

Differential Effects of Medical Marijuana Based on Strain and Route of Administration: A Three-Year Observational Study

Valerie Leveroni Corral

SUMMARY. Cannabis displays substantial effectiveness for a variety of medical symptoms. Seventy-seven patients took part in a study in California to assess the efficacy of organically grown *Cannabis sativa* and *indica* strains in treatment of various medical conditions via smoking or ingestion. HIV/AIDS was the most frequent condition reported, at 51%. Standardized rating forms provided 1892 records that were statistically analyzed. Results demonstrated that in the case of nausea and spasm, symptom expressions are definitely affected by various methods of cannabis administration. However, while *Cannabis indica* strains increased energy and appetite, it is useful to note that in treating nausea in HIV/AIDS and orthopedic diagnosis groups, *Cannabis sativa* and *C. indica* strains proved equivalent. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <<http://www.HaworthPress.com>> © 2001 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Cannabis, medical marijuana, *Cannabis sativa*, *Cannabis indica*, AIDS, HIV

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INTRODUCTION

Marijuana, whether *Cannabis sativa* or *Cannabis indica*, produces its medical and other effects by virtue of the concentration and balance of various active ingredients, especially the cannabinoids, which are unique to marijuana, but also including a wide range of terpenoids and flavonoids. Terpenoids are cannabis constituents that provide the characteristic strong odor of marijuana and hashish. Flavonoids are any of the flavone derivatives. The concentration and relative proportions of these ingredients depend on the plant's genetic structure and applied hybridization techniques, and as such, allow for a substantially varied outcome.

Little is known about how differences in constituent profiles translate into differences in therapeutic effectiveness. A range of effects has been ascribed to THC (tetrahydrocannabinol is the primary psychoactive component of marijuana) and CBD (cannabidiol, a compound related to THC) when administered in purified form. Studies are lacking on the differential clinical effects produced when varying "menus" of constituents are taken together.

Another factor bearing on the effects and the effectiveness of marijuana is the route of administration. Orally administered marijuana is absorbed more slowly than when delivered systemically (e.g., smoking, vaporizers). Moreover, the liver metabolizes orally ingested marijuana to produce a potent and long-acting cannabinoid (11-hydroxy-THC), which induces varied reactions in medical marijuana patients and is often not well tolerated. However, once more, there is little information available concerning the differential clinical effects of oral vs. smoked forms of marijuana.

A major obstacle to obtaining data concerning differential clinical effects is, of course, the illegality of medical marijuana use. Almost equally troublesome, however, is the widespread view that medical knowledge can be gained only through randomized controlled trials. It is becoming increasingly accepted that valid causal inferences can be, and frequently are drawn quite regularly in medicine without such studies. As such, observational studies are quite capable of generating useful information, provided due care is taken to keep careful track of the process. In this case, careful and consistent documentation would be required concerning: (1) which forms of marijuana are being taken and by what route, and (2) what outcome is experienced by patients.

The passage of Proposition 215 in California in 1996 legalized medical marijuana under state law, thus clearing some legal obstacles to research. Prior to the passage of Proposition 215, two or more cannabis buyers' clubs and our collective comprised of patients and caregivers were in operation. Several provider associations have been operating since that time despite harassment of some by law enforcement agencies.

Valerie Leveroni Corral founded the Wo/Men's Alliance for Medical Marijuana (WAMM) in 1993. WAMM is a collective of patients and caregivers attempting to create community, build hope, dissolve barriers, and provide support and medical marijuana at no cost to patient members who possess a signed and verified recommendation from a physician licensed to practice medicine in California. A genetically-monitored, organic, communal garden is tended by WAMM client/ participants under the direction of Mike Corral and Valerie A. Leveroni Corral.

A primary function in this community based educational system is the creation of a database of information regarding the treatment of different symptoms with distinct cannabis varieties. This is achieved through daily effectiveness surveys and statistical analysis (Appendix, Tables 17 and 18). Our present collection of data also includes measures of effectiveness of cannabis on autoimmune illnesses, such as systemic lupus erythematosus, as well the many other disorders, including muscular dystrophy, epilepsy, quadriplegia, paraplegia, Parkinson's disease, glaucoma, arthritis, fibromyalgia, depression and migraine. However, AIDS and HIV-related conditions are the most frequently represented among our clientele.

WAMM initiated a study in 1993 designed to address the question of differential clinical effects between *Cannabis sativa* and *C. indica* strains and hybrids, and also examining effects of inhaled and ingested routes of administration. This study is ongoing and now includes "blind" trials where the varieties used are not apparent to the participating patient. A statistician generated all presented analyses.

MATERIALS AND METHODS

The determination of the variety of cannabis was based on the country of origin of the seeds strains and physical characteristics of each plant variety. We assure the genetic purity through carefully controlled breeding techniques, substantiated by twenty-five years of experience in cultivation and propagation of cannabis. Personal interaction took place with patient use of cannabis in more than one hundred different terminal cases.

An assessment instrument form is provided weekly to participating patients (see Tables 17 and 18). The patient places a label from a weekly supply on the seven day form, denoting the variety and form of cannabis (inhaled or ingested), the number of "puffs" if inhaled medicine is used and the amount or weight employed. All participants were instructed in a specific method of inhaling. Patients were requested to use and denote dosages correlated to the relief of specific symptoms. Participants observed and rated symptoms before and after cannabis use to assess their severity. This was done upon rising from

sleep in all cases except “insomnia” and prior to using any cannabis. Assessments were made weekly, at minimum, or as much as seven times per week, in order to assess effectiveness and of different strains upon different target symptoms.

Findings were derived from data gathered during the time period of June of 1993 into early 1997. Statistical analysis consisted of frequency analysis, paired T-tests of “before” and “after” scores on each measured symptom or condition, and a series of one-way ANOVAs on route of administration (either inhaled or ingested), cannabis strain, and diagnosis.

Because the therapeutic effects of cannabis are sometimes ascribed to its mood-altering effects, we also performed a correlation analysis of the change in mood score with other outcome variables.

Inhalation methods of cannabis consisted mostly of smoking, with some use of vaporization, although patient reports of effectiveness appear substantially lessened when this technique was employed. This could certainly depend on the quality of the vaporizer design.

Ingested forms of cannabis consisted of baked goods and “mother’s milk” (a soymilk-based liquid), and a whole cannabis tincture made with pure grain alcohol with leaf or a combined blend of leaf and flowers. Strains of marijuana were *C. sativa* and *C. indica* and their hybrids. The morphological distinction between these strains was determined by experienced cannabis cultivators associated with WAMM, based on characteristic features of the two sub-species, varieties or strains.

These sub-species varied from week to week and included the following pure strains and hybrid strains: *C. sativa*, *C. indica*, as well as hybrids of both, being the identified female *C. sativa* × male *C. indica*, as well as the identified female *C. indica* × male *C. sativa*. We secured a method of analysis of the chemical content of test materials, although we believe that the findings may be subject to error. Results from a drug detection laboratory indicated that *C. sativa* measured: THC 23.7%, CBD < 0.1% and CBN < 0.1%. Results indicated that *C. indica* strains measured: THC 19.6%, CBD < 0.2% and CBN < 0.5%. Cannabis potency testing results by ElSohly Labs of the same sample of *C. sativa* after storage for eight months yielded a value of THC 17.6%.

RESULTS

Seventy-seven patients completed a total of 1892 forms (range 1-256, median 8) during the three-year study period. Of these, 43 were male (56 percent), 22 were female (29 percent) and 12 were not coded as to gender. The distribution of primary diagnoses is presented in Table 1.

Thirty-nine patients (51 percent) had HIV/AIDS; 14 (18 percent) had neurological diseases, and 7 (9 percent) had a principle diagnosis of cancer.

To avoid biasing results due to a large proportion of questionnaires being completed by relatively few patients, we standardized the analysis by reviewing a maximum of eight records per patient, the median number completed by study subjects. These records were randomly chosen. Accordingly, our analysis contained 432 records. Of these, 261 (61 percent) referred to *C. sativa* experiences; 65 (15 percent) were *C. indica*, while 105 (24 percent) were coded “other.” Certain types of marijuana were donated or undeclared, we labeled these as “other” and included them in our findings. Ingested forms were also recorded (Table 4). Some entries were coded with missing information, entered as slang or incorrectly named; these were excluded.

Paired t-tests of before and after health status revealed that the following symptoms were relieved to a statistically significant extent by therapeutic cannabis (without regard to strain or route of administration): pain, energy, mood, nausea, appetite, and awareness. The remaining symptoms were not reliably relieved to the same extent. Table 5 and Table 6 show the scores on each variable. The magnitude of improvement was unrelated to clinical diagnosis, as determined in ANOVA (Table 10), with one exception: the degree of relief of nausea was greater in the HIV/AIDS group (4.54 units) than in the orthopedic group (1.58 units) to a statistically significant extent ($p = 0.04$).

We next performed ANOVA on the strain of marijuana ingested: *C. sativa* and *C. indica*. The mean change scores, “before” scores minus “after” scores for patients with each condition, were calculated. For the most part, some observed changes were unrelated to strain of marijuana. However, two symptoms, energy and appetite, were improved to a statistically greater extent by *C. indica* than by either *C. sativa* or “other.”

C. indica produced a mean improvement in energy of 3.76 units (vs. 1.53 for *C. sativa* and 2.22 for “other”) and a mean improvement in appetite by 5.22 units (vs. 3.41 for *C. sativa* and 4.32 for *C. indica*). These differences were significant at the 0.012 and 0.005 levels, respectively (Table 8).

ANOVA was then conducted using route of administration as the independent variable (Tables 6 and 7). For the most part, ingested and inhaled marijuana had similar magnitudes of effects. Only one symptom, spasm, showed preferential improvement using smoked over ingested marijuana ($p = .036$) (Table 6). Patients reporting “other” routes of administration had substantially less relief of nausea than patients inhaling or ingesting marijuana (Table 7).

It is reported that THC may reduce spasms associated with both neurological and non-neurological disorders (Hollister, 1986; British Medical Association Report, 1997). It is interesting to note that the non-psychoactive cannabinoid cannabidiol has been shown to exhibit anticonvulsant properties in certain animal studies. In the case of some patients it has been noted to reduce or prevent

the onset of both spasms and seizures when used alone or as an adjunct medicine. It appears that there are receptor sites for cannabinoids that have beneficial effects on seizure activity.

Finally, analysis of the Pearson correlation coefficients between changes in mood scores and changes in other symptom scores revealed only a single statistically significant correlation, between mood and energy level ($p = 0.035$). Mood was not correlated with any other outcomes, including pain relief ($p = 0.817$) (Table 11).

DISCUSSION

We analyzed 432 records of therapeutic cannabis exposures, including information on strain (*C. sativa*, *C. indica*, or other), and route of administration (inhaled, ingested or other). The outcome variables consisted of scores to a series of questions on symptoms, completed by the patient both before and after administering cannabis medicines.

Results indicate that cannabis was uniformly effective in relieving symptoms across a wide range of diagnostic categories. No differences were observed in the extent to which symptoms were relieved based on diagnosis, except that patients with HIV/AIDS experienced more relief of nausea than patients with primary orthopedic diagnoses (Table 13).

On several occasions, terminally ill patients remarked upon a recurrent phenomenon, described as a “shift in consciousness” or “perception” allowing them to approach their impending death more “openly” or in a more “relaxed” manner. This is of particular interest, as each patient also reported a reduction in anxiety often associated with the dying process. Future studies will further examine measures anxiety in the cannabis patient population.

C. indica appeared to be superior to *C. sativa* and “other” in improving energy and appetite (Table 9). Otherwise, no differences in strain effects were observed. Route of administration had little effect on outcome in our series. Two symptoms, spasm (Table 6) and nausea (Table 7) showed preferential improvement with smoking as compared to ingestion. In no condition was the ingested route superior to smoking for symptom management.

Changes in mood were not correlated with changes in other outcomes except for a modest correlation with energy (Table 11). The finding that mood did not correlate with other outcomes casts doubt on the theory that therapeutic cannabis effects are related primarily to improvement in mood. Conversely, this may pertain with the notion suggested by some patients that mood is not necessarily correlated to the concept of “feeling better.” In our findings, it appeared that mood was often independent of symptom expression. This result is interesting because it appears in written testimony by patients in their surveys that they believe

changes in awareness or consciousness do affect overall healing. We plan to further examine the validity of these phenomena in future studies.

These findings support that few differences were noted by patients between *C. sativa* and *C. indica* strains and between ingestion vs. inhaled routes of administration. This is likely due to modest observed differences in cannabinoid content in the supplied strains. We hope that a reliable and accessible means of analysis will become available in the near future to further assess these hypotheses.

This study is limited by the lack of blinding. For this reason, in 1998 a revised protocol was instituted in which patients receive a one-week supply of therapeutic cannabis at a time without knowledge of particular variety provided. Patients continued completing forms on a weekly basis. This method of blinding is expected to provide a more rigorous test of any distinctions between *C. sativa* and *C. indica* strains. Results may have implications for subsequent crossbreeding of strains to maximize therapeutic effects.

This study is only a small first step in the attempt to develop improved cannabis medicines for affected patients. The most significant current limitation to this type of research is the absence of a convenient legal mechanism in the USA for analyzing cannabis samples for biochemical constituent content. Until this limitation is overcome, progress in this area will be slow at best.

On the other hand, we should not underestimate the value of clinical observation in judging cannabis strains and their differential clinical effects irrespective of chemical content. Thus, while the work we report here does not definitively address issues of chemical variability, we believe that our findings provide at the very least a good working hypothesis for use in future studies.

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APPENDIX

Purpose of the Project

- To determine if there are physical, mood and perception changes resulting from use of the test article.
- To determine if the method of delivery affects measures of effectiveness.
- To determine if different types of cannabis affect diagnoses and measures of effectiveness.
- To assess the correlation between changes in mood and other measures of effectiveness.

Summary of Population

N = 77

43 males (56%)

22 females (29%)

12 missing gender distinction (15%)

TABLE 1. Description of Population by Primary Diagnosis

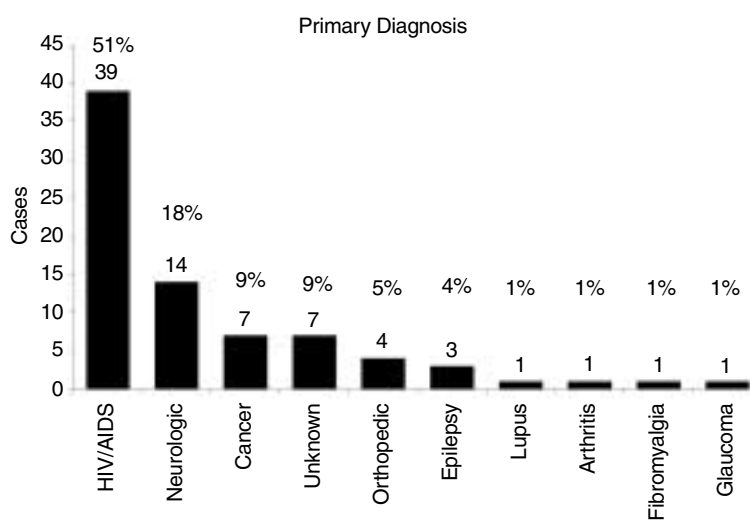


TABLE 2. Description of Patient Population by Secondary Diagnosis

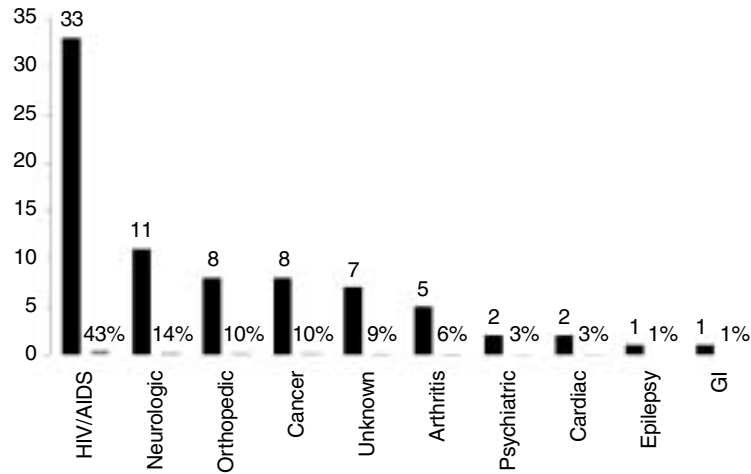


TABLE 3. Questionnaire Structure Measures of Effectiveness

Variable	None	Most	Desired Effect
Pain	1	10	Decrease
Energy	1	10	Increase
Mood	1	10	Increase
Nausea	1	10	Decrease
Appetite	1	10	Increase
Muscle Spasms	1	10	Decrease
Seizures	1	10	Decrease
Ocular	1	10	Decrease
Insomnia	1	10	Decrease
Awareness	1	10	Increase
Neuropathy	1	10	Decrease

Questionnaire Logistics

- 1892 Questionnaires Completed over 3 years
 - Range of 1 to 256 questionnaires
 - Average of 8 questionnaires/patient
 - Analysis completed based on the average number of questionnaires completed (to normalize data for analysis)

TABLE 4

Statistical Methods

- 432 questionnaires analyzed
- Frequency analysis, Paired t-tests, Paired t-test correlations, One Way ANOVA, Post-Hoc (Bonferroni), Pearson Correlation and Multivariate tests performed
- One Way ANOVA conducted on variables using the following 3 groups
- Group 1—test article “ingested”
 - Muffins
 - Mothers milk
- Group 2—test article “inhaled”
 - African Queen
 - Purple Indica
- Group 3—“Other”
- One Way ANOVA performed on the following test article groups:
 - Sativa (261–61%)
 - Other (105–24%)
 - Indica (65–5%)
- Multivariate Tests performed for type of Cannabis, diagnosis, and change in variable
 - Pillai’s Trace
 - Wilks’ Lambda, and
 - Tests of Between-Subjects Effects
- One Way ANOVA, Bonferroni, Post-Hoc tests performed for definition of diagnosis and treatment effectiveness

All tests performed using SPSS (Statistical Program for Social Scientists) Version 9.0

TABLE 5

Question One

- Are there physical, mood and perception changes resulting from use of the test article?

Paired Samples t test

- Comparing means before and after
95% confidence interval (2-tailed)

Variable	Before	After	Difference
Pain	6.98	3.26	-3.72 3
Energy	4.12	6.04	1.92 3
Mood	4.30	7.32	3.02 4
Nausea	7.06	2.78	-4.28 3
Appetite	3.02	6.96	3.94 4
Awareness	5.73	6.97	1.24 3
All are significant			

TABLE 6

Question Two

- Does change in variable vary by method of treatment: ingested, inhaled or other?

Question Two—Means of Variable Changes by Mode of Consumption

	1	2	3	p
Pain	-3.75	-3.45	-3.67	0.274
Energy	2.05	1.14	1.18	0.630
Mood	2.98	2.54	3.81	0.840
Nausea	-4.39	-4.50	-2.22	0.934
Appetite	4.05	2.94	3.28	0.418
Spasm	-3.42	-3.95	-3.60	0.008*
Seizure	-0.14	N/A	-4.75	0.177
Ocular	-2.63	-2.54	-2.86	0.099
Insomnia	-3.88	-3.44	-4.28	0.036*
Awareness	1.31	-0.41	1.72	0.259

*Significant

ANOVA**Question Two**

Examination of the mean change (One way Anova-95% confidence interval)

Significance was found for the following variables

Spasm p = 0.008

Insomnia p = 0.036

TABLE 7

Interpretation of ANOVA Method of Test Article Delivery

- Group 1 is different than group 3.
- Average group 1 (ingested) = -4.39.
- Average group 2 (inhaled) = -4.50.
- Average group 3 (other) = -2.20.
- There is greater improvement in nausea (0.36) with ingestables vs. "other."
- Ingestables and inhaled groups are not different.

TABLE 8

Question Three

- Are changes in variables related to the different types of cannabis and primary diagnoses?

Mean Change of Variables in Treatment Test Article Groups

	Other	Sativa	Indica	p
Pain	-3.49	-3.99	-2.93	0.078
Energy	2.22	1.53	3.06	0.012*
Mood	2.94	2.89	3.76	0.327
Nausea	-4.67	-4.19	-4.01	0.470
Appetite	4.32	3.41	5.22	0.005*
Spasm	-4.33	-3.53	-2.23	0.071
Seizure	-0.67	-2.12	0.50	0.316
Ocular	-3.27	-2.34	-3.00	0.646
Insomnia	-4.53	-3.82	-3.18	0.221
Awareness	1.75	0.96	1.24	0.173

One Way Anova-95% CI

*Significant

TABLE 9

Interpretation of ANOVA Method of Test Article Treatment Group

- The Indica Group is different than Sativa Group
 - Average Indica = 3.06
 - Average Sativa = 1.53
 - Average Other = 2.22
- There is greater improvement in energy (0.012) with Indica vs. Sativa and "Other."
- Sativa and Other treatment groups are not different.

Interpretation of ANOVA Treatment Group

- Indica was more effective to increase energy and appetite in any primary diagnosis group.
- Use of any test article was effective in treating Nausea in the Orthopedic and HIV/AIDS diagnosis group.

TABLE 10

Mean Change in Variable by Primary Diagnosis

	Ortho	Neuro	AIDS	Other	Cancer	p
Mood	4.36	4.05	2.87	1.33	2.64	0.001*
Pain	-4.93	-4.02	-3.31	-3.90	-3.27	0.011*
Energy	3.54	1.33	2.31	1.07	1.23	0.017*
Mood	4.36	4.05	2.86	1.33	2.64	0.094
Nausea	-1.58	-4.21	-4.54	-3.97	-4.18	0.015*
Appetite	4.57	3.50	4.44	3.08	3.00	0.010*
Spasm	-4.17	-4.05	-1.83	-3.29	-4.91	0.401
Seizures	NA	-1.86	-0.89	NA	NA	0.001**
Ocular	NA	-2.91	-2.00	-4.00	NA	0.334
Insomnia	-4.68	-4.66	-3.49	-2.93	-5.08	0.000*
Awareness	2.21	1.07	1.15	0.65	2.25	0.000*

One Way Anova 95% CI

*Significant

**Small sample size unable to correlate

TABLE 11

Interpretation of ANOVA Method for Primary Diagnostic Group

- The Orthopedic and Neurological group are different than the "Other" primary diagnostic group.
- There is greater improvement in Mood ($p = 0.008$) for the Orthopedic group vs. "Other."
- There is greater improvement in Mood ($p = 0.001$) for the Neurological group vs. "Other."

Average Orthopedic	4.36
Average Neurological	4.04
Average HIV/AIDS	2.87
Average "Other"	1.33
Average Cancer	2.64
- There is no difference between the AID/HIV and Cancer groups.

TABLE 12

Interpretation of ANOVA Method for Primary Diagnostic Group

- The Orthopedic group is different than the "Other" primary diagnostic group.
- There is greater improvement in Energy ($p = 0.43$) for the Orthopedic group than "Other."

Average Orthopedic	3.54
Average Neurological	1.33
Average HIV/AIDS	2.31
Average "Other"	1.07
Average Cancer	1.23
- There is no difference between the Neurological, AID/HIV, and Cancer groups.

TABLE 13

Interpretation of ANOVA Method for Primary Diagnostic Group

- The HIV/AIDS group is different than the Orthopedic primary diagnostic group.
- There is greater improvement in Nausea ($p = 0.04$) for the HIV/AIDS group than Orthopedic primary diagnostic group.

Average Orthopedic	-1.58
Average Neurological	-4.21
Average HIV/AIDS	-4.54
Average "Other"	-3.97
Average Cancer	-4.18
- There is no difference between the Neurological, Other, and Cancer groups.

TABLE 14

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Appetite (0.010) for all diagnostic groups.
- There is no difference in mean change for the Appetite variable for specific primary diagnostic groups.

Average Orthopedic	4.57
Average Neurological	3.50
Average HIV/AIDS	4.44
Average "Other"	3.08
Average Cancer	3.00

TABLE 15

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Insomnia ($p = 0.000$) for all diagnostic groups.
- There is no difference in mean change for the Insomnia variable for specific primary diagnostic groups.

Average Orthopedic	-4.68
Average Neurological	-4.66
Average HIV/AIDS	-3.49
Average "Other"	-2.93
Average Cancer	-5.08

TABLE 16

Interpretation of ANOVA Method for Primary Diagnostic Group

- There is improvement in Awareness ($p = 0.000$) for all diagnostic groups.
- There is no difference in mean change for Awareness specific to primary diagnostic groups.

Average Orthopedic	2.21
Average Neurological	1.07
Average HIV/AIDS	1.15
Average "Other"	0.65
Average Cancer	2.25

Correlation Analysis Question Four

- Is change in mood correlated to change in energy?
p = .035*
- Is change in mood correlated to change in pain?
p = .817
- Is change in mood correlated to change in nausea?
p = .434
- Is change in mood correlated to change in insomnia?
p = .647
- Is change in mood correlated to change in awareness?
p = .073

*Significant

Conclusions

- There were observed changes in pain, energy, nausea, appetite, and awareness variables from the use of the test article.

TABLE 18

Comments: (Use additional sheets of paper as needed. We are very interested in your comments.)

Instructions

Each day of the week, fill in the information BEFORE you take your medication for the first time in the day, and then again AFTER you take your medication for the first time of the day. Using a scale of 1 to 10, with **1 meaning WORST** and **10 meaning BEST**, mark how you are feeling in the spaces provided. If the condition (symptom) improves, the number goes up.

Notice that the week begins on Wednesday in order to synchronize with our weekly meetings on Tuesdays.

If a condition does not apply to you, simply leave it blank.

Make sure to fill in at least one date.

Terminology

Appetite	Desire for food or drink	Medicine type	The code that appears on your medicine container or medicine name such as milk, muffins, brownies, buds.
Awareness		Mood	State or quality of feeling at a particular time. Prevailing emotional tone or general attitude
Best	Subjective experience of highest quality	Nausea	Sickness at the stomach, especially when accompanied by a loathing for food and an involuntary impulse to vomit.
Consciousness		Neuropathy	Symptoms of a diseased nervous system like tingly sensations.
Diagnosis	Name of disease such as cancer, HIV, glaucoma	Ocular pressure	Pressure within the eye
Dosage	Number of dosage units	Pain	Physical suffering or distress
Dosage unit	Name of dose, such as puffs, ounces, grams, bites, drops, fraction of weekly allotment (for example 1/7 means 1/7 of the weekly allotment.	Seizures	A sudden attack, as of epilepsy or some other disease
Energy	Capacity for vigorous activity	Spasms	Sudden, abnormal, involuntary muscular contraction
Gender	Male, female, transgendered	Worst	Subjective experience of lowest quality
Insomnia	Inability to sleep		
Libido	Sexual instinct or drive		

Developed by Rick Sinatra