INTRODUCTION

CCIC members and affiliates will be interested to note that the Health Canada/CIHR Medical Marijuana Research Programme has now been expanded to include the Marijuana Open Label Safety Initiative (MOLSI). Details of this program are available on the CIHR website.

A number of abstracts in this months newsletter are from a supplemental issue of Addiction (Addiction 97 Suppl 1: 98-108). As with other dedicated issues, copies may be obtained from the publishers.

BASIC SCIENCE


1 Interactions between the cannabinoid system and the adenosine system were investigated in the myenteric plexus-longitudinal muscle (MPLM) of the guinea-pig ileum. 2 Electrically-evoked contractions of the MPLM were inhibited in a concentration dependent manner by exogenous adenosine and the adenosine receptor agonist 2-chloroadenosine. These inhibitory effects were reversed by the selective A(1) receptor antagonist DPCPX (20 nM). 3 Preincubation of the MPLM with the cannabinoid receptor agonist CP55,940 (1 nM) or the endogenous cannabinoid ligand anandamide caused a significant leftward shift in the concentration-effect curves to adenosine and 2-chloroadenosine. 4 Electrically-evoked contractions of the MPLM were inhibited in a concentration dependent manner by the adenosine uptake inhibitor dipyridamole. This inhibition was reversed by DPCPX (20 nM). 5 Pretreatment with CP55,940 (1 nM) or anandamide (10 micro M) significantly reduced the inhibition produced by dipyridamole, an effect which was completely reversed by the selective CB(1) receptor ligand SR141716 (100 nM). 6 Electrically evoked adenosine release, measured in real time by means of adenosine-specific biosensors, was inhibited by CP55,940 (10 nM). This inhibition was blocked when CP55,940 was applied in the presence of SR141716 (100 nM). 7 These results confirm the presence of presynaptic CB(1) and A(1) receptors in the guinea-pig MPLM, and suggest that CB(1) receptor stimulation reduces electrically-evoked adenosine release. Overall the data raise the possibility that the cannabinoid system plays a role in the modulation of adenosine transmission in the MPLM. British Journal of Pharmacology (2002) 137, 1298-1304. doi:10.1038/sj.bjp.0704985


Despite evidence of an interaction between cannabinoids and estrogen in the brain, little information is available regarding the consequences of this interaction on behavior. A within-subjects design was used to examine the effects of estrogen and delta9-tetrahydrocannabinol (delta9-THC) on learning and memory in ovariectomized rats responding under a multiple schedule of repeated acquisition and performance. Treatment with low physiological levels of estrogen, delivered in Silastic capsules, improved response accuracy without affecting response rate during acquisition. Estrogen also attenuated the ability of delta9-THC (0.56- 3.2 mg/kg) to
decrease response accuracy and rate during acquisition and response accuracy during performance. Results indicate that estrogen can improve accuracy during acquisition of a nonspatial operant task and can attenuate delta9-THC-induced behavioral deficits.


BAY 38-7271 [(−)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl-4,4,4-trifluoro-1-sulfonate] is a novel, highly potent and selective cannabinoid CB(1)/CB(2) receptor agonist with neuroprotective properties. It was the aim of the present study to further confirm its cannabinoid CB(1) receptor agonist properties in a highly sensitive in vivo assay. Male Wistar rats (n=24) were trained to discriminate BAY 38-7271 (0.05 mg/kg, i.p., t-30 min) from vehicle in a fixed-ratio:10, food-reinforced two-lever standard procedure. The animals acquired the discrimination after a median number of 52 training sessions. BAY 38-7271 generalized dose-dependently when tested after different routes of administration (ED(50): 0.018 mg/kg, i.p.; 0.001 &mgr;g/kg, i.v.; 0.18 mg/kg, p.o.). A time-dependency study indicated that the cue (0.05 mg/kg, i.p.) was detectable between 15 min and 4 h, with a maximum of generalization obtained at 30 min after administration. Pretreatment with the selective cannabinoid CB(1) receptor antagonist SR 141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride] completely antagonized the effects of BAY 38-7271 (ID(50): 1.1 mg/kg, i.p.). Dose-dependent and complete generalization was also obtained after i.p. administration of the reference cannabinoid CB(1) receptor agonists HU-210 [(−)-11-OH-Delta(8)-tetrahydrocannabinol-dimethylheptyl, ED(50): 0.003 mg/kg], CP 55,940 {(-)-cis-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol, 0.007 mg/kg}], WIN 55,212-2 [(R)-4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenylcarbonyl)-6H-pyrrolo[3,2,1-ij] quinolin-6-one, 0.28 mg/kg] and (-)-Delta(9)-tetrahydrocannabinol (0.34 mg/kg). The present study confirms that BAY 38-7271 is a highly potent cannabinoid CB(1) receptor agonist in vivo.


We report here the synthesis and characterization of two gene constructs designed to facilitate structure/function studies of the human neuronal cannabinoid receptor, CB1. The first gene, which we call shCB1, is a synthetic gene containing unique restriction sites spaced roughly 50-100 bases apart to facilitate rapid mutagenesis and cloning. A nine amino acid epitope tag (from the rhodopsin C-terminus) is also present in the shCB1 C-terminal tail to enable detection and purification using the monoclonal antibody 1D4. We find that the shCB1 gene can be transiently expressed in COS cells with yield of approximately 10-15 micro g receptor per 15 cm plate and is wild type like in its ability to bind cannabinoid ligands. Our confocal microscopy studies indicate shCB1 targets to the membrane of HEK293 cells and is internalized in response to agonist. To facilitate functional studies, we also made a chimera in which the C-terminus of shCB1 was fused with the N-terminus of a G-protein alpha subunit, Galphai. The shCB1/Galphai chimera shows agonist stimulated GTPgammaS binding, and thus provides a simplified way to measure agonist induced CB1 activation. Taken together, the shCB1 and shCB1/Galphai gene constructs provide useful tools for biochemical and biophysical examinations of CB1 structure, activation and attenuation.


To facilitate purification and structural characterization, the CB2 cannabinoid receptor is expressed in methylotrophic yeast Pichia pastoris. The expression plasmids were constructed in which the CB2 gene is under the control of the highly inducible promoter of P. pastoris alcohol oxidase 1 gene. A c-myc epitope and a hexahistidine tag were introduced at the C-terminal of the CB2 to permit easy detection and purification. In membrane preparations of CB2 gene transformed yeast cells, Western blot analysis detected the expression of CB2 proteins. Radioligand binding assays demonstrated that the CB2 receptors expressed in P. pastoris have a pharmacological profile similar to that of the receptors expressed in mammalian systems.
Furthermore, the epitope-tagged receptor was purified by metal chelating chromatography and the purified CB2 preparations were subjected to digestion by trypsin. MALDI/TOF mass spectrometry analysis of the peptides extracted from tryptic digestions detected 14 peptide fragments derived from the CB2 receptor. ESI mass spectrometry was used to sequence one of these peptide fragments, thus, further confirming the identity of the purified receptor. In conclusion, these data demonstrated for the first time that epitope-tagged, functional CB2 cannabinoid receptor can be expressed in P. pastoris for purification.


Long-term treatment with levodopa in Parkinson's disease results in the development of motor fluctuations, including reduced duration of antiparkinsonian action and involuntary movements, i.e., levodopa-induced dyskinesia. Cannabinoid receptors are concentrated in the basal ganglia, and stimulation of cannabinoid receptors can increase gamma-aminobutyric acid transmission in the lateral segment of globus pallidus and reduce glutamate release in the striatum. We thus tested the hypothesis that the cannabinoid receptor agonist nabilone (0.01, 0.03, and 0.10 mg/kg) would alleviate levodopa-induced dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) -lesioned marmoset model of Parkinson's disease. Coadministration of nabilone (0.1 mg/kg) with levodopa was associated with significantly less total dyskinesia (dyskinesia score, 12; range, 6-17; primate dyskinesia rating scale) than levodopa alone (22; range, 14-23; P < 0.05). This effect was more marked during the onset period (0-20 minutes post levodopa). There was no reduction in the antiparkinsonian action of levodopa. Furthermore, the intermediate dose of nabilone used (0.03 mg/kg) increased the duration of antiparkinsonian action of levodopa by 76%. Thus, cannabinoid receptor agonists may be useful in the treatment of motor complications in Parkinson's disease.


Spinal antinociception produced by delta 9-tetrahydro-cannabinol (Delta(9)-THC) and other cannabinoid agonists has been suggested to be mediated by the release of dynorphin acting at the kappa opioid receptor. Alternatively, as cannabinoid receptors are distributed appropriately in the pain transmission pathway, cannabinoid agonists might act directly at the spinal level to inhibit nociception, without requiring dynorphin release. Here, these possibilities were explored using mice with a deletion of the gene encoding prodynorphin. Antinociceptive dose-response curves were constructed for spinal Delta(9)-THC and WIN 55,212-2 in prodynorphin knock-out mice and in wild-type littermates. WIN 55,212-2 and Delta(9)-THC were equipotent in the wild-type and prodynorphin knock-out mice. Spinal pretreatment with a kappa opioid receptor antagonist, nor-binaltorphimine (nor-BNI), did not alter the dose-response curves for either WIN 55,212-2 or Delta(9)-THC in prodynorphin knock-out and wild-type mice. However, the same dose of nor-BNI used blocked U50,488H-induced antinociception in both wild-type and prodynorphin knock-out mice, confirming kappa opioid receptor activity. Pretreatment with SR141716A, a cannabinoid receptor antagonist blocked the antinociceptive actions of both WIN 55,212-2 and Delta(9)-THC. These data support the conclusion that antinociception produced by spinal cannabinoids are likely to be mediated directly through activation of cannabinoid receptors without the requirement for dynorphin release or activation of kappa opioid receptors.


The psychoactive constituent of cannabis, Delta(9)-tetrahydrocannabinol, produces in humans subjective responses mediated by CB1 cannabinoid receptors, indicating that endogenous cannabinoids may contribute to the control of emotion. But the variable effects of Delta(9)-tetrahydrocannabinol obscure the interpretation of these results and limit the therapeutic potential of direct cannabinoid agonists. An alternative approach may be to develop drugs that amplify the effects of endogenous cannabinoids by preventing their inactivation. Here we describe a class of potent, selective and systemically active inhibitors of fatty acid amide

To clarify the mechanism by which Delta(9)-tetrahydrocannabinol, a major psychoactive component of marijuana, impairs spatial memory in the 8-arm radial maze in rats via the cholinergic system, we used two acetylcholinesterase inhibitors, physostigmine and tetrahydroaminoacridine. Moreover, we examined the effect of Delta(9)-tetrahydrocannabinol on acetylcholine release in the frontal cortex and dorsal and ventral hippocampus using in vivo microdialysis. Physostigmine (0.01-0.05 mg/kg, i.p.) and tetrahydroaminoacridine (1-5 mg/kg, p.o.) improved the impairment of spatial memory induced by Delta(9)-tetrahydrocannabinol (6 mg/kg, i.p.) in the 8-arm radial maze. Delta(9)-tetrahydrocannabinol (6 mg/kg, i.p.) produced a significant decrease in acetylcholine release in the dorsal hippocampus as assessed by microdialysis. Moreover, tetrahydroaminoacridine at a dose of 1 mg/kg, which improved the impairment of spatial memory, reversed the decrease in acetylcholine release induced by Delta(9)-tetrahydrocannabinol in the dorsal hippocampus during 60-120 min after the Delta(9)-tetrahydrocannabinol injection. These findings suggest that inhibition of the cholinergic pathway by reduced acetylcholine release is one of the means by which Delta(9)-tetrahydrocannabinol impairs spatial memory in the 8-arm radial maze.


Several recent studies have demonstrated a neuromodulatory role for endocannabinoids via their ability to act as retrograde inhibitors of synaptic neurotransmission. We utilized the functional hyperemic response to controlled whisker stimulation to determine whether endogenous cannabinoids modulate synaptic transmission within the primary somatosensory cortex of rats. As previously demonstrated, whisker-stimulation resulted in a robust hyperemic response measured using laser Doppler flowmetry within the whisker barrel cortex. Administration of the CB(1) receptor antagonist, SR141716 (1 mg/kg i.v.), significantly potentiated the functional hyperemic response to whisker-stimulation, while having no effect on basal blood flow within the whisker barrel cortex. These data suggest that suppression of endogenous cannabnergic neurotransmission results in increased cortical activity in response to physiological sensory stimulation.


The structural characterization of G-protein coupled receptors (GPCRs) is quite important as these proteins represent a vast number of therapeutic targets involved in drug discovery. However, solving the three-dimensional structure of GPCR has been a significant obstacle in structural biology. A variety of reasons, including their large molecular weight, intricate interhelical packing, as well as their membrane-associated topology, has hindered efforts aimed at their purification. In the absence of pure protein, available in the native conformation, classical methods of structural analysis such as X-ray crystallography and nuclear magnetic resonance spectroscopy cannot be utilized successfully. Alternative methods must therefore be explored to facilitate the structural features involved in drug-receptor interactions. The methods described herein detail the use of covalent probes, or affinity labels, capable of binding covalently to a target GPCR at its binding site(s). Our approach involves the incorporation of a number of reactive moieties in different regions of the ligand molecule each of which is expected to react with different amino acid residues. Information obtained from such work coupled with computer
modeling and validated by the use of site-directed mutagenesis of GPCRs allows for three-dimensional mapping of the receptor binding site. It also sheds light on the different possible binding motifs for the various classes of agonists and antagonists and identifies amino acid residues involved with GPCR activation or inactivation.


The cannabinoid CB1 receptor, a member of the Rhodopsin (Rho) family of G protein coupled receptors (GPCRs), exhibits high levels of constitutive activity. In contrast, Rho exhibits an exquisite lack of constitutive activity. In Rho, W6.48(265) on transmembrane helix 6 (TMH6) is flanked by aromatic residues at positions i-4 (F6.44) and i + 3 (Y6.51), while in CB1 the residues i-4 and i + 3 to W6.48 are leucines (L6.44 and L6.51). Based upon spectroscopic evidence, W6.48 has been proposed to undergo a rotamer switch (chi1 g+ -->trans) upon activation of Rho. In the work reported here, the biased Monte Carlo method, Conformational Memories (CM) was used to test the hypothesis that the high constitutive activity exhibited by CB1 may be due, in part, to the lack of aromatic residues i-4 and i + 3 from W6.48. In this work, the W6.48 rotamer shift (chi1 g+ -->trans) was used as the criterion for activation. Conformational Memories (CM) calculations on WT CB1 TMH6 and L6.44F and L6.51Y mutant TMH6s revealed that an aromatic residue at 6.44 tends to disfavor the W6.48 chi1 g+ -->trans transition and an aromatic residue at 6.51 would require a concomitant movement of the Y6.51 chi1 from trans-->g+ when the W6.48 chi1 undergoes a g+ -->trans shift. In contrast, CM calculations on WT CB1 TMH6 revealed that the presence of leucines at 6.44 and 6.51 provide W6.48 with greater conformational mobility, with a W6.48 transchi1 preferred. Conformational Memories calculations also revealed that the W6.48 chi1 g+ -->trans transition in WT CB1 TMH6 is correlated with the degree of kinking in TMH6. The average proline kink angles for TMH6 were higher for helices with a W6.48 g+ chi1 than for those with a W6.48 transchi1. These results are consistent with experimental evidence that TMH6 straightens during activation. Transmembrane helix (TMH) bundle models of the inactive (R) and active (R*) states of CB1 were then probed for interactions that may constrain W6.48 in the inactive state of CB1. These studies revealed that F3.36 (transchi1) helps to constrain W6.48 in a g+ chi1 in the inactive (R) state of CB1. In the R* state, these studies suggest that F3.36 must assume a g+ chi1 in order to allow W6.48 to shift to a transchi1. These results suggest that the W6.48/F3.36 interaction may act as the 'toggle switch' for CB1 activation, with W6.48 chi1 g+ /F3.36 chi1 trans representing the inactive (R) and W6.48 chi1 trans/F3.36 chi1 g+ representing the active (R*) state of CB1.


In this study we analyzed the responses of cerebellar astroglial cells to pre- and perinatal Delta(9)-tetrahydrocannabinol (THC) exposure in three postnatal ages and both sexes. To determine whether THC during development directly modifies astroglial growth, this study investigated the effects of THC on astroglial morphological changes and on the expression of specific astroglial markers (glial fibrillary acidic protein: GFAP and glutamine synthetase: GS). Our results demonstrated that the administration of THC during development has deleterious effects on astroglial maturation in the cerebellum. These results also indicate that THC might interfere with astroglial differentiation in a way dependent on sex. The effect of cannabinoids on the development of cerebellar astroglial cells (astrocytes and Bergmann glial cells) is to reduce protein synthesis, since both GFAP and GS decreased in astroglial cells, not only during THC exposure but also in adult ages. Our data suggest that pre- and perinatal THC exposure directly interferes with astroglial maturation by disrupting normal cytoskeletal formation, as indicated by the irregular disposition of GFAP and the lower GFAP expression observed at all the ages studied. THC exposure during development may also modulate glutamatergic nervous activity since GS expression is reduced in THC-exposed brains. GS expression increased progressively after THC withdrawal, but GS expression had still not reached control values two months after THC withdrawal. This indicates that glutamate uptake is lower in glial cells exposed to THC, since GS expression is lower than in older controls. Consequently, glutamatergic neurotransmission
may be affected by cannabinoid exposure during gestation. Therefore, cannabinoids exert developmental toxicity, at least on astroglial cells, which could contribute to fetal brain growth retardation.


We have investigated the effects of cannabinoid agonists and antagonists on tumour necrosis factor-alpha (TNF-alpha)-induced secretion of interleukin-8 from the colonic epithelial cell line, HT-29. The cannabinoid receptor agonists ((-)-3-[2-hydroxy-4-(1,1-dimethyl-heptyl)-phenyl]4-[3-hydroxypropyl]cyclo-hexan-1-ol) (CP55,940); Delta-9-tetrahydrocannabinol; [R(+)-[2,3-dihydro-5-methyl-3-[(morpholiny)] methyl] pyrrolo[1,2,3-de]1,4-benzoxazin-6-yl](1-naphthyl) methanone mesylate} (WIN55,212-2) and 1-propyl-2-methyl-3-naphthoyl-indole (JWH 015) inhibited TNF-alpha induced release of interleukin-8 in a concentration-dependent manner. The less active enantiomer of WIN55212-2, [S(-)-[2,3-dihydro-5-methyl-3-[(morpholiny)]methyl]pyrrolo[1,2,3-de]1,4-be nzoazin-6-yl](1-naphthyl) methanone mesylate (WIN55212-3), and the cannabinoid CB(1) receptor agonist arachidonoyl-2-chloroethylamide (ACEA) had no significant effect on TNF-alpha-induced release of interleukin-8. The cannabinoid CB(1) receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1,4- pyrazole-3-carboxamide hydrochloride (SR141716A; 10(-6) M) antagonised the inhibitory effect of CP55,940 (pA(2)=8.3+/-.02, n=6) but did not antagonise the inhibitory effects of WIN55212-2 and JWH 015. The cannabinoid CB(2) receptor antagonist N-(1,S)-endo1,3,3-trimethylbicyclo(2,2,1)heptan-2-yl)-5(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528; 10(-6) M) antagonised the inhibitory effects of CP55,940 (pA(2)=8.2+/-.08, n=6), WIN55212-2 (pA(2)=7.1+/-.03, n=6) and JWH 015 (pA(2)=7.6+/-.03, n=6), respectively. Western immunoblotting of HT-29 cell lysates revealed a protein with a size that is consistent with the presence of cannabinoid CB(2) receptors. We conclude that in HT-29 cells, TNF-alpha-induced interleukin-8 release is inhibited by cannabinoids through activation of cannabinoid CB(2) receptors.


Nonmyelinated (C-) fibers represent the majority of vagal afferents innervating the airways and lung, and play an important role in regulating the respiratory and cardiovascular functions under both normal and abnormal physiologic conditions. Studies of the relationship between the conduction velocities of the vagal afferents and their sensitivities to capsaicin and other chemical irritants reveal that C-fibers are the primary type of chemosensitive afferents in the rat lung. Furthermore, a distinct sensitivity to capsaicin and a weak response to lung inflation are the defining characteristics of these afferents. In cultured rat nodose and jugular ganglion neurons, capsaicin-sensitive cells were identified by measurement of the capsaicin-evoked calcium transients using the Fura-2-based ratiometric imaging technique. The percentage of capsaicin-sensitive neurons gradually decreases as the cell diameter increases. However, the capsaicin-sensitive neurons cannot be precisely identified solely on the basis of the cell size. Anandamide, an endogenous cannabinoid released from leukocytes and epithelial cells, consistently evokes a stimulatory effect on pulmonary C-fiber endings by activating vanilloid receptor type 1 (VR1). The discharge pattern of pulmonary C-fibers evoked by anandamide closely resembles that produced by a much lower (approximately 1/600) dose of capsaicin in the same fibers. Whether anandamide acts as a potential endogenous ligand to VR1 at the C-fiber terminals is unclear, and the physiological role of VR1 in modulating the transduction properties of these afferents also remains to be determined. Anat Rec Part A 270A:17-24, 2003.


Cannabinoids receptors, cellular elements of the endocannabinoid system, have been the focus of extensive studies because of their potential functional role in several important physiological and pathologic processes. To further evaluate the properties of CB receptors,
especially CB(1) and CB(2) subtypes, we have designed, using SR141716A as a benchmark, a new series of rigid 1-aryl-1,4-dihydroindenol[1,2-c]pyrazole-3-carboxamides. Compounds 1 were synthesized from substituted 1-aryl-1,4-dihydroindenol[1,2-c]pyrazole-3-carboxylic acids and requisite amines. The various analogues were assayed for binding both to the brain and peripheral cannabinoid receptors (CB(1) and CB(2)). Seven of the new compounds displayed very high in vitro CB(2) binding affinities, especially 1a, 1b, 1c, 1e, 1g, 1h and 1j which showed K(i) values of 0.34, 0.225, 0.27, 0.23, 0.385, 0.037 and 0.9 nM, respectively. Compounds 1a, 1b, 1c and 1h showed the highest selectivity for CB(2) receptor with K(i)(CB(1)) to K(i)(CB(2)) ratios of 6029, 5635, 5814 and 9810, respectively. Noticeably, 1h exhibited the highest affinity and selectivity for CB(2) receptors.


Most actions of anandamide (AEA) are mediated by the cannabinoid 1 (CB(1)) receptor activation, but on sensory neurones it is also an agonist on the vanilloid subtype 1 receptor (VR(1)). The aim of the present study was to analyse the effect of AEA (10(-6)-10(-4) M) on inhibitory CB(1) and excitatory VR(1) receptors by measuring sensory neuropeptide release such as somatostatin, substance P and calcitonin gene-related peptide, from isolated rat tracheae. AEA (10(-6) M) was without significant effect, 10(-5) M inhibited neuropeptide release, which was abolished by the G protein-coupled receptor blocker pertussis toxin (100 ng/ml) and the CB(1) receptor antagonist SR141716A (5x10(-7) M). High concentrations of AEA (5x10(-5) M, 10(-4) M) increased the release of the peptides and this inhibition was prevented by the competitive VR(1) antagonist capsazepine (10(-5) M). These results indicate a dual, concentration-dependent action of AEA on CB(1) receptors and VR(1) on peripheral sensory nerve terminals.


BACKGROUND: Cannabinoids exert a wide spectrum of effects in men including alterations in the reproductive system. To date, two types of cannabinoid receptors have been cloned in humans, namely CB(1) and CB(2) belonging to the G protein-coupled receptor superfamily. Although cannabinoids have functional and morphologic effects in the prostate gland, the expression of cannabinoid receptors in this tissue has never been investigated. The aim of this study was to analyze the expression of cannabinoid receptors in the human prostate gland and their regulatory effects on adenylyl cyclase activity. METHODS: To investigate the existence of cannabinoid receptors in prostate, we used various methods, including reverse transcriptase-polymerase chain reaction, Western blotting, and immunohistochemistry. Adenylyl cyclase activity was analyzed by measuring the cAMP produced by means of a competitive assay by using PKA. RESULTS: Both mRNA for CB(1) and the corresponding protein are expressed in the human prostate gland at a level comparable with the receptor expressed in cerebellum. The molecular mass of the protein estimated from Western blot analysis was 58 kDa, which is in concordance with previous data for CB(1) in other tissues. Immunohistochemical studies show that CB(1) is preferentially expressed in the epithelia of the prostate. The cannabinoid receptor expressed in the prostate negatively regulates adenylyl cyclase activity through a pertussis toxin-sensitive protein. Prostate 54: 95-102, 2003. Copyright 2002 Wiley-Liss, Inc.

CLINICAL SCIENCE


Cannabis is the most widely used illegal drug in the U.S. population. Surveys have estimated that the lifetime prevalence rate for cannabis dependence is approximately 4%. Though the presence of a psychiatric disorder increases the likelihood of developing substance dependence, the field lacks data regarding the association between mental disorders and cannabis dependence. The aim of this study is to describe the prevalence of psychiatric disorders among individuals with cannabis dependence. The National Comorbidity Survey was used to obtain these data. We found that 90% of respondents with cannabis dependence had a lifetime
mental disorder, compared to 55% without cannabis dependence. Alcohol dependence, antisocial personality disorder, and conduct disorder had the strongest associations with cannabis dependence, followed by anxiety and mood disorders. A large proportion of respondents with internalizing disorders developed mood or anxiety disorders prior to onset of their first cannabis dependence symptom. Data regarding the prevalence of comorbid mental disorders underscore the importance of thorough and systematic evaluation of patients seeking treatment for cannabis dependence. The failure to identify comorbidity may lead to inadequate treatment, and a poorer prognosis.


Background: Cannabis is a possible risk factor for the onset of schizophrenia and can induce neurocognitive, behavioural and motor co-ordination alterations. The aim of this study was to evaluate the role of cannabis in the occurrence of neurological soft signs (NSS) and, considering that this drug has been related to positive symptoms, whereas NSS have been linked to negative symptoms, we also examined the role of clinical features. Methods: The study investigated NSS in 25 male cannabis-consuming and 25 male non-consuming schizophrenic patients, using the Neurological Evaluation Scale. Clinical features were studied using SANS and SAPS. Results: Significant differences emerged after comparison analysis, with more NSS in non-consuming patients. The SANS subscales Alogia and Anhedonia-asociality were also statistically significant in this group of patients. Discussion: If non-consuming patients show a higher incidence of both NSS and negative symptoms, which, according to the literature, seem to be associated, then these findings suggest that NSS are relatively independent from cannabis, but not from clinical features.


INTRODUCTION: Despite the recent discovery of the potential mechanisms underlying the analgesic effects of cannabis, few clinical studies have so far assessed its analgesic effects, notably in the treatment of chronic non-malignant pain. All the studies used administration of cannabis alone. The aim of this open, pilot, study was to assess the efficacy and side effect profile of oral dronabinol (tetrahydrocannabinol - THC) in the treatment of refractory neuropathic pain. METHODS: Seven patients (3 women/4 men), aged 60 +/- 14 years, suffering from chronic refractory neuropathic pain, received oral THC titrated to the maximum dose of 25 mg/day (mean dose: 15 +/- 6 mg), during an average of 55,4 days (range: 13-128). Various components of pain (continuous, paroxysmal and brush-induced allodynia) were assessed using VAS scores. Health-related Quality of Life (HRQL) was evaluated using the Brief Pain Inventory, and the Hospital Anxiety and Depression scale was used to measure depression and anxiety. RESULTS: THC did not induce significant effect on the various pain, HRQL and anxiety and depression scores. Numerous side effects (notably sedation and asthenia) were observed in 5 patients out of 7, requiring premature discontinuation of the drug in 3 patients. CONCLUSION: The present study did not reveal any significant efficacy of THC in a small cohort of patients with chronic refractory neuropathic pain, but underlined the unfavorable side effect profile of the drug. These results may partly relate to the fact that oral dronabinol exhibits a poor therapeutic ratio (efficacy at the price of side effects). The development of new and better tolerated cannabinoids is warranted.


This prospective study evaluated the relations between maternal alcohol, tobacco and marijuana use during pregnancy and children's growth at 6 years. In this cohort of pregnant teenagers and their offspring, mothers were recruited from an urban prenatal clinic between 1990 and 1995, and observed from their fourth prenatal month. At the delivery assessment, there were 413 live-born singletons. At the 6-year visit, 345 children and mothers were evaluated. Prenatal alcohol and marijuana exposure were significantly associated with growth deficits, after controlling statistically for other prenatal substance use, current maternal substance use, current
environmental tobacco exposure (ETS) and sociodemographic and growth-related covariates. There was a significant negative association between the second and third trimester alcohol exposure and offspring height. Third trimester alcohol exposure predicted reduced skinfold thickness. Exposure to any prenatal marijuana in the second trimester was significantly associated with shorter stature. First trimester tobacco exposure was associated with increased skinfold thickness among the 6-year-olds. The effects of prenatal alcohol exposure on growth at birth persisted in older children despite a low level of exposure during gestation. Effects of prenatal marijuana exposure on reduced height were not anticipated and occurred only when use was categorized as any/none. These data are consistent with an emerging body of evidence indicating that, by contrast to the growth deficits associated with smoking during pregnancy, which are evident at birth, the shorter stature associated with prenatal alcohol exposure continues to be evident during childhood.


RATIONALE. Studies in non-human animals suggest that opioid antagonists block the reinforcing effects of cannabinoids. OBJECTIVE. The present studies in humans investigated how naltrexone modulates (1) the subjective and physiological effects of oral THC in comparison to methadone, (2) the reinforcing effects of oral THC, and (3) plasma levels of oral THC. METHODS. In study 1, marijuana smokers (n = 9) received naltrexone (0, 50 mg) followed 30 min later by THC (0, 15, 30 mg) or methadone (5, 10 mg). Subjective effects, task performance, pupillary diameter, and cardiovascular parameters were measured repeatedly. In study 2a, marijuana smokers (n = 23) were randomly assigned to one THC dose condition (0, 15 or 30 mg). One set of color-coded capsules containing THC and active naltrexone (50 mg) was given in one session, while another set of color-coded capsules containing THC and placebo naltrexone was given in another session. In the final three sessions, participants chose which color capsules they would receive. In study 2b, a subset of participants from study 2a (n = 7) received naltrexone (0, 50 mg) 30 min prior to oral THC (30 mg) administration, and blood was drawn repeatedly. RESULTS. Pretreatment with naltrexone significantly increased many of the "positive" subjective effects of oral THC (30 mg) e.g. ratings of Good Drug Effect and Capsule Liking. Naltrexone tended to increase the reinforcing effects of oral THC (30 mg), as indicated by performance in a drug choice test. Naltrexone did not alter plasma THC levels. CONCLUSIONS. These studies demonstrate that naltrexone increases the subjective effects of oral THC. Thus, oral THC's effects are enhanced rather than antagonized by opioid receptor blockade in heavy marijuana smokers.


RATIONALE. Although smoked marijuana contains at least 60 cannabinoids, Delta(9)-tetrahydrocannabinol (Delta(9)-THC) is presumed to be the cannabinoid primarily responsible for many marijuana-related effects, including increased food intake and subjective effects. Yet, there has been no systematic comparison of repeated doses of oral Delta(9)-THC with repeated doses of smoked marijuana in the same individuals. OBJECTIVE. To compare the effects of oral Delta(9)-THC and smoked marijuana in humans under controlled laboratory conditions. METHODS. Eleven healthy research volunteers, who reported smoking an average of six marijuana cigarettes per day, completed an 18-day residential study. Marijuana cigarettes (3.1% Delta(9)-THC, q.i.d.) were smoked or Delta(9)-THC (20 mg, q.i.d.) was taken orally using a staggered, double-blind, double-dummy procedure for three consecutive days. Four days of placebo administration separated each active drug condition. Psychomotor task performance, subjective effects, and food intake were measured throughout the day. RESULTS. Relative to
placebo baseline, oral Delta(9)-THC and smoked marijuana produced similar subjective-effect ratings (e.g., "high" and "mellow"), although some effects of smoked marijuana were more pronounced and less prone to the development of tolerance. Additionally, participants reported "negative" subjective effects (e.g., "irritable" and "miserable") during the days after smoking marijuana but not after oral Delta(9)-THC. Both drugs increased food intake for 3 days of drug administration, but had little effect on psychomotor performance. **CONCLUSION.** These results indicate that the behavioral profile of effects of smoked marijuana (3.1% Delta(9)-THC) is similar to the effects of oral Delta(9)-THC (20 mg), with some subtle differences.


**OBJECTIVE:** This was a prospective longitudinal multisite study of the effects of prenatal cocaine and/or opiate exposure on neurodevelopmental outcome in term and preterm infants at 1 month of age. **METHODS:** The sample included 658 exposed and 730 comparison infants matched on race, gender, and gestational age (11.7% born <33 weeks' gestational age). Mothers were recruited at 4 urban university-based centers and were mostly black and on public assistance. Exposure was determined by meconium assay and self-report with alcohol, marijuana, and tobacco present in both groups. At 1 month corrected age, infants were tested by masked examiners with the NICU Network Neurobehavioral Scale and acoustical cry analysis. Exposed and comparison groups were compared adjusting for covariates (alcohol, marijuana, tobacco, birth weight, social class, and site). Separate analyses were conducted for level of cocaine exposure. **RESULTS:** On the NICU Network Neurobehavioral Scale, cocaine exposure was related to lower arousal, poorer quality of movement and self-regulation, higher excitability, more hypertonia, and more nonoptimal reflexes with most effects maintained after adjustment for covariates. Some effects were associated with heavy cocaine exposure, and effects were also found for opiates, alcohol, marijuana, and birth weight. Acoustic cry characteristics that reflect reactivity, respiratory, and neural control of the cry sound were also compromised by prenatal drug exposure, including cocaine, opiates, alcohol, and marijuana and by birth weight. Fewer cry effects remained after adjustment for covariates. **CONCLUSIONS:** Cocaine effects are subtle and can be detected when studied in the context of polydrug use and level of cocaine exposure. Effects of other drugs even at low thresholds can also be observed in the context of a polydrug model. The ability to detect these drug effects requires a large sample and neurobehavioral tests that are differentially sensitive to drug effects. Long-term follow-up is necessary to determine whether these differences develop into clinically significant deficits.

**BEHAVIOURAL SCIENCE**


As the use of marijuana among adolescents remains high, more effective interventions are needed. We conducted this cross-sectional survey at an outpatient, university-based, adolescent clinic to determine the prevalence of marijuana use in an inner-city adolescent population and to examine the relationship of stress and coping methods to marijuana user status (never user, experimenter, and frequent user). The subjects were 918 adolescents aged 12-21 years. Lifetime use in this population was 59% (n = 611) with 18.4% (n = 191) reporting frequent weekly use. Almost all (97%) marijuana users acknowledged marijuana use by friends. Stepwise logistic regression analysis showed that negative life events, greater use of the negative coping method of anger and less frequent use of the positive coping method of parental support were significantly and independently related to marijuana user status. In the presence of high peer use, exploring parent-child relationships and use of anger coping and intervening accordingly may decrease marijuana use.

BACKGROUND: Estimates of who is most at risk from violence by people with mental illness rest mainly on identified patient samples. This study, without such selection bias, examined the targets of violence committed by young adults with as-yet untreated alcohol dependence, marijuana dependence, or schizophrenia-spectrum disorders, to determine the extent to which their victims were co-residents or non-household members. METHODS: In a total birth cohort of 21-year-olds (n = 956), past-year prevalence of alcohol dependence, marijuana dependence and schizophrenia-spectrum disorders were diagnosed using standardized DSM-III-R interviews. None of the people with schizophrenia-spectrum disorder has been hospitalized in the past year. Past-year violence and victim targets were measured using self-reports. RESULTS: Compared with controls, cohort members with substance dependence or schizophrenia-spectrum disorders had higher prevalence and frequency rates of assault against co-residents, against non-household members, and also robbery and gang fights. Out of 39, five individuals with schizophrenia-spectrum disorder committed violent street crimes. Persons with substance dependence had similar proportions of violence against co-resident and non-household members, but persons with schizophrenia-spectrum disorders tended to victimize co-residents more than others. CONCLUSIONS: At the age when they are most likely to contribute to the community's violence burden, young untreated offenders with alcohol or marijuana dependence or with schizophrenia-spectrum disorders assault not only co-residents, but others as well, and commit violent street crimes. Families, schoolteachers and primary care physicians have an important potentially preventive role in early identification and treatment of the disorders.


AIMS: To evaluate the construct and predictive validity of six different subtyping classifications selected on the basis of their empirical support in the literature on adolescent substance abuse. METHODS: Typological data were collected from a heterogeneous sample of 600 adolescents presenting for marijuana treatment. The classification schemes were gender, onset age, family history, externalizing disorders, internalizing disorders and temperament. Subgroups were compared in terms of substance use frequency, substance abuse problems, social support for substance use, family conflict, school problems and negative peer associations. RESULTS: Each of the categorical classification schemes differentiated subtypes significantly on some or all of the construct validation measures after controlling for demographic factors, thereby indicating that each has valuable explanatory power from a theoretical perspective. Externalizing disorders, onset age, difficult temperament and internalizing disorders continued to add unique variance to discrimination after the effects of the other subtypes had been removed. At 12-month follow-up there were no differences between subtypes on substance use frequency, but adolescents with higher levels of externalizing disorders and internalizing disorders continued to experience more substance use problems. CONCLUSION: Categorical subtypes may have particular relevance to the development of treatment interventions as well as prevention measures.


AIMS: To evaluate the agreement between adolescent self-reported cannabis use, "on-site" qualitative urine screening, and quantitative laboratory testing. DESIGN: A cross-sectional study of intake and follow-up data from 248 adolescents entering substance abuse treatment for cannabis use disorders (abuse or dependence). This is part of the multi-site cooperative agreement Cannabis Youth Treatment study. SETTING: Data collected from adolescents randomly assigned to one of five outpatient treatments at four sites: Operation PAR, Inc., Florida; Chestnut Health Systems, Illinois; University of Connecticut Health Center, Connecticut; and Children's Hospital of Philadelphia, Pennsylvania. PARTICIPANTS: The data represent 248 unique individuals from a sample of 297 adolescents ranging in age from 12 to 18 years. MEASUREMENTS: Prevalence, agreement, kappa, sensitivity, specificity, positive and negative
predictive value. FINDINGS: The self-report rates were higher at intake than either urine test (82.4% vs. 77.0% vs. 52.7%), but both lower and higher at the 3-month follow-up (55.5% vs. 70.0% vs. 47.3%) and 6-month follow-up (60.2% vs. 73.5% vs. 55.8%). The disagreements went in both directions and the kappa coefficients were only in the moderate range (0.4). Over two-thirds of these frequent cannabis users tested positive when they said they had not used in 1 week and one-third tested positive even though they said it had been more than 4 weeks since last use. CONCLUSIONS: The findings suggest both the advantages of multiple sources of information and the need for further work on the latency of cannabis metabolites in clinical populations.


The extent to which the family environment is characterized by stress may have a substantial impact on life-course trajectories of young people. Illicit drug use is a fairly common part of these trajectories. This paper estimates the direct impact of family stressors on the progression to problem cannabis use, as well as their indirect effects via the youth's school experience among adolescents in Ontario. The results suggest that family stressors have direct and indirect effects increasing the probability of cannabis use outcomes. The implications of these more complex associations between factors believed to influence adolescent drug use trajectories are discussed. Copyright 2002 The Association for Professionals in Services for Adolescents Published by Elsevier Science Ltd.


AIMS: To probe recent evidence on apparent excess occurrence of marijuana dependence when marijuana smoking starts in adolescence. DESIGN AND PARTICIPANTS: A national sample of recent-onset marijuana users was identified within public data files of the National Household Survey on Drug Abuse (NHSDA), 1995-98 (1866 adolescents and 762 adults). MEASUREMENTS: Marijuana dependence was assessed via seven standardized questions about its clinical features, such as being unable to cut down. Multivariate response models (GLM/GEE and MIMIC) were used to evaluate adolescent excess risk and possible item biases. FINDINGS: Among people who had just started to use marijuana, clinical features of marijuana dependence occurred twice as often among adolescents compared to adults, even with statistical adjustment for other covariates (P < 0.01 from GLM/GEE). MIMIC analyses suggest that adolescent-onset users have somewhat higher levels of marijuana dependence, and they also provide evidence of age-associated response bias for some but not all clinical features of marijuana dependence. That is, even with level of marijuana dependence held constant, adolescent recent-onset users were more likely than adults to report being unable to cut down (P = 0.01) and tolerance (P = 0.029). CONCLUSION: Nosologic, methodological and substantive reasons for observed age-related excess in occurrence of marijuana dependence problems among early onset users deserve more attention in future research.


The article describes the development of drug-related problems in the context of the rapid sociopolitical and economic changes in the Czech Republic and the Slovak Republic. The period of the last decade is marked by an increase in drug use in both countries; 17% of adults in the Czech Republic and 12% of the Slovaks report lifetime drug use. The respective figures are even higher for the population of adolescents. According to the data from the ESPAD survey carried out in 1999, 36% of young Czechs and 19% of young Slovaks used marijuana. Metamphetamine is the most misused substance among problem drug users in the Czech Republic, and heroin dominates in Slovakia. The response of the society to social and health problems caused by drugs is discussed in the following areas: institutional differentiation, political coordination and legislative development. The need for further social research is stressed.

AIMS: This paper provides a description of the rationale, study design, treatments and assessment procedures used in the Cannabis Youth Treatment (CYT) experiment. DESIGN: CYT was designed to (a) test the relative effectiveness, cost and benefit-cost of five promising treatment interventions under field conditions and (b) provide evidence based manual-guided models of these interventions to the treatment field. SETTING: The study involved two community-based treatment programs and two major medical centers. PARTICIPANTS: Participants were 600 adolescents recruited from the regular intake who were between the ages of 12 and 18, had used marijuana in the past 90 days, and met one or more criteria of dependence or abuse. INTERVENTIONS: Participants were randomly assigned to one of five interventions: Motivational Enhancement Therapy (MET), Cognitive Behavioral Therapy (CBT), Family Support Network (FSN), Adolescent Community Reinforcement Approach (ACRA), or Multidimensional Family Therapy (MDFT). MEASUREMENTS: Self-report data were collected at intake, 3, 6, 9 and 12 months post discharge using the Global Appraisal of Individual Needs (GAIN), as well as several supplemental self-reports, collateral reports, urine testing, and service logs. FINDINGS: This paper reports on the study's implementation including the psychometric properties of the measures (alphas over 0.8), validity of self-report (kappa over 0.6), high rates of treatment completion (81% completed two or more months), and high rates of follow-up (over 94% per wave). CONCLUSIONS: The feasibility of implementing the CYT manual-guided treatment and quality assurance model in community-based adolescent treatment programs is discussed.


During the late 1960s, cannabis emerged from relative obscurity to become the most common illicit drug used in the United States, and has remained so ever since. From an epidemiological perspective, three major waves of successively younger new users can be identified during the past 40 years. Contrary to popular opinion, cannabis use can be problematic for many people (particularly adolescents). Moreover, the drug has become increasingly more potent. Cannabis is currently one of the leading substances reported in arrests, emergency room admissions, autopsies and treatment admissions. Like alcohol and tobacco, the need for effective approaches to treating cannabis use disorders transcends debates about whether it should be legal. Moreover, the costs to society are continuing to mount from past neglect of this continuing public health problem. This paper provides background on the need to develop effective models for treating cannabis use disorders.


The five manual-guided treatment models tested in the Cannabis Youth Treatment study funded by the Center for Substance Abuse Treatment are described. The five models include (a) a 6-week intervention consisting of two sessions of individual motivational enhancement therapy plus three sessions of group cognitive behavioral therapy (MET/CBT5); (b) a 12-week intervention consisting of two sessions of motivational enhancement therapy plus 10 sessions of group cognitive behavioral therapy treatment (MET/CBT12); (c) a 12-week intervention consisting of MET/CBT12 plus the family support network (FSN), a multi-component intervention that includes parent education, family therapy and case management; (d) a 12-week intervention based on the adolescent community reinforcement approach (ACRA), an individual behavioral treatment approach designed to help adolescents and their parents reshape their environment and learn new skills; and (e) multi-dimensional family therapy (MDFT), a multi-faceted, developmentally and contextually oriented family-based model targeting individual, family and social systems. For each model, we describe the treatment background and/or its empirical support, its theoretical underpinnings, its goals and proposed treatment mechanism and the structure and content of each treatment. Procedures used for maintaining treatment fidelity and monitoring quality assurance are also described. These interventions represent the first readily
available, manual-guided interventions to be evaluated in a large randomized field study for this population. Consequently, these manuals have the potential to advance treatment and research for adolescents with substance use disorders.


This study examined the relation of the Five-Factor Model (FFM) of personality to symptoms of alcohol and marijuana abuse before and after controlling for symptoms of antisocial personality disorder (APD) and internalizing psychopathology. The 481 participants completed a well-validated measure of the FFM and a structured diagnostic interview at age 21 years. Hierarchical regression analyses indicated that unique constellations of personality characteristics were associated with symptoms of alcohol abuse, marijuana abuse, APD, and internalizing disorders. For example, symptoms of alcohol abuse were associated with high Extraversion and low Conscientiousness, whereas symptoms of marijuana abuse were characterized by low Extraversion and high Openness to Experience. Findings have implications for models of the etiology and treatment of substance use and abuse.


**AIMS:** Despite recent advances in the economic evaluation of adult substance abuse treatment, information and basic research is lacking on the cost of adolescent substance abuse treatment. The present study conducted an economic cost analysis of several outpatient adolescent treatment approaches. **DESIGN:** The Cannabis Youth Treatment (CYT) study evaluated five structured treatments for cannabis-using adolescents. One of the approaches was implemented by all of the four geographically and institutionally diverse treatment facilities collaborating in CYT; each of the other four approaches was implemented in two of the sites. Using the Drug Abuse Treatment Cost Analysis Program (DATCAP), the economic cost of each site-specific treatment was determined. **FINDINGS:** The average economic costs of the five types of outpatient treatments ranged from $837 to $3334 per episode, and varied by both direct factors (e.g. hours of treatment, treatment retention) and indirect factors (e.g. cost of living, staff level, case-load variation). **CONCLUSIONS:** These adolescent treatment cost estimates are examined in terms of their calculation, variability by condition, variability by site within condition and comparability with previous DATCAP results from outpatient drug-free programs for adults. Future research will integrate treatment outcomes and costs to complete cost-effectiveness and benefit-cost analyses of the five therapies.


**BACKGROUND:** Little is known about genetic factors that underlie the interrelationships among antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), and marijuana dependence (MJD). We examined the contribution of genetic effects associated with ASPD to the comorbidity of MD and substance use disorders. **METHODS:** The Vietnam Era Twin Registry is a general population registry of male veteran twins constructed from computerized Department of Defense files and other sources. A telephone diagnostic interview was administered to eligible twins from the Registry in 1992. Of 5150 twin pairs who served on active military duty during the Vietnam era, 3360 pairs (1868 monozygotic and 1492 dizygotic) in which both members completed the pertinent diagnostic interview sections were included. The main outcome measures were lifetime DSM-III-R ASPD, MD, AD, and MJD. RESULTS: Structural equation modeling was performed to estimate additive genetic, shared environmental, and nonshared environmental effects common and specific to each disorder. The heritability estimates for lifetime ASPD, MD, AD, and MJD were 69%, 40%, 56%, and 50%, respectively. Genetic effects on ASPD accounted for 38%, 50%, and 58% of the total genetic variance in risk for MD, AD, and MJD, respectively. After controlling for genetic effects on ASPD, the partial
genetic correlations of MD with AD and with MJD were no longer statistically significant. Genetic effects specific to MD and AD and familial effects specific to MJD remained statistically significant. Nonshared environmental contributions to the comorbidity in these disorders were small. CONCLUSIONS: In this sample, the shared genetic risk between MD and both AD and MJD was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders.


RATIONALE. Understanding the cognitions underpinning substance use has stalled using the Stroop paradigm. OBJECTIVE. To employ a novel version of the flicker paradigm for induced change blindness to independently compare information processing biases in social users of alcohol and cannabis. METHOD. Alcohol and cannabis experiments were independently run. In both, participants were asked to view successively and repeatedly on a monitor two versions of a visual scene (an original and a slightly changed version) until the change was detected. In fact, in both experiments two simultaneous changes competed for detection: a substance-neutral and a substance-related change. RESULTS. In both the alcohol and the cannabis experiments, participants detecting the substance-related change reported higher levels of use than those detecting the substance-neutral change. CONCLUSION. A substance-related processing bias was independently revealed for both substances. The utility of the flicker paradigm for substance use research is demonstrated as sensitive and quick to administer (taking only 1 min).


AIMS: Strong associations between marijuana use and initiation of hard drugs are cited in support of the claim that marijuana use per se increases youths' risk of initiating hard drugs (the 'marijuana gateway' effect). This report examines whether these associations could instead be explained as the result of a common factor-drug use propensity-influencing the probability of both marijuana and other drug use. DESIGN: A model of adolescent drug use initiation in the United States is constructed using parameter estimates derived from US household surveys of drug use conducted between 1982 and 1994. Model assumptions include: (1) individuals have a non-specific random propensity to use drugs that is normally distributed in the population; (2) this propensity is correlated with the risk of having an opportunity to use drugs and with the probability of using them given an opportunity, and (3) neither use nor opportunity to use marijuana is associated with hard drug initiation after conditioning on drug use propensity. FINDINGS: Each of the phenomena used to support claims of a 'marijuana gateway effect' are reproduced by the model, even though marijuana use has no causal influence over hard drug initiation in the model. CONCLUSIONS: Marijuana gateway effects may exist. However, our results demonstrate that the phenomena used to motivate belief in such an effect are consistent with an alternative simple, plausible common-factor model. No gateway effect is required to explain them. The common-factor model has implications for evaluating marijuana control policies that differ significantly from those supported by the gateway model.


Blood, urine, oral fluid (by spitting or with a Salivette), and sweat samples (by wiping the forehead with a fleece moistened with isopropanol) were obtained from 180 drivers who failed the field sobriety tests at police roadblocks. With quantitative GC-MS, the positive predictive value of oral fluid was 98, 92, and 90% for amphetamines, cocaine, and cannabis respectively. The prevalence of opiate positives was low. The proposed SAMHSA cut-off values for oral fluid testing at the workplace, proved their usefulness in this study. The positive predictive value of sweat wipe analysis with GC-MS was over 90% for cocaine and amphetamines and 80% for cannabis. The accuracy of Drugwipe was assessed by comparing the electronic read-out values obtained on-site after wiping the tongue and the forehead, with the corresponding GC-MS results in
plasma, oral fluid, and sweat. The accuracy was always less than 90% except for the amphetamine-group in sweat.


Accumulating evidence suggests that psychosocial treatment for cannabis dependence is effective. Earlier investigations were well designed and sought to evaluate efficacy of manual-guided therapies with particular attention to protecting the independent variable. The Marijuana Treatment Project (MTP) represents an effort to build upon previous knowledge about cannabis dependence treatment through an evaluation of an integrative therapy, which was meant to allow for greater therapist latitude in its delivery, and to be more responsive to a potentially more diverse population of clients. The treatment intervention developed for delivery in the Marijuana Treatment Project (MTP) reflects an effort to find a true compromise between the needs of the scientific community to have clearly specified and measurable treatments, and the realities of the treatment community, which demand flexibility, appreciation of the multi-determined nature of most problems, and individualized approaches. This paper will describe the clinical interventions used with the MTP participants, the theoretical rationale guiding their design and practical aspects related to implementation and treatment response.


AIMS: Recent findings regarding the prevalence of marijuana dependence and associated consequences indicate the need for empirically validated treatments for this population. The Marijuana Treatment Project (MTP) was a multi-site study of two treatments for adults with marijuana dependence. DESIGN: Participants (N= 450) were randomly assigned to one of three conditions at each of three sites: 1) a 9-session cognitive behavioral treatment (CBT) with motivational enhancement therapy (MET) and case management (CM) components; 2) a 2-session MET intervention; or 3) a delayed treatment control (DTC). SETTING: The study was conducted in outpatient drug treatment clinics in three U.S. cities. PARTICIPANTS: Participants were individuals aged 18 or over who met diagnostic criteria for cannabis dependence and who voluntarily presented for treatment. MEASUREMENT: Study variables included DSM-IV dependence criteria, timeline follow-back assessment of drug use, Addiction Severity Index composite scores, and problems related to marijuana use. FINDINGS: Participants were daily users, who smoked marijuana multiple times per day, and had been doing so for more than 15 years. They reported multiple dependence symptoms and negative consequences related to marijuana use. Approximately 32% of the sample was female, and 30% of the sample was either Hispanic (17%), African American (12%), or of mixed racial backgrounds (1%). CONCLUSIONS: The multi-site nature of the MTP allowed for the recruitment of a more ethnically and gender diverse sample than had been studied previously but there were few differences in the clinical characteristics of participants at the geographically and sociodemographically diverse study sites.


AIMS: Risk factors among adolescent substance abusers have been shown to correlate with substance use severity. Characteristics related to severity, such as demographic and family factors, peer influences, psychiatric co-morbidity and HIV risk behaviors, are examined for a sample of adolescent cannabis users entering treatment. DESIGN: These data are from a clinical trial study utilizing blocked random assignment of clients to one of five treatment conditions. The study targeted adolescents entering outpatient treatment for primarily cannabis abuse or dependence. SETTING: Treatment and research facilities in four metropolitan areas of the US were used to recruit study participants. Treatment was delivered in outpatient drug-free settings. PARTICIPANTS: Participants were 600 clients, ages 12-18, admitted to outpatient substance abuse treatment programs for cannabis problems, 96% with DSM-IV diagnoses of substance abuse or dependence, with the remaining 4% having at least one symptom of dependence plus significant problems indicating need for treatment. MEASUREMENTS: The Global Appraisal of Individual Needs (GAIN) was used to collect the information presented in this paper. The GAIN
incorporates DSM-IV criteria for substance use disorders, conduct disorder and attention deficit hyperactivity disorder, as well as dimensional (scale) measures for physical and mental health. FINDINGS: All participants reported at least one symptom of substance use disorders, and 46% met the DSM-IV criteria for substance dependence, while 50% met criteria for a diagnosis of abuse. Only 20% of the participants perceived any need for help with problems associated with their drug or alcohol use. Clients participating in the study typically presented multiple problems at treatment entry, most often including conduct disorder, attention deficit hyperactivity disorder (ADHD), internal (mental) distress, and physical health distress. The co-occurrence of conduct disorder and ADHD was found in 30% of the sample. Clients meeting criteria for substance dependence tended to have more co-occurring problems and significantly less denial at admission. CONCLUSIONS: The characteristics of this sample exemplify the complex nature of adolescent substance use and abuse among adolescents entering outpatient treatment programs. Patterns of co-occurring problems are at rates comparable to those found in other clinical studies. Those with more severe substance use disorders tend to manifest more problems of social functioning, more mental health problems, and physical health problems. Implications of these findings are discussed in terms of treatment needs, challenges, and prognostic implications.


AIMS: Our objective was to identify client characteristics and other factors associated with pre-treatment drop-out by people with marijuana dependence. DESIGN AND PARTICIPANTS: Data from the Marijuana Treatment Project's screening assessment were used to examine correlates of pre-treatment drop-out. Information from all eligible study participants (n = 813) (i.e. those who were interested in receiving treatment for their marijuana dependence and were determined to be eligible for the randomized treatment efficacy trial) was used to examine differences between the 450 participants who initiated treatment (by enrolling in the trial) and the 363 individuals who declined enrollment. SETTING: The study was conducted at three community-based outpatient treatment facilities in Farmington, CT, Seattle, WA and Miami, FL. MEASUREMENTS: The information gathered in the screening interview included demographic characteristics, residential stability variables, employment and education history and referral source. Substance use variables included the number of days and the number of times per day marijuana was used, self-perceived dependence on marijuana, alcohol or other drugs, other drug use history and current treatment (i.e. substance abuse, medical, psychiatric) situation. FINDINGS: Stepwise logistic regression was conducted to confirm variables associated with treatment initiation in bivariate analyses. Pre-treatment drop-out was associated with being younger, unmarried, unemployed, less educated and Asian American or Native American. It was also associated with self-perceived dependence on marijuana and use of other drugs. CONCLUSIONS: By recognizing demographic and substance use factors that may serve as barriers for individuals accessing treatment for marijuana dependence, clinicians may target clients with these characteristics proactively to encourage treatment initiation and subsequent attendance.


AIMS: This study investigated the characteristics and substance abuse treatment experience of two differentially defined groups of juvenile offenders, those who were referred or otherwise involved with the legal system and those who reported recent criminal behavior. DESIGN: Six hundred adolescents from the Cannabis Youth Treatment (CYT) Project were classified by criminal justice system involvement and recent criminal behavior. Multivariate and repeated-measures techniques explored substance use frequency, substance use problems, psychological and social risk factors and treatment outcomes as functions of criminal status. FINDINGS: Adolescents reporting criminal justice system involvement were comparable to adolescents reporting no legal involvement. Adolescents reporting past crime presented with heavier substance use, more substance use problems and greater psychological and environmental risks. Criminally active adolescents had greater reductions in substance use
frequency and substance use problems during the course of treatment. CONCLUSION: Juvenile offender status, whether defined by criminal justice system involvement or criminal behavior, does not seem to mitigate the potential for adolescents to benefit from manual-guided outpatient treatments.


This supplement issue on the treatment of marijuana use disorders describes two large multi-site field experiments: the Cannabis Youth Treatment (CYT) study with adolescents and the Marijuana Treatment Project (MTP) with adults. The papers cover multiple aspects of the treatment of cannabis users, including the rationale for studying cannabis use disorders, descriptions of the CYT and MTP studies, characteristics of adolescents and adults presenting for treatment of cannabis use disorders, court diversion issues, economic evaluation and confirmation of self-reported cannabis use, among other topics. This Introduction provides background information and an overview of the papers from the perspective of the funding agency.

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