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Controlled Clinical Trial of Cannabidiol in Huntington's Disease

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CONSROE, P., J. LAGUNA, J. ALLENDER, S. SNIDER, L. STERN, R. SANDYK, K. KENNEDY AND K. SCHRAM. *Controlled clinical trial of cannabidiol in Huntington's disease*. PHARMACOL BIOCHEM BEHAV **40**(3) 701–708, 1991.— Based on encouraging preliminary findings, cannabidiol (CBD), a major nonpsychotropic constituent of *Cannabis*, was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with Huntington's Disease (HD). The effects of oral CBD (10 mg/kg/day for 6 weeks) and placebo (sesame oil for 6 weeks) were ascertained weekly under a double-blind, randomized cross-over design. A comparison of the effects of CBD and placebo on chorea severity and other therapeutic outcome variables, and on a *Cannabis* side effect inventory, clinical lab tests and other safety outcome variables, indicated no significant ($p>0.05$) or clinically important differences. Correspondingly, plasma levels of CBD were assayed by GC/MS, and the weekly levels (mean range of 5.9 to 11.2 ng/ml) did not differ significantly over the 6 weeks of CBD administration. In summary, CBD, at an average daily dose of about 700 mg/day for 6 weeks, was neither symptomatically effective nor toxic, relative to placebo, in neuroleptic-free patients with HD.

Cannabidiol (CBD) Oral administration Cannabis Marijuana Huntington's disease Huntington's chorea Chorea Neurological disease Functional disability Memory impairment Pulse rate Blood pressure Controlled clinical trial Therapeutic effects Symptoms Efficacy Side effects Safety Toxicity Placebo Sesame oil Double-blind Plasma levels of CBD Gas chromatography/mass spectroscopy (GC/MS)

CANNABIDIOL (CBD) is a nonpsychotropic cannabinoid of *Cannabis sativa* (marijuana) with a possible therapeutic potential in epilepsy and some hyperkinetic movement disorders (8). Anecdotal accounts (8), and results of preliminary open trials in patients with dystonia (7) and with Huntington's disease (HD) (26) suggest that CBD can reduce dystonic and choreiform movements, respectively, of these conditions. Supporting evidence for these suggestions is found in animal studies. CBD can reduce the spontaneous dyskinesias of the dystonic rat (6), the latter a putative genetic model of human torsion dystonia. CBD also can reduce apomorphine-caused turning behavior of the 6-hydroxydopamine-treated rat (9), a model of the presumed biochemical abnormality (striatal dopamine supersensitivity or hyperfunction) which mediates clinical chorea. Further, CBD can augment hypokinesia of the rat treated with tetrabenazine (6), a drug with (striatal) antidopamine activity and some clinical efficacy against chorea. Lastly, CBD can reduce aggressive behavior of the rat treated with the neurotoxin L-pyroglutamate (9), a possible model of pathologic (striatal neuronal degeneration) and symptomatologic aspects of HD.

HD is a dominantly inherited neurodegenerative disease characterized clinically by disabling chorea, intellectual decline and psychiatric illness (24). Currently available pharmacotherapy of HD remains limited to symptomatic relief of the movement disorder, mental depression and some of the more severe behavioral disturbances. While neuroleptic drugs are commonly used to treat chorea, their use is associated with only modest improvement for some, and with intolerable side effects for many, patients with HD (24).

The present study was undertaken to evaluate the symptomatic efficacy and safety of CBD for HD patients in a controlled clinical trial.

METHOD

Patients

Approval for our protocol was granted by the University of Arizona Human Subjects Committee and the U.S. Food and Drug Administration. Patients were solicited via contacts with neurologists, and review of patient charts at our University Medical Center. Patients were eligible for the trial if they: a) had a confirmed diagnosis of HD (characteristic signs and course, and positive family history of the disease were essential criteria); b) had mild or moderate progression of HD, i.e., either stage 1, 2, 3 or 4 of the disease (see below); c) were cooperative, lucid, and ambulatory, and able to come to our clinic every week for 15 consecutive weeks during the trial; d) had adequate home support and a reliable guardian to monitor medication consumption, patient progress and side effects, in the home environment; e) were devoid of active or progressive hematologic, renal, hepatic, endocrine, cardiac or pulmonary disease; f) were not taking neuroleptics (or related drugs) during

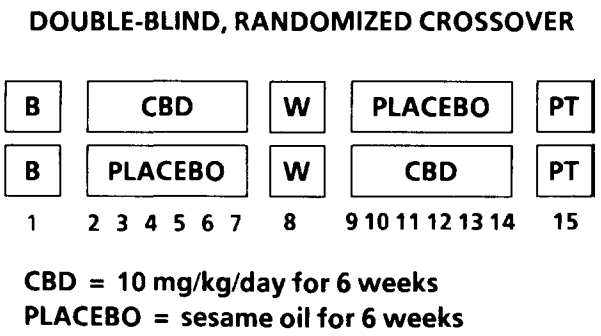

FIG. 1. Study design of the cannabidiol (CBD) trial in Huntington's disease. Patients, randomly assigned to one of the two treatment orders above, were evaluated weekly for 15 weeks during baseline (B), CBD or placebo administration (weeks 2–7 and 9–14), washout (W), and posttreatment (PT) conditions.

our trial and were off neuroleptics for at least 2 weeks prior to the start of our trial; and if women of child-bearing potential, g) had a hysterectomy, a tubal ligation, or were using an IUD or oral contraceptive, and were not pregnant (confirmed by pregnancy testing). Informed consent was obtained from each study patient and his/her guardian. Subsequently, each patient was randomly assigned to a treatment order (CBD-placebo or placebo-CBD) and a starting date of his/her trial.

Design and Treatments

A schematic of the (double-blind, randomized crossover) study design is presented in Fig. 1. CBD (obtained from the US National Institute on Drug Abuse) was dissolved in sesame oil, N.F. (Ruger Chemical Company), and the drug solution was incorporated into soft gelatin, amber-colored capsules (R. P. Scherer Company). The total daily dose of CBD (10 mg/kg) was divided into 4 capsules. Patients were instructed to take 2 capsules at 8:00 a.m. and 2 capsules at 2:00 p.m. every day, on an empty stomach, and with a (8 ounce) glass of water. (Capsules were supplied weekly). Placebo capsules, identically appearing to CBD capsules, contained only sesame oil, N.F., and they were given in the same dosing schedule as CBD.

Dependent Variables and Measures

Weekly ("live") evaluations of patients (and the dependent variables described below) were made by the same evaluators (J.L. and J.A.) to assess neurological and psychological status for 15 consecutive weeks, and patient clinical lab tests and videotapings were carried out 4 times (during baseline, CBD, placebo and posttreatment periods). A given patient was evaluated (for 1–2 hours) at the same time each week. The following dependent variables were assessed.

The Marsden and Quinn's (M and Q) chorea severity evaluation scale (20) is an ordinal scale based on assessment of speech, gait, postural stability, manual dexterity, and chorea severity of body parts. The total score ranges from 0–24 (most severe). Videotapes of this variable also were made according to a standardized protocol (4). These videotapes were evaluated blindly and independently by 2 neurologists (S.S. and L.S.) to provide a "nonlive" assessment of chorea severity.

The Shoulson and Fahn's (S and F) functional disability scale for HD (27) is an ordinal scale based on assessment of capacities to perform various activities of daily living and of the type of care required. The total score ranges from 13–0 (most disabled). The HD staging scheme (27) is derived from the S and F functional disability scale, and the stage of the disease ranges from 1–5 (most severe).

The tongue extension test (17) measures the duration (an average of 3 attempts) of sustained tongue protrusion following patient instructions to hold the tongue out as long as possible. The finger tapping test (14) measures the number of taps (average of three 10-second trials) recorded by a mechanical counter following instructions to the patient to tap a key with the index finger of his/her dominant hand as rapidly as possible. The screw-and-nut test (14) measures the time (seconds) it takes a patient to screw 3 nuts on their respective screws following instructions to complete the task as rapidly as possible. The Hopkins symptom checklist or SCL-90R (11) measures the degree of distress (on a 1–4 ordinal scale) in relation to 90 target symptoms of emotional disturbances. The 90 ratings were collapsed into a global severity index which ranges from 0–360. The Buschke-Fuld (B-F) selective reminding tasks (5) measures recall and storage of information. The procedure involves verbal presentations of a list of 12 nouns and asking patients to recall the words, both before and after reminding them of omitted words. Four 12-item lists, equated for word frequency (15), were used to minimize learning effects across repeated weeks of testing. The data were expressed as average recall (range of 0–12), maximum recall (range of 0–60), and maximum storage (range of 0–48) of information. The physician and patient assessment scale was a subjective global assessment of treatment. Values ranged from 100% (worse) to 100% (better), in increments of 25%.

The *Cannabis* side effect inventory was a checklist of 69 subjective, undesirable effects, constructed from a published list of 105 effects of marijuana intoxication and withdrawal (30). Each effect (read to the patient) was recorded as having occurred or not, and the results were expressed as the total number of side effects reported.

The clinical lab tests included a blood chemistry 20 profile, complete blood counts and differential, platelet count, prolactin level and urinalysis. The test and normal range values were reported for each of the individual tests. Arterial blood pressures (systolic and diastolic in mm Hg) and pulse rate (beats/minute) were measured in recumbent and then upright (head-up tilt to 70 degrees) postures. Mean blood pressures were calculated as the diastolic + ⅓ × systolic − diastolic pressures. Body weight also was measured.

Plasma levels of CBD were determined by use of gas chromatography (GC) and mass spectroscopy (MS) techniques. The full details are reported elsewhere (see Consroe et al., this volume). Briefly, these involved organic solvent extraction of plasma CBD (13), trimethylsilyl (TMS) derivatization of CBD and the internal standard delta-6-THC (22), GC [(13); Varian model 3400 gas chromatograph using a 30 meter DB-5 WCOT capillary column], and MS [(18); Finnigan-MAT ITDS-800 ion trap mass spectrometer in positive ion chemical ionization mode using isobutane]. Calculations of CBD levels were based on peak ion intensity of the 387 M+H peak of delta-6-THC-TMS and the 459 M+H peak of CBD-2TMS. The sensitivity of the assay was about 500 pg/ml. The precision was about 10% at 1 ng/ml and above, and about 15% at concentrations below 1 ng/ml.

Primary Variables and Null Hypotheses

The major therapeutic response variable was the M and Q chorea severity score, and the null hypothesis was that no reliable difference existed between CBD and placebo on chorea severity. A two-tailed alpha level of 0.05 was adopted to decide whether or not to reject this hypothesis. The major safety re-

sponse variables were the *Cannabis* side effect inventory and the clinical lab tests, and the null hypothesis was that there were no important differences between CBD and placebo. In this case the decision of whether or not to reject the null hypothesis was based on statistical evidence (differences in the numbers of side effects at a two-tailed alpha of 0.05) and/or clinical judgement (e.g., types, patterns and/or severity of abnormal lab tests and subjective side effects).

Statistics

Each study variable was analyzed statistically using the appropriate nonparametric tests (19,28). Computations were made on a (MS-DOS) minicomputer using a self-written program for Nemenyi's test (19) and a commercial program (16) for all the other tests. For ordinal and interval data, Friedman (two-way analysis of variance by ranks) test followed by Nemenyi's test (for post hoc pairwise comparisons) were used to assess within-subjects differences among/between weeks for potential effects of study conditions across time. The Mann-Whitney test was used to assess between-subjects differences for potential order of treatment effects (with treatment data collapsed across time). Subsequently, the Wilcoxon signed ranks test was used to evaluate differences between CBD and placebo for each measure (with the two treatment order combined). Other statistical tests used were the Spearman rank-order correlation test (to evaluate the strength of association between "live" and videotape assessments of chorea severity), and standard descriptive statistical tests. A two-tailed probability (alpha) level of 0.05 was used for the inferential tests of significance.

Prior to the beginning of the trial, estimates of required sample sizes were made based upon our preliminary data (26) and other factors. For these (computer-assisted) calculations (12) we specified alpha at 0.05 for a two-sided, paired Student's *t*-test, power at 0.9, and delta at both 2.5 and 5.0 units; the latter being two differences in population means on the M and Q chorea scale we considered clinically important to detect. We estimated the SDd's (standard deviations of the paired differences) at 1.0, 2.0 and 3.0 units. Lastly, we increased the calculated sample sizes by 15% because of an estimated 10% subject dropout rate, and a known 5% difference in the power-efficiency (28) of the Student's *t*-test (used for these calculations) and the Wilcoxon signed ranks test (used for the trial). Estimates of 4–20 subjects were obtained. We then made power calculations (12) based on the parameters above and a total sample size of 20 subjects. The estimated power of the trial for detecting a minor therapeutic effect (delta of 2.5 units = 20% difference) was 1.00, 0.99 and 0.94 for SDd's of, respectively, 1.0, 2.0 and 3.0. Further, the estimated power of the trial for detecting a major therapeutic effect (delta of 5.0 units = 40% difference) was 1.00, 1.00 and 0.99 for the above SDd's, respectively. Power estimates were reassessed after completion of the trial and these are presented in the Results section.

RESULTS

Study Patients

Eighteen patients were enrolled in the trial. Three (male) patients withdrew for reasons unrelated to the trial after completing 5 (baseline and 4 weeks of CBD treatment), 6 (baseline and 5 weeks of CBD) or 10 (baseline, 6 weeks of CBD, washout week, and 2 weeks of placebo) weekly visits. Fifteen patients, 8 men and 7 women, completed the entire 15 week trial. Table 1 presents some of their salient clinical features at baseline. Additionally, 6 of these patients currently were taking 1 or more medications for other conditions such as for essential hypertension (atenolol; furosemide; prazosin), peptic ulcer (cimetidine), arthritis (indomethacin), glaucoma (levobunolol) and pregnancy prevention (Brevicon). Also, 6 of the patients alleged current alcohol and tobacco use, but no patients alleged current use of marijuana or other substances. Moreover, only one patient alleged ever using marijuana in the past.

TABLE 1

CLINICAL PROFILE AT BASELINE OF STUDY PATIENTS COMPLETING THE TRIAL

Variable*	N§	Median	Mean ± SD§	Range
Men/Women	8/7			
Age (years)	15	52	47.8 ± 15.3	17–66
Body Weight (kg)§	15	70.2	67.6 ± 16.9	40–101
HD Duration (years)†	15	4	5.0 ± 2.8	1–11
Chorea Severity (0–24)	15	13	11.7 ± 5.5	2–22
Disability Score (13–0)	15	6	6.7 ± 2.4	2–12
HD Staging Scheme (1–5)	15	3	2.8 ± 0.5	2–4
Neuroleptic Use (years)‡	8	2	2.6 ± 1.9	0.5–6

*Numbers and words in parentheses are the normal ranges and/or units of measure of the variables; see Method section for details.

†Duration (in years) of Huntington's disease (HD) from first diagnosis.

‡Neuroleptics were discontinued prior to the trial at intervals of 1 month (2 patients), 2 months (2 patients), 7 months (1 patient), 2 years (2 patients) and 4 years (1 patient); 7 patients had not taken neuroleptics previously.

§N = number of patients; SD = ± standard deviation of the mean; kg = kilograms.

Effects of Order of Assessments and Treatments

Of the 15 completed study patients, 9 patients were evaluated in the baseline-placebo-washout-CBD-posttreatment order, and 6 patients were evaluated in the baseline-CBD-washout-placebo-posttreatment order (see Fig. 1). The differences in M and Q chorea severity occurring over the 6 weeks each of the 2 placebo conditions and the 2 CBD conditions were evaluated by Friedman analysis and the probabilities (p) obtained were 0.81, 0.39, 0.57 and 0.74, respectively. Thus the data of each condition were averaged across weeks and examined for possible effects of the treatment order by the Mann-Whitney test. The differences in scores between the 2 placebo conditions and between the 2 CBD conditions were not significant ($p = 0.56$ and 0.77, respectively). Similarly, chorea severity differences between the 2 baseline, the 2 washout and the 2 posttreatment conditions were not significant ($p = 0.59$, 0.77 and 0.68, respectively). Lastly, the same analyses were carried out on the other dependent measures above, and the combined results also indicated there were no systematic or important effects of the order of assessments and treatments utilized in our trial. Thus the data for all 15 patients were combined in the placebo condition and in the CBD condition for comparative (within-subjects) analyses. These analyses are presented below.

Effects of CBD and Placebo on Therapeutic Variables

The major therapeutic response variable was chorea severity as measured by the M and Q chorea severity evaluation scale. Table 2 presents the median (mean and standard error = SE) of chorea scores for the CBD and placebo treatments, and an assessment of the overall difference between the 2 treatments (Wilcoxon signed ranks test). Although the direction of the treatment responses appeared to favor CBD (e.g, a lower median chorea severity score for CBD than for placebo), the difference was small and clearly not significant ($p = 0.71$).

TABLE 2

EFFECTS OF CANNABIDIOL (CBD) AND PLACEBO (PBO) TREATMENTS ON THE THERAPEUTIC RESPONSE VARIABLES

Dependent Variable*	CBD† MD, Mean, ± SE	PBO† MD, Mean, ± SE	*p* Value‡
Chorea Severity (0–24)	11.5, 11.2, 1.4	13.7, 11.4, 1.4	0.71
Disability Score (13–0)	7.0, 6.9, 0.5	6.5, 6.7, 0.5	0.14
HD Staging Scheme (1–5)	3.0, 2.9, 0.1	3.0, 3.0, 0.1	0.18
Tongue Extension (seconds)	8.1, 16.5, 4.8	7.8, 16.6, 4.9	0.30
Finger Tapping (No. taps)	59.1, 64.9, 7.7	72.3, 66.1, 7.7	0.49
Screw-and-Nut Test (seconds)	68.7, 109.6, 18.9	71.1, 97.5, 16.9	0.22
Hopkins SCL-90R (0–360)	12.5, 20.0, 7.7	10.3, 15.5, 5.0	0.50
Average Recall (0–12)	4.6, 4.9, 0.5	5.9, 5.1, 0.5	0.90
Maximum Recall (0–60)	6.5, 6.0, 0.6	7.5, 6.4, 0.6	0.37
Maximum Storage (0–48)	10.8, 9.8, 0.6	11.3, 9.9, 0.6	0.58
Physician's Assessment (−100% to + 100%)	16.7, 13.9, 3.8	0.8, 8.9, 3.4	0.41
Patient's Assessment (−100% to +100%)	25.0, 29.7, 8.4	21.7, 32.4, 7.6	0.67

*Numbers and words in parentheses are the normal ranges and/or units of measure of the variables listed; HD = Huntington's disease; see the Method section for details.

†Numbers are the median (MD), mean, and standard error of the mean (± SE) values of the averaged treatment data in 15 HD patients (i.e., the scores of each patient were averaged over the 6 weeks of CBD and 6 weeks of PBO treatments, and the respective values were calculated from these averaged data).

‡Numbers are the two-tailed probability (*p*) of the difference between the CBD and PBO treatments as assessed by the Wilcoxon signed ranks test; associated z values, from top to bottom, were 0.38, 1.48, −1.34, 1.0, 0.68, 1.22, 0.40, −0.13, −0.89, −0.55, 0.82 and −0.43.

On the related issue, an evaluation of the correlations among these ("live") assessments and 2 (independent and blinded) videotape assessments of chorea severity was carried out. The correlation coefficients (rhos) were calculated by the Spearman rank-order correlation test, where values of rho can range from −1.00 to +1.00. For comparison of the assessments over the whole trial (15 patient evaluations each in baseline, CBD, placebo and posttreatment conditions), rhos of +0.74, +0.72 and +0.64 were calculated for live versus videotape-1, live versus videotape-2 and videotape-1 versus videotape-2 assessments, respectively. Further each of these correlations was statistically significant ($p<0.05$), indicating an acceptable level of interrater reliability.

The effects of CBD and placebo treatments on the secondary therapeutic response variables are presented also in Table 2. The median (mean and SE) values of CBD and placebo treatments are given for the S and F disability score, HD staging scheme, tongue extension test, finger tapping test, screw-and-nut test, Hopkins symptom check list (SCL-90R) total responses, B-F selective reminding tasks: measuring average recall, maximum recall, and maximum storage, physician's assessment of treatment, and patient's assessment of treatment. The magnitudes of the differences were relatively small, and the directions of treatment responses were generally inconsistent (i.e., favoring CBD on some measures and favoring placebo on others). Evaluation of the differences in treatments for all 11 of these variables yielded no significant differences (all *p* values were >0.05).

Effects of CBD and Placebo on Safety Variables

The major safety response variables were the clinical lab tests and the *Cannabis* side effect inventory. The former included about 70 individual measures performed under the categories of a blood chemistry 20 profile, complete blood counts and differential, platelet count, prolactin level and urinalysis. The *Cannabis* side effect inventory was comprised of 69 undesirable effects related specifically to marijuana intoxication and withdrawal. Very little detailed information is available on any clinical effects of CBD. Thus the relatively large number of dependent variables was used as a means for systematically seeking objective and subjective data which could relate to the safety of this novel drug.

For the clinical lab tests, each abnormal lab value for each patient which occurred in baseline, CBD, placebo and posttreatment conditions was cataloged. A visual inspection of these data indicated that many of the abnormal values occurred in non-CBD conditions, or occurred across conditions including the CBD treatment. It was reasoned that a major consideration was the occurrence of abnormalities specifically associated with the CBD treatment. Thus the data were sorted into CBD and non-CBD conditions. Table 3 presents a listing of the lab tests which yielded abnormal results exclusively in the CBD condition (i.e., an abnormal result occurring in the CBD condition but not occurring in baseline, placebo and/or posttreatment conditions). Quantitatively, there were only 15 abnormal lab values that could be associated with the CBD treatment. These occurred in only 12 of the 70 tests performed, and in only 8 of the 15 patients in the study. Four patients had multiple abnormalities accounting for the majority of the total abnormalities found. Qualitatively, the magnitude of virtually every abnormality was not greatly outside of the normal values for the respective test. Further, there were no obvious patterns to the abnormalities (and associated normal test results) either within or between the patients to suggest clinical problem or concern.

For the *Cannabis* side effects, patients reported whether they

TABLE 3

ABNORMALITIES OF PATIENTS' CLINICAL LAB TESTS OCCURRING ONLY DURING CANNABIDIOL (CBD) TREATMENT*

Lab Test (normal values)†	Patient's (abnormality)*
CO_2 Content (24–32 mmol/l)	J.H. (21.0)
Glucose-Blood (70–110 mg/dl)	F.D. (125)
Albumin-Serum (3.4–4.8 g/dl)	B.J. (5.1)/H.C. (3.3)
Iron (50–150 mcg/dl)	B.J. (44)/F.D. (167)
Uric Acid (3.5–7.2 mg/dl)	M.S. (3.3)
LDH (95–170 IU/l)	H.C. (189)
Alkaline Phosphatase (37–107 IU/l)	H.C. (167)/R.P. (110)
White Cell Count (4.0–11.0 × 1000)	H.C. (11.8)
Hemoglobin (12/14–16/18 g/dl)	N.S. (16.1)
Hematocrit (37/40–47/54%)	S.O. (36.9)
Platelet Count (150–350 × 1000)	N.S. (358)
Urine WBC (0–4/HPF)	F.D. (18)

*Patient's initials and abnormal lab value (in parentheses) listed represent a patient abnormality which occurred during the CBD treatment period and did not occur at any other time in the trial (i.e., baseline, placebo treatment and/or posttreatment periods).

†The lab tests and their associated normal ranges (in parentheses) were part of a larger test battery of a blood chemistry 20 profile, complete blood counts and differential, platelet count, prolactin blood level, and a standard urinalysis; abbreviations are CO_2-carbon dioxide, LDH-lactic dehydrogenase (serum), WBC = white blood cells, mmol-millimoles, l = liter, g = grams, dl = deciliter, IU = international units; HPF = high powered field.

did or did not experience (during the previous week) each of the 69 effects on the inventory. A visual inspection of the results indicated that virtually each of the 69 effects was reported by patients in both treatments. Thus the total number of the 69 effects reported by each patient (each week) first were summed over the 6 weeks each of CBD and placebo treatments. For the 15 patients, the total numbers (and individual ranges) of side effects were 477 (0–267) for CBD and 471 (0–207) for placebo. Subsequently, these data were averaged over the 6 weeks each of CBD and placebo for the purpose of statistical analysis. Table 4 presents the median (mean and SE) of CBD and placebo for these averaged data, and an assessment of the difference between the 2 treatments. As shown, there was no significant difference ($p = 0.98$; Wilcoxon test).

Table 4 also illustrates the effects of CBD and placebo on the other variables related to safety, i.e., recumbent mean blood pressure, recumbent pulse rate, upright mean blood pressure, upright pulse rate, and body weight. Once again, the magnitudes of the differences were small, and there were no significant differences between the two treatments (p values >0.05).

Plasma Levels of CBD

Figure 2 illustrates the mean (and SE) plasma levels of CBD in the HD patients over the 6 weeks of CBD administration and at 1 week following discontinuation of the drug. During the 6 weeks of CBD administration, CBD levels were present in low nanogram (ng) concentrations and were within a relatively narrow range. Mean levels ranged from a low of 5.9 ng/ml (with 95% confidence limits of 3.5–8.3 ng/ml) to a high of 11.2 ng/ml (with 95% confidence limits of 6.7–15.7 ng/ml). One week after CBD was discontinued, CBD levels were still present but at a much reduced concentration. The mean level was 1.5 ng/ml (with 95% confidence limits of 1.0–1.9 ng/ml). Statistical evaluation of these data (median levels over the 7 weeks were 5.5, 6, 6.25, 4.5, 8, 9.5 and 2 ng/ml, respectively) indicated a significant effect over time (Friedman test, $p = 0.0001$). Subsequent analyses between weeks (by the Nemenyi's test) revealed that the washout week was significantly different from each week of CBD administration ($p<0.05$, each comparison). However, there were no significant differences between weeks during the CBD administration (p values >0.05). Additionally, no CBD was detected in the placebo conditions, and no delta-9-THC was de-

TABLE 4

EFFECTS OF CANNABIDIOL (CBD) AND PLACEBO (PBO) TREATMENTS ON OTHER SAFETY RESPONSE VARIABLES

Dependent Variable*	CBD MD, Mean, ± SE†	PBO MD, Mean, ± SE†	p Value‡
Cannabis Side Effects (No.)§	3.7, 5.3, 2.8	2.5, 5.2, 2.3	0.98
Mean Blood Pressures (mmHg):			
Recumbent	91.9, 90.8, 2.8	90.6, 91.2, 2.5	0.61
Upright	91.6, 90.8, 2.9	89.8, 91.8, 2.6	0.28
Pulse Rates (beats/min):			
Recumbent	73.2, 76.4, 1.7	73.8, 73.7, 2.0	0.16
Upright	75.0, 77.9, 1.7	77.2, 75.4, 1.9	0.11
Body Weight (kg)	69.0, 67.9, 4.3	68.4, 67.6, 4.7	0.88

*Units of measure of the variables are in parentheses, i.e., No. = number, mmHg = mm of mercury, beats/min = beats/minute, and kg = kilograms; see the Method section for details.

†Numbers are the median (MD), mean, and standard error of the mean (± SE) values of the averaged treatment data in 15 Huntington's disease patients (i.e., the scores of each patient were averaged over the 6 weeks of CBD and 6 weeks of PBO treatments, and the respective values were calculated from these averaged data).

‡Numbers are the two-tailed probability (p) of the difference between the CBD and PBO treatments as assessed by the Wilcoxon signed ranks test; associated z values, from top to bottom, were 0.03, −0.51, −1.08, 1.39, 1.59 and 0.16.

§The summated (over 6 weeks each of CBD and PBO) number of *Cannabis* side effects for the 15 patients was 477 for CBD and 471 for PBO.

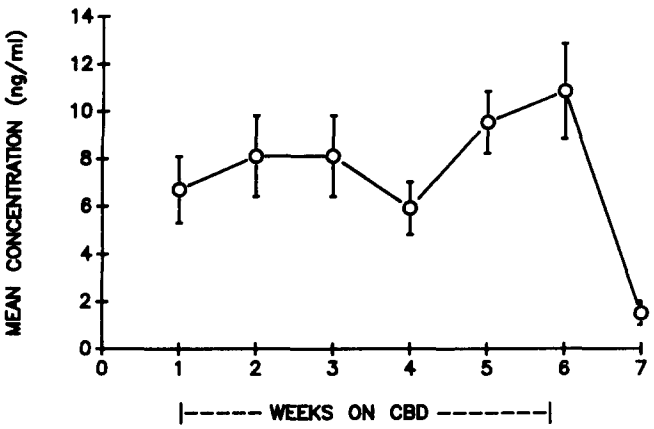

FIG. 2. Mean cannabidiol (CBD) plasma levels of Huntington's disease patients given CBD (10 mg/kg/day) for 6 weeks. The number 7 on the Abscissa is the week after discontinuation of CBD. Vertical lines are ± standard errors of the mean concentrations (open circles). Data are from 14 of our 15 patients (as 1 patient refused venopuncture/collection of blood for this assay).

tected in any condition of the trial (see Consroe et al., this volume).

Power of the Trial

Post hoc power calculations (12) were made for our major therapeutic response variable, M and Q chorea severity. The calculations were based on known parameters of a 0.05 alpha level, 15 subjects, and a SDd of 1.69 for the variable. The power for detecting a minor (delta of 2.5 units = 20% difference) and major (delta of 5.0 = 40% difference) therapeutic effect was 0.99 and 1.00, respectively. Correcting (i.e., subtracting) for the 5% power efficiency difference of the (Wilcoxon and Student's *t*) tests yielded power values of 0.94 and 0.95, respectively.

DISCUSSION

A major finding of the present controlled investigation was the ineffectiveness of CBD, given daily for 6 weeks, to reduce chorea severity, the major therapeutic outcome variable, in 15 patients with HD. Chorea severity was assessed by the same investigator using the M and Q chorea severity evaluation scale (7). Chorea severity values for CBD and placebo were virtually identical, and the extremely small difference between the two treatments was not statistically significant (Table 2). Additionally, overall comparisons between the "live" and 2 videotape evaluations of the latter chorea scale yielded correlations (rhos of .74 and .72) that were positive and statistically significant. The correlation between the 2 videotape assessments of the same dependent variable also was positive and significant, but was less marked (rho of .64). While these correlations were substantial, they were not as high as one might expect. One noticeable problem perceived during live evaluations of some patients was the occasional difficulty of interpretation between some of the adjacent scaled items on the evaluation instrument and the clinical presentation. This problem also occurred, and apparently to a greater degree, with the videotape assessments. Nevertheless, the positive trend and strength of association among the 3 assessments of chorea severity support the conclusion that there were no important differences between CBD and placebo on this variable.

Comparisons of CBD and placebo effects on the other therapeutic outcome variables [i.e., S and F disability score, HD staging scheme, tongue extension test, finger tapping test, screw-and-nut test, Hopkins symptom check list (SCL-90R), B-F selective reminding tasks, treatment assessments of both physician and patients] yielded similar findings of the ineffectiveness of CBD. As the statistical values of CBD and placebo clearly show (Table 2), the differences were relatively small, and not significant, for this relatively large number of measures. Further, the directions of treatment responses of CBD and placebo were generally inconsistent among these measures. For example, treatment responses favoring both CBD (e.g., lower median response on the screw-and-nut test; higher median response on the tongue extension test) and placebo (e.g., higher median responses on the finger tapping test and the memory tests) were observed. Motor impairments of HD are related in large part to the severity of chorea (14,17), and there is evidence that memory impairments of HD are related to, or at least correlate with, chorea severity as well (29). Inasmuch as these impairments appear to serve as indicators of chorea severity, the lack of any systematic trend for improvement of the motor and cognitive measures of the present study strengthens the view that CBD had no important effect on our major therapeutic outcome variable.

The lack of effectiveness of CBD in the present trial is obviously not a confirmation of the findings from our preliminary trial of CBD in 4 HD patients (26). The latter was the first investigation of CBD in HD patients, and as such, usual medical practice and requirements dictated a conservative study approach (notably, dose limitations, small number of patients, and a nonblinded and nonplacebo controlled design) for this little studied, investigational drug. Obviously, as several potential biases were not eliminated with this type of study, the preliminary results required a reassessment by a controlled trial. The present study controlled for (or at least minimized) potential biases due to investigator and patient expectations, order of assessments and treatments, and placebo treatment response. Also, standard evaluation instruments for HD (20,27) were used, and a sufficient evaluation period was employed to detect reliable drug effects, if present. We considered the detection of a 40% difference between CBD and placebo to be a major therapeutic effect, and the detection of a 20% difference to be a minor therapeutic effect. These differences were based on clinical impressions, and data (2) suggesting that a 20–40% improvement in chorea severity may be the expected range of maximal improvement with appropriate steady-state blood levels of haloperidol, a standard treatment of HD. From our power calculations, the probability of detecting major and minor therapeutic effects, if they existed, was 95% and 94%, respectively. In view of these considerations and of the trial data obtained, the results do not support a rejection of the therapeutic null hypothesis.

The effects of CBD and placebo on the safety variables were equally clear, showing no significant or clinically important differences. The clinical lab tests were major safety variables and the data clearly show that the abnormalities associated with CBD were few and were mostly just outside the normal ranges for the given tests (Table 3). There was no obvious specific abnormality or pattern of abnormalities which would suggest clinical concern, and we consider the abnormalities associated with CBD to be only random occurrences. The other major safety variable was the *Cannabis* side effect inventory, and the data indicate that side effects can be elicited when they are deliberately sought. Surprisingly, however, the patients' responses were relatively few over the course of the trial, and there was no significant difference between the CBD and placebo conditions (Table 4). The additional variables related to safety were the blood pressures, pulse rates and body weight, and there were no signifi-

cant differences between CBD and placebo on any of these measures (Table 4).

It was not totally unexpected to find that CBD was without side effects since previous investigations in humans have shown CBD to be completely devoid of typical *Cannabis*-like effects [e.g., (23)]. However, there have been only about 10 separate human investigations of CBD [see (8) for review], and most of these have used relatively low acute doses and have used very few outcome measures to assess the effects of the drug. Further, virtually all previous studies were uncontrolled, and no previous study has reported a detailed systematic-seeking of subjective or objective adverse effects. In view of these considerations, the present study was novel in its methods and in its findings. Concerning the latter, the results of the present study clearly do not support a rejection of the safety null hypothesis.

Considering the negative findings of CBD on both therapeutic and safety measures, there is a question of the possible adequacy of the oral dose and dosing schedule (ranging 400–1000 mg/day, for 6 weeks) used in the present study. These were based on published, albeit limited and preliminary, data (and on practical considerations). We had utilized CBD in dose escalations of 100–600 mg/day over 6 weeks (7) and 300–600 mg/day over 4 weeks (26) in dystonic and HD patients, respectively. Others had used CBD in doses of 600 mg/day up to 12 days in normal subjects (3), and 200–300 mg/day up to 4.5 months in epileptic patients (10). These were the highest and/or longest repeated dosing regimens of CBD previously used; moreover, they were used with apparent benefit and/or without apparent side effects. Thus we considered the present doses and dosing schedule to be reasonable for therapeutic and safety concerns. (Also, because of governmental concern over the lack of published data on the human safety of CBD, these were the highest repeated doses that were allowed for our trial).

Dose, blood level, and clinical effect are inextricably linked, and the present study is the first to report combined measurements of CBD effects and blood levels after repeated daily dosing of the cannabinoid. A detailed discussion of the pharmacokinetic implications of these findings is presented in a companion paper (Consroe et al., this volume). Additionally, the following are some conspicuous points about the plasma level data (Fig. 2) which specifically relate to the present clinical findings.

Firstly, the CBD plasma levels were in the low ng range following high (mg) dose oral CBD. This supports the view that the oral bioavailability of CBD in humans may be very low, perhaps only about 6% (1,21). Whether the low systemic availability is due to a first pass effect, as has been shown in the dog (25), or to incomplete absorption, will require additional study. Nevertheless, the present data indicate that CBD did reach the blood (and presumably the brain), and that our patients were compliant in taking their CBD on schedule.

Secondly, the plasma levels of CBD were relatively constant, and not reliably different, over the 6 weeks of administration of the drug. This suggests that there was a steady-state condition for CBD, and thus the clinical measures were not influenced by significant fluctuations of CBD blood levels.

Lastly, the plasma levels of CBD were very low after 1 week following CBD discontinuation, and were undetectable during placebo administration. These findings indicate that our (a priori) choice of a 1 week washout period between CBD and placebo was appropriate, and did not cause a drug crossover effect.

In conclusion, CBD is neither symptomatically beneficial nor toxic in patients with HD. While CBD might have promise in other conditions such as epilepsy and dystonia, its therapeutic efficacy must be established by similar rigorous double-blind, well-controlled clinical trials.

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