



Methodological Issues in the Neuropsychological Effects of Cannabis

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Abstract

Despite its long history of human use, cannabis use remains in controversy for both recreational and therapeutic uses. Δ^9 -tetrahydrocannabinol is the principal psychoactive chemical, which activates cannabinoid receptors and mimics endogenous cannabinoid neurotransmitters. The subjective and physiological effects of cannabis are well characterized. Cognitive effects are most pronounced in the areas of attention and memory, which can be characterized as mild in magnitude but dose-dependent. Like all mood-altering drugs, cannabis carries some risk for dependence. Evidence for neurotoxicity is limited except perhaps for heavy chronic use. Multiple potential therapeutic uses exist for cannabinoids, including treatment of pain, nausea, appetite loss, glaucoma, agitation, and movement disorders. Several methodological issues prominently affect the outcome of cannabis studies. These include experimental variables (e.g. drug variables, task variables, and research design) and subject variables (e.g. prior experience, other drug use, and expectations). Methodological recommendations are made to reconcile inconsistent findings and aid rational decision-making.

Keywords: Cannabis; Cognitive; Attention; Memory; Executive

INTRODUCTION

Cannabis is one of the most commonly used illegal drugs. A survey by the Substance Abuse and Mental Health Services Administration indicated that 14.6 million Americans were cannabis users in 2002. This is less surprising in light of the fact that it is one of civilization's oldest cultivated non-food plants, used in many ancient cultures. The earliest recorded psychoactive use of cannabis dates from 2000 B.C.E. in a Chinese pharmacopoeia, where it was recommended for absentmindedness and pain (Schultes & Hofman, 1992). Other ancient Chinese writings recommend hemp resin and wine as an anesthetic for surgery. The Hindu Vedas list cannabis as a divine substance and cite several medical uses including appetite-stimulation and

treatment of agitation. Among the ancient Greeks, Galen wrote that cakes made with hemp were intoxicating (Bibra, 1995). Herbalists in medieval Europe also used cannabis for medicinal purposes.

Unlike alcohol, which has also been used at least since the beginning of civilization, cannabis remains a controversial drug with a questionable legal status in the United States and other countries, even for medical use. It is abundantly researched: a recent literature search at the time of this writing yielded over 12,400 publications on the topic. One of the primary concerns over cannabis is its neuropsychological effects and potential for causing impairment. This paper will review some

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of the effects of cannabis, focusing especially on psychoactive effects. These will be used to illustrate methodological issues that affect the outcomes of the studies and the conclusions drawn.

Botany & Chemical Constituents

Three species of cannabis are recognized: *C. indica*, *C. ruderalis*, and *C. sativa* (Schultes & Hofman, 1992). There are approximately 400 chemicals in the cannabis plant, 61 of which are unique and referred to as cannabinoids. The principal psychoactive chemical is Δ^9 -tetrahydrocannabinol (THC), but other psychoactive cannabinoids include Δ^8 -tetrahydrocannabinol, 11-hydroxy- Δ^8 -tetrahydrocannabinol, and 9-nor- Δ^9 -tetrahydrocannabinol (Tripathi, 1987; Robbers, Speedie, & Tyler, 1996). Non-psychoactive cannabinoids include cannabidiol and cannabidiol. In the dried resin exuded from the female flowers, *hashish* or *charas*, THC content ranges from 10-20%. *Ganja* and *sinsemilla* are the dried tops of the female plants, which averages 5-8% THC. *Marijuana* and *bhang* derived from the rest of the plant and have the lowest THC concentration at 2-5%.

Mechanism of Action

THC is an agonist of the endogenous cannabinoid, or endocannabinoid system. Several endocannabinoid neurotransmitters have been identified, including anandamide (arachidonylethanolamide) and *sn*-2 arachidonylglycerol (2-AG), both of which have THC-like effects and cross-tolerance with THC (DiMarzo, 1998). These neurotransmitters are synthesized from phospholipid precursors and inactivated by the enzyme fatty acid amide hydrolase (FAAH) (Goparaju, 1998). Endocannabinoids appear to play normal roles in many diverse functions, including memory, cognition, movement and pain perception (Stella, Schweitzer, & Piomelli, 1997).

There are two principal subtypes of cannabinoid receptor: CB₁ receptors in the brain mediate the psychoactive effects of cannabis, while CB₂ receptors are only found peripherally (Childers & Breivogel, 1998). Both are metabotropic, G-protein linked membrane receptors. Cannabinoid receptors are differentially distributed to structures in the nervous system: highest density is seen in the basal ganglia and cerebellum, while intermediate density exists in the cortex (particularly frontal cortex) and

limbic system (e.g. hippocampus, amygdala and cingulate gyrus), and low density in the spinal cord, brainstem, and diencephalon (Herkenham et al., 1991). This distribution well-accounts for the cognitive, motor, and emotional effects of cannabis, as well as its lack of respiratory suppression. Chronic exposure to THC causes a regulation of cannabinoid receptors in rats, which return to normal levels by 3 weeks after cessation (Zhuang et al., 1998).

Pharmacokinetics of THC

Pharmacokinetics, or how a drug is absorbed, distributed, metabolized, and excreted, has an enormous bearing on the effects produced by a drug. These factors influence how much and how fast the drug reaches the brain and thus the intensity of psychoactive effects. For example, orally administered THC has a slower and more erratic absorption compared to inhalation, which is rapid.

Cannabis is most commonly consumed by smoking. An average cannabis cigarette contains 0.5 to 1 g of cannabis. Accounting for typical THC content, delivery of THC in smoke, and pulmonary absorption, about .4 to 10 mg could be absorbed from one full cannabis cigarette (Julien, 2001). People tend to alter the length and depth of inhalation to titrate blood levels, akin to tobacco smoking (Heishman, Stitzer, & Yingling, 1989). Acute intoxication starts within 6 to 12 minutes, maximum effects occur at 15 to 30 minutes, and effects typically last 2 to 4 hours. THC remains in fatty tissues and has a long half-life (57 hours). The lungs and liver convert THC to 11-OH-THC, which is also active and there is re-circulation of 10-15% of hepatic metabolites. 11-OH-THC is further converted by the liver to inactive metabolites, which are eliminated by the kidneys.

Psychological Effects of Cannabis

Subjective Effects

As with many psychoactive drugs, the psychoactive effects of cannabis vary with the degree of prior use, as well as the expectations and personality of the user, and environmental setting (Taylor, 1998). The acute subjective effects of cannabis typically include relaxation, mild euphoria, and giddiness. Appetite is stimulated (Graceffo & Robinson, 1998). There is a heightening of sensory perceptions and time is perceived to pass more slowly. Adverse effects include a panic or anxiety

reaction and are more common in novice users. Half of users report having experienced adverse effects at least once (O'Brien, 1996). Other adverse effects may include dissociative symptoms such as derealization and depersonalization (Mathew, Wilson, Humphreys, Lowe, & Weithe, 1993).

Electrophysiology

Cannabis has complex electrophysiological effects. THC produces both CNS excitation and depression, depending on the cannabinoid dosage and paradigm used (Turkani, & Karler, 1981). THC produced a biphasic pattern on the electroencephalogram (EEG) in rhesus monkeys, with an initial phase of high-voltage slow waves starting lasting for 3-4 hours, followed by high-voltage fast waves (Matsuzaki, Casella, & Ratner, 1987). In humans, long-term chronic cannabis users (i.e. daily use for 15-24 years) showed elevations in absolute power of theta activity over bilateral frontal-central cortex, as well as significantly increased interhemispheric coherence of theta activity across central and posterior regions (Struve, Patrick, Straumanis, Fitz-Gerald, & Manno, 1998). Also reported is an increased absolute and relative power and interhemispheric coherence of EEG alpha activity over the bilateral frontal-central cortex in daily cannabis users, termed "alpha hyperfrontality" (Struve, Straumanis, & Patrick, 1994). Mood changes due to cannabis simultaneously correspond to EEG changes in the alpha range and plasma THC levels (Lukas, 1995). Several studies of ERPs and brain function have produced mixed results due to methodological confounds. When subjects are screened for medical and psychiatric illness and age effects were controlled, THC does not alter brain stem and auditory or visual P300 responses (Patrick, Straumanis, Struve, Fitz-Gerald, & Manno, 1997). Despite daily cannabis use in subjects, the only finding consisted of an elevated auditory P50 amplitude. Daily doses (70 to 210 mg) of THC reduce REM sleep and increase stage 4 sleep (Feinberg, Jones, Walker, Cavness, & Floyd, 1976). Cannabis use does not appear to induce a "hangover" syndrome like that produced with alcohol or sedative-hypnotics (Chait, 1990).

Functional Neuroimaging

Several studies have looked at the effects of THC with functional neuroimaging. The results, both within and between studies have been variable. This is not surprising given the influence of set and setting on subjective effects. Overall, influences in

prefrontal-subcortical systems correspond with subjective aspects of intoxication.

The effects of an acute dose of THC on cerebral blood flow (CBF) were examined in volunteers who had prior histories of exposure to cannabis (Mathew, Wilson, Coleman, Turkington, & DeGrado, 1997; Mathew et al., 2002). THC increased CBF in the frontal regions bilaterally, insula and anterior cingulate gyrus and subcortical regions with somewhat greater effects in the right hemisphere. Changes in the right frontal and anterior cingulate CBF correlated with subjective feelings of depersonalization (Mathew, Wilson, Chiu et al., 1999). THC-induced increases in CBF in the cerebellum correlated with subjective ratings of intoxication and plasma THC concentration (Volkow et al., 1991). Decreases in cerebellar CBF were related to alterations in time sense (Mathew, Wilson, Turkington, & Coleman, 1998).

Cognitive Effects

Impairment is observed in some studies on measures of concentration and attention, including reaction time, digit span, and digit symbol tasks. In some studies, the effect only occurred at the higher (2.7%) but not lower (1.3%) dose of THC (Wilson, Ellinwood, Mathew, & Johnson, 1994). Some studies did not show an effect on divided attention tasks, while other studies showed effects correlating with THC plasma levels for approximately 2 hours after smoking (Heishman et al., 1989). The nature and complexity of the attention task may be a relevant factor. No effects are seen on simple measures of immediate or sustained attention (Rafaelsen, Christrup, Bech, & Rafaelsen, 1973; Waskow, Olsson, Salzman, & Katz, 1970; Hooker & Jones, 1987). Casual and heavy cannabis users did not differ on a simple vigilance task, but both were impaired on a Goal Directed Serial Alternation task, requiring mental calculations, working memory, and alternating attention (Casswell & Marks, 1973a, 1973b). Cannabis (with 1.2% THC) increased the Stroop effect, decreasing subjects' ability to inhibit automatic responses (Hooker & Jones, 1987). Yet, performance was not affected on the Paced Auditory Serial Attention Test (PASAT), a demanding task requiring attention, working memory, and mental calculations.

The effects of cannabis on memory were examined in numerous studies, and again the results are variable. For example, fewer words are recalled

from a list by subjects administered cannabis compared to placebo, but no effects were seen on a verbal paired-associate learning (Abel, 1971; Hooker & Jones, 1987). The effect sizes for significant differences tend to be small, but are often dose-dependent. The most consistent effects of cannabis perhaps are consolidation of information from short-term memory (Dornbush, Fink, & Freedman, 1971; Murray, 1986). In contrast, cannabis does not appear to impair access to information already in long-term memory (Darley, Tinklenberg, Roth, Vernon, & Kopell, 1977; Parker et al., 1977). While cannabis and placebo groups performed equally well on a word list recognition task, the cannabis group made more false positive errors (Abel, 1970, 1971). Another effect on memory reported in several studies is increased intrusion of irrelevant material (Abel, 1970, 1971; Clark, Hughes, & Nakashima, 1970; Tinklenberg, Melges, Hollister, & Gillespie, 1970; Pfefferbaum, Darley, Tinklenberg, Roth, & Kopell, 1977).

THC produced small but consistent detrimental effects on a battery of sensory and perceptual-motor

tests (Peters, Lewis, Dustman, Straight, & Beck, 1976). This effect is mild in magnitude compared to the profound subjective effects concurrently reported on subjective measures. Subjective changes reported in mood and perceptual experiences were more pronounced among occasional users compared to frequent cannabis users.

Few studies have addressed the effects of cannabis on executive functions, except for those done on long-term, heavy users, which is discussed in the following section. However, one study found no effects in controlled verbal fluency (Controlled Oral Word Associations) (Hooker & Jones, 1987). Chronic use has been associated with an "amotivational syndrome" characterized by loss of interest in social activities, school, work, or other goal-directed activities. Cannabis use is cited as the cause of this phenomenon, but there is no evidence to support any causal relationship. There is evidence, however, that the symptoms of the "amotivational syndrome" are due to depression in a subset of users (Musty & Krabak, 1995).

Table 1.
Cognitive Effects of Cannabis

Attention/Concentration	Simple and sustained attention are unaffected Mild impairment of some forms of complex attention
Memory	Impairment of recent memory, consolidation Increased recognition false positive errors Remote memory unaffected
Perceptual & Motor	Mild effects at low doses Hallucinations and catalepsy at high doses
Executive functions	Mild increase in perseverative responses with heavy use

Cognitive Effects in Experienced Users

A study of experienced cannabis smokers tested them on cognitive measures using two doses (1.75% or 3.55%) and placebo (Wilson et al., 1994). The cognitive functions most sensitive to THC were mental processing speed (digit-symbol substitution) and reaction time. When compared with cannabis non-users, chronic users of cannabis with a mean duration of use 6.8 years and average daily intake 150 mg of THC, were found to have slower reactions on perceptual-motor tasks, but no differences on intelligence or memory tests (Varma, Malhotra, Dang, Das, & Nehra, 1988).

Compared to infrequent (monthly) users of cannabis, regular (daily) users show decreases in attention, memory, and executive functions, such as greater perseverations on the Wisconsin Card

Sorting Test and reduced learning of word lists (Pope & Yurgelun-Todd, 1996). In a study by Fletcher and coworkers (1996), long-term users tended to experience greater difficulty in complex tasks of memory and attention. However, it was concluded that these deficits are relatively subtle. The older long-term users were functional, employable, and did not show the degree of

cognitive deficits that are associated with comparable use of alcohol.

Cognitive Effects of THC and Ethanol

Comparisons have been made of the cognitive effects of THC and alcohol alone and in combination. Separately, THC and alcohol were found to produce comparable impairments on the digit-symbol substitution test and word recall (Heishman, Arasteh, & Stitzer, 1997). The interaction of THC and ethanol was studied in a signal detection paradigm (Marks and MacAvoy, 1989). Cannabis users were less impaired in peripheral signal detection than non-users while intoxicated by cannabis and/or alcohol. These findings suggest the development of tolerance and cross-tolerance in regular cannabis users and/or the ability to compensate for intoxication effects.

Both THC and ethanol increase reaction time and alter psychomotor coordination (Belgrave et al., 1979). Whereas the peak effects of ethanol appeared quickly and wore off quickly (after 280 minutes), THC's effects were slower in onset and longer in duration. The effects of combined THC and ethanol are additive and not synergistic, and THC did not alter blood-ethanol levels. Interactions occur between ethanol and THC on psychomotor skills necessary for driving, although there were no interactions on the subjective intoxication, heart rate, or THC plasma concentration (Perez-Reyes, Hicks, Bumberry, Jeffcoat, & Cook, 1988).

Therapeutic Uses of Cannabinoids

THC has been used to control nausea and vomiting during chemotherapy, where it has proven superior to placebo (Vincent, McQuiston, Einhorn, Nagy, & Brames, 1983). Side effects of THC are generally well tolerated, though use may be limited in the elderly or with higher doses. THC preparations are also beneficial for nausea and appetite loss associated with cancer chemotherapy (Voth & Schwartz, 1997). Benefits are also seen in studies of treatment of AIDS-related anorexia (Beal et al., 1997). Cannabis reduces intraocular pressure and may be useful for treatment of glaucoma (Merritt, Perry, Russell, & Jones, 1981). THC shows clinical analgesic efficacy in cancer, even at doses lower than that needed to produce psychoactive effects (Noyes et al., 1975).

Cannabis may relieve spasticity, pain, and tremors associated with multiple sclerosis (e.g. Consroe,

Kennedy, & Schram, 1997). A more recent study failed to support the anti-spasticity effect, but confirmed improvements in mobility and pain (Zajicek et al., 2003). Randomized studies of THC show that it reduces symptoms of Tourette's syndrome, without apparent detrimental effects on neuropsychological tests (Muller-Vahl, 2003; Muller-Vahl et al., 2003). Most recently, animal studies show potential for cannabinoid therapeutic drugs for Parkinson's disease (Sieradzan et al., 2001). A randomized, controlled trial of dronabinol shows it has potential efficacy for agitation, disinhibition, and appetite loss in Alzheimer's disease (Van Reekum, 2003). Animal studies of endocannabinoids underscore the neuroprotective potential of cannabinoid drugs (Mechoula, Spatz, & Shohami, 2002).

Abuse and Dependence

Cannabis has the potential to produce dependence (Taylor, 1998). Like many drugs of abuse, cerebral dopamine is involved in the pleasurable effects of cannabis, and corticotropin-releasing factor is involved in the unpleasant withdrawal phenomena. On the other hand cannabis is less addictive and produces milder withdrawal symptoms compared to cocaine, alcohol, and heroin. Nonetheless, dependence to cannabis may develop in some individuals who engage in heavy chronic use.

Cessation of cannabis use is known to produce a withdrawal syndrome consisting of restlessness, irritability, insomnia, nausea, and muscle cramping (O'Brien, 1996). However, this syndrome is only seen in people who use high daily amounts and abruptly stop. These symptoms are uncommon in clinical practice, and frequent users of cannabis are not driven by a fear to avoid a withdrawal syndrome, as seen in opioid addiction. In a study utilizing literature review, surveys, and interviews with medical and law enforcement personnel, it was concluded that there was no evidence of abuse or illegal diversion of medically-available, oral THC (Dronabinol) (Calhoun, Galloway, & Smith, 1998).

Toxicity

Cannabinoids are teratogenic and should be avoided during pregnancy (Sherwood et al., 1999). Another major toxicity issue of cannabis consumption relates to the fact that it is most often smoked, and its smoke has carcinogenic potential (Nahas & Latour, 1992).

Several studies have shown neurotoxicity of THC, but Scallet (1991) points out significant methodological differences that would have influenced the outcome of existing studies. Studies showing neurotoxicity in rats and primates required high daily, chronic doses. However, Chan and colleagues (1998), showed selective hippocampal toxicity neurons at THC micromolar concentrations which are more likely to be reached by normal human doses. The toxicity was inhibited by treatment with nonsteroidal anti-inflammatory drugs (e.g. aspirin) and antioxidants such as vitamin E. However, THC and other cannabinoids also have neuroprotective effects. For example, cannabidiol and THC reduced neurotoxicity induced by glutamate in cortical neurons, more so than vitamin C or E (ascorbate or α -tocopherol) (Hampson et al., 1998). Dexamabinol is a synthetic non-psychoactive cannabinoid being evaluated for neuroprotective effects (Brewster et al., 1997). Cannabinoids can inhibit or facilitate seizures depending on the experimental paradigm used (Karler & Turkanis, 1980). Acute psychotic reactions can occur with heavy cannabis use, but only a small percentage of cannabis users develop a chronic psychosis and at a rate that is equivalent to the base rate of psychotic disorders in the general population (Boutros & Bowers, 1996). Cannabis may promote relapse into psychosis in individuals who have had prior psychotic episodes.

METHODOLOGICAL ISSUES

There are multiple methodological issues in the study of cannabis (Murray, 1986). These apply to both studies of psychoactive and non-psychoactive effects, but are illustrated by many of the cognitive studies discussed above (Table 2). One broad category of methodological issues concerns experimental variables. Studies use different preparations of cannabis (herbal form or isolated THC). THC can be administered through a number of different routes (e.g. injection, smoked, oral tablets). Oral absorption of cannabinoids is poor and irregular, while injection and inhalation allow for rapid increases in blood levels. These pharmacokinetic differences are reflected in intensity of effects produced. While THC is often substituted for cannabis since it is the principal psychoactive drug, the two are not equivalent. For example, THC alone has both neurotoxic and neuroprotective effects, while cannabidiol has neuroprotective effects.

Some studies employ a repeated dosing regimen while others use a single dose before testing. This could alter the degree of tolerance to effects or cumulative effects, depending on the dosage. Conversely, studying chronic users shortly after cessation would be assessing them in a withdrawal state, which would not necessarily be representative of long-term function.

Another experimental variable is the cognitive tasks employed in the research study. While both the Stroop test and PASAT are considered demanding and valid measures of attention, differential effects were seen between these measures. Also worthy of consideration are the effect sizes found in studies, although many have not reported this. Effects are typically statistically significant but small to moderate in magnitude, depending on the dose used. Linked to this issue is use of the term "impairment." In a clinical sense, impairment is reserved for individuals falling two standard deviations below the mean of a normal distribution. However, in experimental studies, this has been used to describe any statistically significant decrement, regardless of effect size the fact that subjects are still performing in the average range. Wert and Raulin (1986) examined both American and cross-cultural studies, and concluded that cannabis use may produce subtle impairment, but there is no evidence that cannabis produces gross structural cerebral changes or functional impairment. Many cannabis users remain functional and productive members of society (Grinspoon, 1999; Davidson, 1999). Thus, differential use of "impairment" nomenclature can be confusing or misleading.

Perhaps the most important, but most abused experimental factor is the correlational versus experimental design of the study. While this matter is one of the most fundamental issues of research design, the limitations of each type of design are rarely emphasized. Experimental studies involve manipulation of a variable, but are limited in their scope and size due to the control conditions that needs to be exercised. Correlational studies can be done using large-scale surveys or epidemiological data, but cannot be used to infer causality. However, the vast majority of laypersons, and seemingly some researchers, are not aware of this subtle but paramount distinction. As such, it is irresponsible to discuss results, particularly in a public forum, without emphasizing the limitations of a correlational study. To do otherwise implicitly

suggests that a causal relationship has been established.

There are also numerous subject variables in cannabis research that affect outcome. Perhaps the foremost is how much prior experience subjects have with cannabis. Drug-naïve subjects may experience more unpredictable or intense effects of the drug due to a lack of behavioral tolerance. Among cannabis users, the frequency of past use (e.g. yearly versus daily use) and the amount used also matter. This distinction not only applies to cannabis use, but how much experience with psychoactive drugs overall do the subjects have. One may not have experience with cannabis per se, but may be familiar with the experience of using a drug to alter consciousness. Heavy users are a self-selecting group, and may differ from other cannabis users in ways other than their amount of use, i.e. they may have pre-existing cognitive deficits that

contribute to their heavy use. As such, deficits in this group cannot be generalized to all cannabis use. Some cannabis users are polysubstance users, and this group may differ in characteristics from cannabis users as a whole. Indeed, abstinent polysubstance users were found to have lesser gray matter in prefrontal cortex than non-users (Liu et al., 1998).

Finally, the expectations of the subject would affect the outcome. These include knowledge about the drug being used in the study, which may be required for informed consent but would prevent a double or single blind. Expectations would also be affected by subject instructions during the testing sessions.

Table 2.
Methodological Issues in Cannabis Research

Experimental Variables	A. Drug variables (dosage, chronicity, route)
	B. Task variables
	C. Research design (correlation, experimental)
Subject Variables	A. Prior experience with cannabis
	B. Prior experience with any psychoactive drugs
	C. Polysubstance use
	D. Expectations

CONCLUSIONS

Cannabis has been used by humans for thousands of years for both psychoactive and non-psychoactive purposes. Though illegal in most countries, it remains in popular use for recreational purposes, and its medical uses remain controversial. To be certain, cannabis is not an innocuous substance, and it has effects in multiple neurotransmitter and neuroanatomical systems. Effects in physiological, cognitive, emotional, and behavioral domains are well documented. A variety of methodological issues emerge from reviewing such studies.

Results vary with the preparation and route of administration, dosage, and chronicity, as well as the cognitive task employed. The research design limits what conclusions can be drawn, although the limitations of correlational research is are not made

clear to the public and left to imply causality. The subjects employed in studies also affect outcome, particularly in terms of their prior experience with cannabis or other drugs, and expectations about the study.

Accounting for the above-mentioned influences, there is ample evidence for effects on cognitive functions, most prominently attention, memory and executive functions. These effects are best characterized as small in magnitude but dose-dependent. They are also task-dependent and only may become prominent in heavy chronic users. It is reasonable to conclude that cannabis use would best be avoided at times when peak cognitive performance is essential.

In addition to effects on cognition, cannabis carries some potential for dependence and addiction. Compared to cocaine, heroin, alcohol, and nicotine,

cannabis has lesser addictive potential and withdrawal effects, but some users nonetheless develop compulsive and maladaptive use patterns that require treatment (Taylor, 1998). Use is especially contraindicated in individuals with pre-existing mental illness or addictions. However, comparable cognitive effects and abuse potential occur with recreational drugs like alcohol and therapeutic drugs like codeine. From a pharmacological and neurobehavioral vantage point, the legal status of cannabis appears somewhat inconsistent. While opioids carry some risk for dependence, their abuse is minimal for the majority who use them under medical supervision (Joranson, Ryan, Gilson, & Dahl, 2000).

Therapeutic use of cannabis is an issue separate from recreational use. The drug shows several

potential therapeutic applications including cancer, AIDS, multiple sclerosis, muscle spasticity, pain, glaucoma, Tourette's syndrome, and Alzheimer's disease, Parkinson's disease and brain injury. Certainly, more controlled research is warranted in order for cannabinoids to become a legitimate treatment for any of these conditions. The Administrative Law Judge of the Drug Enforcement Agency (DEA), Francis J. Young, reviewed the evidence for medical use of cannabis in 1988 and stated that it met the standard for a schedule II drug, with acceptable safety under medical supervision. He also added that to conclude otherwise would be "unreasonable, arbitrary, and capricious" (Grinspoon, 1999).

Table 3.
Recommendations for Future Cannabis Studies

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1. Control for non-cannabis drug use
 2. Report effect sizes and overlap between groups
 3. Report scores in the context of normative data
 4. Use convergent methods (subjective, objective, physiological measures)
 5. Compare effects to those of other common drugs
 6. Clarify causality issues (e.g. correlation versus causation; self-selecting groups)
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Several recommendations could help to reduce confusion and seemingly contradictory reporting of results (Table 3). Many studies have not controlled for the quantity and frequency past cannabis use, and even fewer control for the use of other psychoactive drugs. Given the importance of these factors, they should be routine aspects of any human cannabis study. Secondly, all studies should not only report statistical significance, but also effect sizes. Many studies neglect this statistic, making it easier to exaggerate or underestimate the magnitude of effects. Zakzanis (2001) recommends reporting percentage overlap between experimental groups as an extension of effect size. Thirdly, the results of neuropsychological testing should be reported in the context of normative data, with means and standard deviations given for the groups tested. This would reduce imprecise or inappropriate use of the term "impairment" in favor of terms with greater quantitative accuracy. Fourth, convergent methodology should be employed whenever possible, integrating results from subjective measures, objective neuropsychological tests, and physiological measures such as functional

neuroimaging. Consistency of results across methods creates a stronger case for the findings. Fifth, the effects of cannabis should be reported in comparison to those of other psychoactive drugs under the same conditions. Results would have more meaning when comparisons are made to commonly used drugs such as alcohol, opioids, or antihistamines. Lastly, issues of causality should be at the forefront when discussing results, particularly when results are so likely to be made public.

To be certain, the legal status of cannabis is influenced by political, cultural, and historical factors. In order to make rational decisions regarding cannabis or any other drug, empirical research must be considered, with proper methodological considerations addressed. It is hoped that the recommendations discussed here will allow those decisions to be made with greater clarity.

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