brief Psychiatric Rating Scale (Scale Activation), Clyde Mood Scale (Scales Sleepy/Clear Thinking), Comprehensive Psychiatric Rating Scale (AMDP) (Scale Alertness), Drug Effect Questionnaire (DEQ) (Scales Sluggish/ Stuffy Feeling/Thinking Clearer/Concentration), Feeling Scale of Janke (Composite Scale Vital), Medical Questionnaire (Scale Impaired Concentration), Observer Rated Signs, POMS Scales Confusion/ Clear Headedness/Energy/Confused-Bewildered/Vigour/Stimulation, Scale Stimulated, Subjective Effect Rating Scale (Scales Concentration Impairment/Interest), VAS Scales Sedation/Stimulation Alertness/Attentiveness/Interest/Clear headed/Confused/Energetic/Sluggish/Sleepiness/Drowsy/ Concentration/Forgetfulness	39	50	11	21, 23, 24, 28, 30, 37, 38, 40, 46, 49, 50, 58, 60, 61, 62, 63, 67, 70, 71, 72, 73, 96, 97, 105, 108, 126, 128, 130, 131, 132, 133, 139, 146, 149, 157, 164, 175, 178 (n=38)
Scale anxiety	Ditman's DWM Scale (6-8), Drug Effect Questionnaire (DEQ) (Scale Anxiety), Gottschalk-Gleser Content Analysis Scales (Scale Anxiety), POMS Scales Anxiety-Tension/Anxiety, Primary Affect Scale (PAS) (Scale Fear), State Trait Anxiety Inventory, Taylor Manifest Anxiety Scale (MAS), Thematic Apperception Test (TAT), VAS (Scale Anxiety/Anxious/Panic)	29	67	5	20, 23, 24, 30, 33, 38, 49, 50, 58, 59, 60, 61, 62, 70, 71, 72, 73, 96, 97, 101, 108, 133, 139, 150, 152, 157, 165, 179, 180 (n=29)
Scale calmness	Ditman's DWM Scale (1-20), Drug Effect Questionnaire (DEQ) (Scales Relaxation/Tension/Excited), Feeling Relaxed, Feeling Scale of Janke (Scale Passive), POMS (Scales Anxiety-Tension/Tension/ Arousal), Primary Affect Scale (PAS) (Scale Arousal), VAS (Scales Feelings of Tranquility/Calm/ Relaxed/Mellow/Arousal)	23	53	24	20, 23, 24, 30, 33, 38, 49, 50, 58, 59, 60, 63, 67, 71, 78, 91, 96, 97, 98, 106, 108, 128, 130, 131, 132, 133, 146, 149, 157, 164, 165, 178, 179 (n=33)
Scale craving	Drug Effect Questionnaire (DEQ) (Scales Like Drug/Want More/Take Drug Again), End-of-Session Questionnaire (Scales Dislike/Like a Lot), Pleasantness Rating Scale, Subjective Effect Rating Scale (Scales Feel Like Smoking/Like Drug Effect/Want More/Price Willing To Pay), VAS (Scales Like Drug/ Like Effect/Desire)	50	18	32	17, 21, 23, 25, 30, 32, 38, 49, 52, 53, 54, 55, 56, 57, 70, 71, 72, 73, 78, 91, 107, 128, 132 (n=23)
Scale dizziness	Clyde Mood Scale (Scale Dizzy), Ditman's DWM Scale (1-20), Drug Effect Questionnaire (DEQ) (Scale Dizzy), Medical Questionnaire (Scales Disturbed Equilibrium/Faintness), Subjective Effect Rating Scale (Scale Dizziness)	58	42	0	105, 128, 130, 164 (n=4)
Scale drug effect	Addiction Research Center Inventory (ARCI) (Scale Drug Effect), Ditman's DWM Scale (6-8), Drug Effect Questionnaire (DEQ) (Scales Good/Bad/Strong/Feel Effect), End-of-Session Questionnaire (Scales Like/Feel/Strength), Estimation of Received Drug, Feeling of Intoxication, Numeric Scale Cannabis, Observer Rated Signs, Potency Rating Scale, Psychological Subjective Effect Ratings (Scale Drug Effect), Scale Intoxication, Subjective Effect Rating Scale (Scales Intoxication/Drunk/ Drug Effect/Placebo-THC/Feel Marijuana Effect), Subjective Psychological Effects Ratings, VAS (Scales Drug Effect/Feel Drug/Intoxication/Drunk/Good Drug Effect/Bad Drug Effect/Comparison to Usual Smoke)	7	26	67	21, 23, 24, 25, 26, 29, 30, 31, 32, 33, 37, 38, 39, 40, 41, 44, 46, 49, 50, 51, 52, 53, 54, 55, 56, 57, 63, 65, 66, 67, 70, 71, 72, 73, 79, 81, 82, 88, 91, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 107, 108, 109, 110, 128, 130, 131, 132, 139, 145, 146, 149, 151, 160, 165, 167, 178, 179 (n=67)
Scale fatigue	Drug Effect Questionnaire (DEQ) (Scale Fatigue), Karolonsika Sleepiness Rating (Scale Tiredness), POMS (Scale Fatigue), VAS (Scale Tired)	33	67	0	20, 23, 30, 38, 49, 50, 62, 63, 67, 71, 93, 96, 97, 106, 130, 133, 139, 157 (n=18)

Scale high	Addiction Research Center Inventory (ARCI) (Scale High), Drug Effect Questionnaire (DEQ) (Scales High/Euphoria), Feeling High, Subjective Effect Rating Scale (Scales High/Stoned/Euphoria), VAS (Scales High/Stoned)	0	4	96	17, 20, 21, 23, 24, 27, 30, 33, 38, 39, 40, 42, 44, 47, 48, 49, 50, 58, 59, 60, 61, 64, 65, 70, 71, 72, 73, 74, 76, 77, 78, 79, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 96, 97, 104, 106, 110, 111, 116, 117, 118, 119, 125, 128, 130, 131, 132, 134, 135, 139, 144, 146, 153, 155, 156, 160, 173, 178, 181, 182 (n=70)
Scale mood	Brief Psychiatric Rating Scale (Scales Anergia-Depression/Anergia), Clyde Mood Scale (Scale Unhappy), Comprehensive Psychiatric Rating Scale (AMDP) (Scales Sexual Desire/Euphoria), Ditman's DWM Scale (1-20), Ditman's DWM Scale (6-8), Drug Effect Questionnaire (DEQ) (Scales Well-Being/Dysphoria/Feel Free/Feel Serious), Jackson Personality Research Form (Scale Exhibitionism), Observer Rated Signs, Pleasantness Rating Scale, POMS (Scales Composure/ Depression/Depression-Dejection/ Elation/Mood/Positive Mood), Positive and Negative Symptom Scale (PANSS), Primary Affect Scale (PAS) (Scale Depression), Primary Affect Scale (PAS) (Scale Happiness), Scale Depression, Subjective Effect Rating Scale (Scales Enjoyability/Pleasantness), Thematic Apperception Test (TAT), VAS (Scales Content/Down/Mood/Withdrawn/Sociability Feelings)	23	61	17	20, 23, 28, 30, 37, 38, 40, 46, 49, 50, 51, 62, 63, 67, 70, 71, 83, 84, 88, 91, 96, 97, 105, 114, 126, 128, 130, 131, 132, 133, 139, 146, 149, 152, 157, 164, 165, 175, 177 (n=39)
Scale performance	Drug Effect Questionnaire (DEQ) (Scales Psychomotor Activity/Control/Control/Accelerated-Improved Cognition), Instructor's Performance Rating, Mental Status Examination (Scale Intellectual Efficiency), Subjective Effect Rating Scale (Scales Difficulty/Driving Ability/Impaired/ Motivation/Memory Impairment/Performance), Subjective Effect Rating Scale (Scales Difficulty/ Driving Ability/Impaired/Motivation/Memory Impairment/Performance), Subjective Performance Rating, Subjective Performance Rating, VAS (Scale Impaired)	65	24	12	21, 24, 40, 58, 70, 79, 93, 97, 116, 128, 130, 145, 146, 160 (n=14)
Scale psychotomimetic	Brief Psychiatric Rating Scale (Scale Thought Disorder), Clinician Administered Dissociative Symptoms Scale (CADSS) (Scale Perceptual Alternations), Comprehensive Psychiatric Rating Scale (AMDP) (Scale Thought Disorder), Depersonalization Inventory, Ditman's DWM Scale (1-20), Ditman's DWM Scale (6-8), Drug Effect Questionnaire (DEQ) (Scales Weird/Silly/Increased Sensitivity/Perceptual and SensorySharpness/Timesense/Dreamlike/ Giddy/Floating/Unreal Perception/Detachment/ Enhanced Awareness/Slow Speech/Fast Thoughts), Mental Status Examination (Scales Illusions/Hallucinations/Paranoid/Delusional), Positive and Negative Symptom Scale (PANSS), Ratings of Narrative Quality, Temporal Disintegration Inventory, Vividness of Imageries	80	20	0	20, 28, 33, 46, 59, 60, 61, 88, 101, 108, 114, 116, 130, 144, 150, 164, 175, 179 (n=18)
Scale satiety	Drug Effect Questionnaire (DEQ) (Scale Hunger), Feeling Hungry, Food Intake, VAS (Scales Hungry/ Hunger)	52	48	0	30, 38, 46, 49, 50, 70, 71, 72, 73, 80, 127, 131, 132, 139 (n=14)
Scale sensory	Comprehensive Psychiatric Rating Scale (AMDP) (Scale Disturbance of Sensory Perception), Medical Questionnaire (Scales Heat Ebulations/Cold Sensation), Scale Taste/Harshness/Draw, Subjective Effect Rating Scale (Scale Enhanced Sensations), VAS (Scale Loud Noise)	9	64	27	24, 28, 93, 97, 131, 164 (n=6)
Scale sleep	Sleep Questionnaire	0	100	0	49 (n=1)
Scale symptoms	Comprehensive Psychiatric Rating Scale (AMDP) (Scales Headache/ Nausea), Cornell Medical Index (CMI), Ditman's DWM Scale (1-20), Drug Effect Questionnaire (DEQ) (Scales Sick Feeling/ Symptoms/Heart Pounding/Dry Throat), Medical Questionnaire (Scales Tremor/Headache/ Dysphagia), Observer Rated Signs, Somatic Sensation Scale, Subjective Effect Rating Scale (Scales Heart Pounding/Dry Mouth), VAS (Scale Nauseous/Symptoms)	52	46	2	28, 33, 37, 46, 59, 60, 70, 71, 80, 85, 87, 91, 100, 108, 128, 130, 131, 132, 160, 164, 179 (n=21)

Table 4 Dose-response relationship of clusters studied in more than 20 articles. Results are given in % per THC dose group for each cluster and listed with their functional domain.

Domain	< 7 mg			7-18 mg			>18 mg		
Cluster	-	=	+	-	=	+	-	=	+
Autonomic									
Heart rate	0	22	78	0	1	99	2	0	98
Motor									
Motor control	71	29	0	50	50	0	27	73	0
Visuo-motor control	68	32	0	64	36	0	19	81	0
Memory									
Auditory/verbal memory delayed recall	23	77	0	63	38	0	78	22	0
Auditory/verbal immediate recall	50	50	0	75	25	0	45	55	0
Attention									
DSST-like	31	69	0	50	50	0	47	53	0
Focused selective attention	57	43	0	33	67	0	14	86	0
Reaction time	46	54	0	52	45	3	47	53	0
Executive									
Inhibition	50	50	0	52	48	0	57	43	0
Working memory	52	48	0	42	58	0	9	91	0
Reasoning/association	33	67	0	37	63	0	43	57	0
Subjective experiences									
Scale aggression	20	80	0	24	71	5	40	50	10
Scale alertness	43	50	7	43	50	7	35	51	14
Scale anxiety	11	83	6	35	62	4	33	63	4
Scale calmness	10	60	30	31	50	19	26	48	26
Scale craving	53	22	25	61	11	28	20	20	60
Scale drug effect	12	32	56	4	18	78	3	21	76
Scale high	0	6	94	0	0	100	0	5	95
Scale mood	29	61	10	17	66	17	19	59	22
Scale psychotomimetic	83	17	0	81	19	0	76	24	0
Scale symptoms	64	36	0	58	37	5	41	59	0

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