Appendix 2 (as supplied by the authors): Study protocol

OVERVIEW

The present study is designed to explore the short-term effectiveness and safety of medicinal cannabis on spasticity in patients with multiple sclerosis (MS). Spasticity is a common problem in MS, causing pain, spasms, loss of function, and difficulties in nursing care. There has been significant public discussion on the potential therapeutic uses of cannabis for various neurologic conditions, including MS; however the scientific evidence is weak. Cannabinoids have shown efficacy as immune modulators in animal models of experimental allergic encephalomyelitis (EAE) and neuritis, suggesting that cannabinoids might modify the presumed autoimmune cause of MS. Evidence that cannabis relieves spasticity produced by MS is largely anecdotal; potential therapeutic effects, in addition to risk and safety issues regarding medicinal cannabis use, remain to be clarified.

The present study seeks to assess the safety and efficacy of smoked medicinal cannabis vs placebo over 17 days in MS patients with spasticity in the outpatient setting, using university clinical research center (CRC) facilities for administration of product and assessments. Short-term safety, particularly in terms of neuropsychiatric side effects, will be stressed. Spasticity ratings, cognitive ratings, and additional global measures will be obtained before and after treatment with either placebo or active product for three days. Following an eleven-day washout period, patients will be crossed over to active treatment if they had previously been on placebo or placebo if they had previously been on active drug. Although there is some suggestion that medicinal cannabis can help control spasticity in MS patients, the efficacy on objective testing, variability across individuals, time course of this effect, and possible adverse effects are unknown. The present study is designed to obtain comprehensive data on these issues.

A. SPECIFIC AIMS

***Aim #1*:** To determine if short-term exposure to smoked medicinal cannabis improves spasticity in MS patients with symptomatic spasticity. **Hypothesis #1:** Smoking medicinal cannabis will result in improved scores on the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, and Visual Analog Scale of Pain compared to the placebo condition.

Aim #2: To determine acute and short-term tolerability of cannabis from a neuropsychiatric standpoint. For this aim, repeated neurocognitive and psychiatric assessments will be performed. **Hypothesis #2:** Smoking medicinal cannabis will result in impairment on cognitive measures of attention, concentration, and memory in addition to adverse neuropsychiatric features as measured by the Brief Symptom Inventory, the Subjective Ratings of High and Sedation - Revised, and UKU Side Effect Rating Scale.

Aim #3: To determine the short-term effects of smoked cannabis on global functioning and quality of life in MS. **Hypothesis #3:** Smoking medicinal cannabis will result in improvement in global abilities and quality of life as measured by the Multiple Sclerosis Quality of Life-Inventory.

B. BACKGROUND AND SIGNIFICANCE.

Spasticity is a common and disabling symptom for many patients with MS. It tends to affect the lower extremities more than the upper extremities and associated signs include increased muscle tone, contractures, impaired dexterity, and spontaneous muscle spasms. Spasticity not only produces discomfort for patients but may greatly interfere with their functioning by compromising independence in activities of daily living. Physiotherapy, including passive range-of-motion exercises and stretching, is an essential component of anti-spasticity regimens; however, physical measures alone are usually insufficient. In most patients, adjunctive pharmacologic therapy with agents such as baclofen, benzodiazepines, and tizanadine is usually

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.

necessary. Unfortunately, many patients suffer sufficient side-effects from these medications to preclude their use at potentially effective doses. For others, severe spasticity may persist despite adequate dosing. Baclofen has been associated with elevated liver enzymes and typical side effects include drowsiness, fatigue, weakness, nausea, and dizziness. Side effects of benzodiazepines include sedation and cognitive impairment, in addition to the potential for dependence. Tizanadine has been associated with dry mouth (45%), drowsiness (54%), dizziness (19%), blood pressure effects, visual hallucinations, and elevated liver enzymes. Thus, for individuals with MS, spasticity remains a significant medical problem that does not, at present, have a wholly satisfactory treatment.

Studies of cannabinoids for spasticity in MS have had mixed results but clinical studies have been small, generally not properly controlled, with results controversial, and difficult to interpret. A report of the first questionnaire on cannabis use and MS in 53 UK and 59 US MS patients described improvement in spasticity, chronic pain of the extremities, acute paroxysmal phenomenon, and tremor with smoked cannabis (Consroe et al, 1997). Open label evaluations of oral cannabinoids in small mixed populations of subjects have reported significant reductions in spasticity (Petro and Ellenberger, 1981; Meinck et al, 1989) and dystonia by clinical measurement (Consroe et al, 1986).

Recently, investigators in the UK and US tested the ability of cannabinoids to control spasiticity and tremor symptoms of the MS-like disease, experimental allergic encephalomyelitis, in mice (Baker et al, 2000). The authors found that four different cannabinoids quantitatively ameliorated both tremor and spasticity in diseased mice; thus, providing a rationale for patients' reports of the therapeutic effects of cannabis in the control of their MS symptoms.

The most prominent adverse effects of acute marijuana intoxication appear to be euphoria, stimulation of the senses, and impaired short-term memory and linear thinking (Taylor, 1998). Depersonalization and panic attacks have also been described. Common physical effects include increased heart rate and reddened conjunctivae. Because this literature has been reviewed in recent major reports by the Institute of Medicine (Marijuana and Medicine: Assessing the Science Base, 1999) and an NIH Ad Hoc Group of Experts (Workshop on the Medical Utility of Marijuana, 1997), I shall not devote space to this issue here. However, as described below, the neuropsychiatric side-effects of cannabis will be monitored in the proposed clinical trial.

It is now known that there are at least two types of cannabinoid receptors: CB1 receptors, present mainly on central and peripheral neurons, and CB2 receptors, present mainly on immune cells (Pertwee, 1999). Two cannabinoid CB1 receptor agonists, THC and nabilone, are already used clinically, as antiemetics or as appetite stimulants. Other possible uses for CB1 receptor agonists include the suppression of muscle spasm/spasticity associated with MS or spinal cord injury. For the therapeutic potential of cannabis or CB1 receptor agonists to be fully exploited, it will be important to establish objectively and conclusively whether these agents have efficacy against spasticity that is of clinical significance and, if so, whether the benefits outweigh the risks.

C. PRELIMINARY STUDIES AND WORK COMPLETED: n/a

D. RESEARCH DESIGN AND METHODS

1. Overall Study Design

The study will be randomized, placebo-controlled, crossover in design and conducted in the outpatient UCSD Clinical Research Center (CRC). Cannabis product will be provided by the UCSD Center for Medicinal Cannabis Research (CMCR) through the National Institute on Drug Abuse (NIDA). CMCR is establishing a fully equipped, ventilated smoking room in the outpatient CRC on the UCSD La Jolla campus. Efficacy and safety will be assessed by clinical evaluation and sensitive measures of spasticity, cognition, neuropsychiatric effects, and global functioning.

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.

Thirty persons with MS will be randomized to either placebo or smoked cannabis. Patients will be assessed before and after treatment for 3 consecutive days (phase I); undergo wash out for a total of 11 days; and then cross over to either placebo or active treatment (phase II) depending on what they received during Phase I. Since each phase of treatment requires 2 assessments (before and after inhaled product) on each of 3 consecutive days, the study will allow comparisons to be made on spasticity, cognitive, neuropsychiatric, safety and global measures before and after treatment with cannabis or placebo for a total of twelve assessments. Blood will be drawn for quantitative analysis of serum THC before and immediately following each treatment session as an estimate of systemic exposure.

Considering start-up time, training and recruitment of personnel, procurement of equipment and supplies, and unanticipated initial delays, we expect that one-third (n=10) of the required subjects will be recruited and tested during the first year and that the remaining two-thirds (n=20) of the required subjects will be recruited and tested during the second year of the study.

The following schedule of visits is planned:

	Screening I	**Screening II**	**PHASE I Treatment Days 1-3**		**Washout (Days 4-14)**	**PHASE II Treatment Days 15-17**	
			B	A		B	A
Consent	x						
Eligibility Checklist	x	x					
Medical Hx/Screens	x						
Concomitant meds	x	x					
UrineToxicology	x		x#			x#	x#
Adverse Events			x	x		x	x
EDSS		x					
Modified Ashworth Scale	x	x	x	x		x	x
Timed 25-ft Walk		x	x	x		x	x
Pain Analog Scale			x	x		x	x
Cognitive Battery		x	x	x		x	x
Neuropsychiatric Assessment		x	x	x		x	x
Tx Emergent Effects				x			x
MSQLI			x†	x†		x†	x†
Practice Session		x					
THC Assays			x	x		x	x

B=before treatment; A=after treatment; †=Days 1, 3 and 15, 17 only; #= Days 1,15, and 17 only

Screening visit I will include informed consent, systematic semi-structured interview of medical history, screen for substance abuse, psychiatric screen, review of concomitant medications, and completion of inclusion/exclusion criteria. The Substance Abuse Module of the Diagnostic Interview Schedule for DSM-IV will be administered to exclude individuals with current substance use disorders. A psychiatric screen will be conducted using the Screening Module of the Structured Clinical Interview for DSM-IV. Individuals reporting potential histories of anxiety, psychotic disorders, or substance dependence disorders will be interviewed using the appropriate module, and excluded if an Axis I diagnosis is established. The Beck Depression Inventory-II will also be administered (Beck et al 1996) and individuals who exceed a cut-off score of 17, suggesting mild depression, will be interviewed by a collaborating psychiatrist for mood disorder. Those with current mood disorder (dysthymia, major depression, bipolar disorder) will be

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.

excluded. The Modified Ashworth Spasticity Scale will be administered. If the patient remains eligible, urine will be collected for toxicologic screen. A positive toxicologic screen for drugs of abuse including cannabis will exclude the patient from further participation.

Eligible patients will return for Screening visit II which must be within 7 days of Screening visit I. At Screening visit II, concomitant medications and inclusion/exclusion criteria will be reviewed. An Expanded Disability Status Scale (EDSS) score will be calculated for each patient. The EDSS rates disabilities experienced by MS patients on a zero to 10 scale and is a reliable and valid measure of impairment and disability (Coulthard-Morris, 2000). The Modified Ashworth Spasticity Scale, Timed 25-ft Walk, and cognitive battery will be administered to reduce subsequent practice effects. Patients will undergo a "practice session" with placebo product to ensure subsequent performance. **They will not be told that the practice session involves placebo.** Patients will be randomized to their treatment arm.

Patients will then return to the CRC to begin **Phase I** treatment within 7 days of Screening Visit II. At baseline (**Day #1**), urine will be collected for toxicologic screen. A positive toxicologic screen for drugs of abuse including cannabis will exclude the patient from further participation. The Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neurospychiatric assessments, and MSQL-I will be administered. Blood will be drawn for total THC. Following their first treatment session with smoked product, blood will be drawn for peak THC levels and patients will be assessed on the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, and treatment-emergent effects beginning 30 minutes after their treatment session. On **Day #2**, they will return to the CRC at approximately the same time of day to ensure regulation of food, medication, and time of cannabis intake. Blood will be drawn for total THC. Patients will be assessed with the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, and neuropsychiatric assessments. Following treatment with smoked product, blood will be drawn for peak THC levels and patients will again be assessed on the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, and treatment-emergent effects, beginning 30 minutes after their treatment session. On **Day #3**, the patient will return to the CRC at approximately the same time of day for their third treatment. Blood will be drawn for total THC. Patients will undergo assessment with the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, and neuropsychiatric assessments. Following completion of the third treatment, blood will be drawn for peak THC levels and patients will be assessed with the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, treatment-emergent effects, and MSQL-I.

Patients will take no treatment for the next eleven days and will return to the CRC to begin Phase II on **Day #15**. A positive toxicologic screen for drugs of abuse other than cannabis will exclude the patient from further participation. (A positive urine toxicologic screen for cannabis and a peak plasma THC concentration greater than Day #3 will suggest illicit use and exclude the patient from further participation.) The Modified Ashworth Spasticity Scale, Spasm Frequency Score, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, and MSQL-I will be administered. Blood will be drawn for total THC. Patients will undergo treatment with smoked product and blood will be drawn for peak THC levels. Patients will be assessed on the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, and treatment-emergent effects, beginning 30 minutes after their treatment session. Patients will return to the CRC at approximately the same time of day on **Day #16**. Blood will be drawn for total THC. Patients will be assessed on the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, and neuropsychiatric assessments. Following treatment with smoked product, blood will be drawn for peak THC levels and patients will again be assessed on the Modified Ashworth

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.

Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, and treatment-emergent effects, beginning 30 minutes after their treatment session. On the last day of the protocol, **Day #17**, the patients will return to the CRC for their third treatment of Phase II. Blood will be drawn for total THC. Patients will undergo assessment with the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, and neuropsychiatric assessments. Following completion of the third treatment, blood will be drawn for peak THC levels, and patients will be assessed with the Modified Ashworth Spasticity Scale, Timed 25-ft Walk, Visual Analog Scale of Pain, cognitive battery, neuropsychiatric assessments, treatment-emergent effects, and MSQL-I beginning 30 minutes after their treatment session.

2. Study Site

The study will be performed at the UCSD La Jolla Clinical Research Center. The CRC is a self-contained organized research unit that is fully staffed by nursing, dietary and core laboratory personnel to support the clinical research project described herein. A room will be equipped with a Tepco 750 smoke scrubber or a HEPA filter (BioSafety, RS 1000).

3. Subjects

We estimate that 30 subjects will be necessary (see Section 7) in this crossover design and therefore plan to enroll 36 MS subjects, expecting attrition of up to 6 subjects over the course of the study. MS patients will be obtained through the UCSD MS Clinic and/or the private practices of their neurologists. These patients will have received extensive neurological evaluation and represent a well-studied MS patient population. MS patients will be solicited by Dr. Corey-Bloom, and contacted for appointment by the Research Coordinator. Patients of all ethnic and racial backgrounds are eligible. Prior use of cannabis is not required. Patients will be allowed to continue other currently available treatments for spasticity other than benzodiazepines, if they have been on a stable dose of the medication for at least three months.

3.a. Inclusion Criteria

Subjects will be included if they:

Have clinically definite or probable, laboratory-supported MS; are between the ages of 18-65

Have complaints of spasticity and at least moderate increase in tone as evidenced by a score of $\geq$3 on the Modified Ashworth Scale at either the elbow, hip or knee. **Enrolled patients should be receiving optimum conventional therapy; i.e., receiving maximum benefit from existing tolerable therapy but not realizing sufficient relief of symptoms.**

Have been on a stable dose of disease-modifying ("ABC") therapy for at least six months

Are fluent in English (the spasticity instruments and global measures have not yet been validated for use in individuals with other primary languages)

Are previously cannabis-naïve or –exposed; however, if the patients are not cannabis naïve, they will need to have refrained from smoking cannabis for one month prior to screening and cannabis-free status must be confirmed by urinalysis. .

Have been on a stable dose of either lioresal (Baclofen®) or tizanadine (Zanaflex®) for at least three months;

3.b. Exclusion Criteria

Subjects will be excluded if they:

Report any Axis I psychiatric disorder especially depression or significant neurological disease other than MS (epilepsy, head trauma, etc.)

Have a recent history of active substance use or abuse defined as daily use for at least 14 days within the past month

Have any unstable medical health problem

Have any known pulmonary disorders, including tuberculosis, asthma, or COPD

Are pregnant or nursing

Require benzodiazepines to control their spasticity

Require high doses of narcotic analgesic medications on a daily basis

4. Cannabis Product and Administration

*Product***.** Since cannabis is a Schedule I drug, Dr. Corey-Bloom will obtain her own Schedule I license from the FDA. The cannabis required for this study will be requested from the National Institute of Drug Abuse (NIDA). NIDA has informed us that they are able to provide cigarettes ranging in strength from 3% to 7% THC, and can hand roll them to insure that the cigarettes meet the desired potency.

A placebo-controlled design will be used to diminish the potential for bias in the ascertainment of assessment outcomes. The use of the placebo control will also enable accurate estimates of the side effects of smoked cannabis, which would be necessary to any scientific consideration of its widespread use for treatment of spasticity. Placebo cigarettes will be available from NIDA and will be made from whole plant with the cannabinoids removed. This does not result in any changes in taste, therefore making it difficult by this means alone to distinguish between active-THC and placebo cannabis cigarettes.

Storage and dispensing. Cannabis and placebo cigarettes will be received, stored and dispensed by the pharmacy service at the UCSD CRC. Accountability records will be maintained according to policies and procedures for both Schedule I and investigational drugs. The final disposition of each dose will be recorded. Residual drug supplies will be disposed of as directed by NIDA. Storage of the cannabis and placebo cigarettes will be maintained as directed by NIDA. The cigarettes will arrive frozen from the University of Mississippi. They will be stored in a padlocked freezer, in a research pharmacy, which is locked. Only the licensed pharmacists listed on the DEA registration will have access to the freezer where the cannabis and placebo cigarettes are stored. Any and all additional security precautions dictated by NIDA or other institutional officials will be instituted to be in complete compliance before the start of the study. Dispensing of the cannabis and placebo cigarettes will occur in compliance with NIDA, DEA and FDA regulations.

Each shipment of cannabis cigarettes from the appropriate official at NIDA will be received personally by the research pharmacist, and the number of cigarettes at each dosage level double counted. A record of the materials will be kept in a locked file cabinet by the PI or pharmacist, with each cigarette used noted in the log along with date, time, experimental procedure, subject name, and responsible individual. A signature by the PI or Senior Staff Member will be required for the cigarette removal. At the end of each cigarette use, all unused materials will be collected and stored in a sealed container also placed in a locked freezer, with the exact amount noted and dated in the log. All records will be made available to the DEA and the local Environment, Health, and Safety Office, which supervises all controlled substance research use.

At the end of each major study, accounting for all cigarettes will be made by counting the number used as per the experimental protocol details, comparing this number against the log records, and recounting the remaining (unused) cigarettes. Any discrepancies will be immediately reported by the PI to the Security Office of UCSD and an immediate investigation made. All laboratory staff members will be made aware of the legal, ethical, and professional seriousness concerning controlled substance presence for appropriate scientific assessment. Any violation of

the relevant laws, procedures, and uses of the cannabis will result in immediate termination of employment and legal prosecution as necessary.

All participants will utilize the Foltin Uniform Puff Procedure (Foltin et al., 1986) for cannabis administration. The Foltin Uniform Puff Procedure is a standardized method for smoking that involves five seconds of inhalation, followed by a ten second breath hold, exhalation, and 45 second waiting period before repeating the process. While there are still variations in individual smoking performance (e.g. strength of inhalation), utilizing a standard timing procedure will reduce the variability in dosing. All subjects will be instructed in this method, practice the procedure before initiating treatment, and be observed during treatment to ensure compliance.

5. Subject Placebo/Cannabis Treatment Conditions

During Screening visit II, all subjects will be given information about the range of subjective effects they may experience from smoking cannabis, as well as relaxation techniques if the subjective effects of the cannabis are in any way disturbing or disorienting. Participants will be trained in the smoking procedure in a practice session during this visit. Under supervision of staff each participant will be exposed to one placebo cigarette using the Foltin Puff Procedure, and ratings will be recorded regarding the subjective and physical effects of cannabis (eg, UKU Side Effects Rating Scale, BSI). Staff will observe participants until the effects have abated.

During the actual experimental conditions, subjects will be assessed at the same time of day to regulate food, medication, and time of cannabis intake. The placebo and cannabis conditions will be administered by having subjects smoke one placebo or cannabis cigarette using the Foltin Puff Procedure. The cannabis cigarettes will contain 4% THC by weight; the placebo cigarettes will be constructed from the same base material but with the THC removed. The selection of the 4% THC cigarette is based on the strength of cannabis cigarette available from NIDA that most closely approximates the strength available in the community. Both placebo and cannabis cigarettes will be smoked in the fully equipped, ventilated smoking room at the UCSD La Jolla CRC. After smoking, subjects will have blood drawn for peak THC levels (two minutes after the last puff) and exhaled carbon monoxide measured for smoke exposure. Plasma THC levels will be measured as the most direct way to estimate systemic exposure. Plasma concentrations of THC are also expected to best predict physiologic response.

Subjects will remain in the laboratory under direct observation by Staff for 2 hours after the cannabis procedures are completed. At that time a final vital sign and self-report status check will be made and upon satisfactory readings, the subject will be released and driven back to his domicile by taxi cab or prearranged transportation. The return transport procedure also will be observed directly by staff to ensure compliance. Any serious adverse reactions will be reported immediately to the monitoring physician, the local IRB, and the Research Advisory Panel. This policy will be made explicit to all staff personnel, with the appropriate names, addresses, and telephone numbers of all relevant parties provided and posted.

6. Assessment Measures. Coincident with study aims, the following will be used to assess 1) spasticity and mobility; 2) cognitive, neuropsychiatric, and treatment-emergent features; 3) quality of life and global functioning:

Spasticity and Mobility (will be administered before and after each treatment session):

The **Modified Ashworth Scale** (Lee, 1989) is the most commonly used clinical measure of spasticity. Based on an evaluation of the degree of resistance to passive range of motion at one or more joints, it is an ordinal scale of muscle tone intensity (zero to 4): 1=no increase in tone; 1.5=slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remained (less than half) of the range of movement; 2=slight increase in tone, giving a catch when the limb is moved in flexion or extension; 3=more marked increase in tone,

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.

but limb easily flexed; 4=considerable increase in tone, passive movement difficult; 5=affected part is rigid without any possible passive mobilization. Each assessment will involve ratings according to the Modified Ashworth Scale of the bilateral elbows, hips, and knees for a combined possible total point score of 30. **The Modified Ashworth Scale will be the primary outcome measure.**

The **Timed 25-Foot Walk Test** is a mobility and leg function performance test in which the patient is timed walking 25 feet. It is similar to the Ambulation Index, differing only with regard to scoring and is strongly recommended for clinical trials to examine ambulation and leg function.

The **Visual Analog Scale of the McGill Pain Questionnaire** is used to assess the intensity of pain. It is a 10-centimeter line anchored at one end by the descriptor "No Pain" and at the other by the words "Worst Pain Imaginable." The subject is asked to mark along the line indicating the severity of pain experienced; a score is derived by directly measuring the number of centimeters from the zero point to the subject's mark.

Cognitive, Neuropsychiatric, and Treatment-Emergent Effects):

Cognition will be assessed before and after each treatment session by means of the PASAT, WAIS-III Digit Symbol Subtest, Trail Making Test, and Hopkins Verbal Learning Test. The **PASAT** is a multiple computational task that is designed to measure attention and information processing speed. It measures how rapidly a person can perform numeric operations on digits held in short-term memory and provides an estimation of the amount of information a person can handle at one time. The **WAIS-III Digit Symbol Subtest** (Wechsler, 1997) is a test of psychomotor speed, concentration, and graphomotor abilities which requires the respondent to match symbols to numbers as quickly as possible. The **Trail Making Test** is a measure of psychomotor speed, attention and cognitive sequencing. The **Hopkins Verbal Learning Test** (Benedict et al, 1998) provides information on the ability to learn and immediately recall verbal information across trials, as well as the ability to retain, reproduce, and recognize this information after a delay 10-15 minutes. Six alternate forms of the test are available.

Neuropsychiatric symptoms will be assessed before and after each treatment session by the **Brief Symptom Inventory** (Derogatis, 1978) which is interpreted in terms of 9 primary symptom dimensions: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. It is a 53-item, self-report symptom inventory derived from the Symptom Checklist-90 Revised, which requires the patient to respond to each item in terms of a 5-point scale of distress, ranging from "not-at-all" to "extremely". Typically, it requires 10 minutes for patient completion.

Treatment Emergent Effects of cannabis will be assessed after each treatment by interview and self-report of physical and psychological symptoms using the Subjective Ratings of High and Sedation - Revised (SRHS-R) and the UKU Side Effect Rating Scale. The **Subjective Ratings of High and Sedation - Revised** has been adapted from Block, et al (1998) for use in the present study to evaluate the subjective effects of cannabis. This scale consists of 10 ratings of different aspects of stimulation vs. sedation (alert/drowsy, attentive/dreamy, tense/relaxed, interested/bored, capable/incompetent, excited/calm, clear-headed/fuzzy, well-coordinated/clumsy, quick-witted/mentally slow, and energetic/lazy). The **UKU Side Effect Rating Scale** is a semi-structured interview that evaluates a wide range of unwanted side effects including psychological (eg, concentration difficulties, failing memory, lassitude), neurological (eg, hypokinesia, paraesthesias), autonomic (eg, accommodation disturbance, orthostatic dizziness, nausea, sweating), and miscellaneous effects (eg, weight gain, diminished sexual desire) (Lingjaerde et al 1986). Each treatment emergent symptom is defined on a four-point scale of intensity (0 = not present; 3 = severe), and rated separately with regard to being causally related to the study drug (improbably related, possibly related, probably related). In addition, sitting and standing blood pressure, heart rate, respirations, and oral temperature will be obtained before

drug administration and at 0.5, 1 and 2 hours after administration to monitor the subject's health status as well as to quantify cannabis's general effects.

Quality of Life (administered at the beginning and end of each phase):

The **Multiple Sclerosis Quality of Life-Inventory** is both a generic and an MS-specific quality of life measure (Coulthard-Morris, 2000). It consists of 138 items and 10 separate scales that assess the following domains: general health status, fatigue, pain, sexual satisfaction, bladder control, bowel control, vision, cognitive function, mental health, and social support. It is self-administered and takes about 30 minutes to complete.

7. Laboratory Assessments

Assay for Total THC. Total THC will be determined using commercially available immunoassay in the UCSD Medical Center Laboratory of Dr. Tony Yaksh.

Urine Toxicology. Qualitative urine toxicology screens for nonprescribed substances will be obtained at screening, baseline for each phase, and study exit. The substances assayed will be amphetamines, ethanol, barbiturates, benzodiazepines, cocaine and benzoylecgonine, methadone, methaqualone, methylphenidate, phencyclidine, opioids, and tetrahydrocannabinol.

Carbon monoxide (CO). Exhaled CO levels will be measured by using an Ecolyzer. Expired CO levels before and after each treatment session will provide a measure of smoke exposure.

8. Statistical Considerations

Hypothesis #1: Smoking medicinal cannabis will result in improved scores on the Modified Ashworth Spasticity Scale and Visual Analog Scale of Pain compared to the placebo condition. Means and bootstrap-based bias-corrected confidence intervals will be computed for each assessment time of each specified measure. For each subject the response is the change between a before-after placebo difference and a before-after treatment difference on the specified measures. We will then evaluate the aggregate differences using a one-sample t-test (i.e. perform a paired-sample t-test). Here we define as clinically important any departure from zero in the hypothesized direction that is greater than one standard deviation of paired differences. A power analysis indicates that a sample size of 30 individuals will yield well over 80% power (alpha = 0.05) to detect an effect of one SD; or greater. In addition the relationship between total plasma THC and spasticity scores will be examined using Pearson correlation.

Hypothesis #2: Smoking medicinal cannabis will result in impairment on cognitive measures of attention, concentration, and memory in addition to adverse neuropsychiatric features as measured by the Paced Auditory Serial Addition Test, Brief Symptom Inventory, Perceived Deficits Questionnaire, Modified Fatigue Impact Scale, the Subjective Ratings of High and Sedation - Revised, and UKU Side Effect Rating Scale. Means and bootstrap-based bias-corrected confidence intervals will be computed for each assessment time of each specified measure. For each subject the response is the change between a before-after placebo difference and a before-after treatment difference on the specified measures where before and after treatment measurements were taken (e.g. PASAT), and a change between the post-placebo and post-active scores when only the post- treatment measurements were taken (e.g. SRHS-R). We will evaluate the aggregate differences using a one-sample t-test (i.e. perform a paired-sample t-test). Here again we define as clinically important any departure from zero in the hypothesized direction that is greater than one standard deviation of paired differences. In

addition the relationship between total plasma THC and cognitive, neuropsychiatric and treatment-emergent effect scores will be examined using Pearson correlation.

Hypothesis #3: **Smoking medicinal cannabis will result in improvement in global abilities and quality of life as measured by the Multiple Sclerosis Quality of Life-Inventory.** For each subject the response is the change between a post-placebo and a post-treatment score on the MSQOL-I. The aggregate differences will be evaluated using a one-sample t-test (i.e. perform a paired-sample t-test).

Regression and covariate analysis will also be applied to determine the association between the major efficacy/safety outcomes and important clinical variables such as EDSS score, smoking history, exhaled CO levels, concomitant medications, etc.

E. HUMAN SUBJECTS

A total of 30 individuals will be enrolled over a two-year period. Individuals will be recruited as participants based upon specific medical and treatment characteristics, detailed previously as inclusion and exclusion criteria. All participants will be fully informed by trained personnel regarding the potential risks and benefits of participating in medical research. The purpose of the research, the schedule of visits, and the procedures to be performed will be fully explained. Participants will be informed that they may discontinue participation at any time and that discontinuation will not affect their future medical care. This information is also provided in a written document. After reviewing this document and asking any questions, the participant is asked to sign, indicating an awareness of the study requirements and a desire to take part in the research study. This consent is witnessed and is signed by medically competent personnel. The participant receives a copy of his/her signed consent forms (containing a name and contact number in case of emergency) and the original form is retained. The participant also receives a copy of “The Experimental Subject’s Bill of Rights”.

Potential Risks. Potential risks of data collection in this study include mental and/or emotional distress that may result from questions asked during assessment or as a result of the time taken in the assessment process. In addition, some neuropsychological tests may require concentrated effort and may be frustrating to the participant to complete. There are no potential physical risks posed by neurobehavioral examinations. Standard risk is associated with venipuncture include pain, bruising, and a very low risk of infection. Risks of inhaled cannabis products may include psychomotor coordination difficulties, eye irritation, throat irritation, increased heart rate, possible hypotension, reversible appetitie/mood/memory/cognition effects. Smoking marijuana may prejudice application for future employment, if drug screening is a condition of employment. It is likely that detectable traces of marijuana will remain in the hair or blood for a minimum of six weeks after smoking.

Risk Management Procedures. To guard confidentiality, only the participant’s identification number will appear on questionnaires, and paper-based records, forms, and data will be kept in secure file cabinets. Computer records are protected by standard measures that limit access to the data to selected research project personnel. To reduce fatigue, the time needed to complete the cognitive and behavioral interviews will be minimized by thoroughly familiarizing the interviewers with the contents of the questionnaires. Our interviewers are trained not to press participants to answer questions that seem to be excessively distressing to them, and interviews will be terminated if the participant is too distressed, too fatigued, or too frustrated by the effort. Psychologists or psychiatrists will be consulted and will make an assessment in the event: (1) that an individual becomes distressed during the course of the interviews; (2) that the Beck

Depression Inventory score is greater than or equal to 12; or (4) that suicidal ideas are endorsed on the Beck assessments. Community referrals will be made when appropriate.

Subjects will be given information about the range of subjective effects they may experience from smoking marijuana, as well as relaxation techniques if the subjective effects of the marijuana are in any way disturbing or disorienting. Throughout the study the subject's health status as well as the general effects of the ingestion of cannabis will be monitored. Any adverse reactions will be reported immediately to the monitoring physician, the local IRB, and the Research Advisory Panel. This policy will be made explicit to all staff personnel, with the appropriate names, addresses, and telephone numbers of all relevant parties provided and posted.

Potential Benefits. Participants may benefit from participation by experiencing relief from their spasticity. The long term benefits from the study stem from a greater understanding of how cannabis affects spasticity in multiple sclerosis, and how it affects neuropsychological function and cognition.

Risk Benefit Ratio. The risk-benefit ration is low, since the participants will be carefully screened and followed and the importance of the knowledge gathered about the safety and effectiveness of cannabis should be significant.

Expense to Subject. None, other than time and effort taken.

Payment to Subject. No specific payments to subjects will be made for participation; however, if subjects need financial support with transportation or child care while they are participating in this project, funds will be available.

Appendix to: Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 2012. DOI:10.1503/cmaj110837.