JAOA ORIGINAL CONTRIBUTION

Cannabimimetic Effects of Osteopathic Manipulative Treatment

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Endogenous cannabinoids activate cannabinoid receptors in the brain and elicit mood-altering effects. Parallel effects (eg, anxiolysis, analgesia, sedation) may be elicited by osteopathic manipulative treatment (OMT), and previous research has shown that the endorphin system is not responsible for OMT's mood-altering effects. The authors investigate whether OMT generated cannabimimetic effects for 31 healthy subjects in a dual-blind, randomized controlled trial that measured changes in subjects' scores on the 67-item Drug Reaction Scale (DRS). Chemical ionization gas chromatography and mass spectrometry were also used to determine changes in serum levels of anandamide (AEA), 2-arachidonoylglycerol (2-AG), and oleylethanolamide (OEA). In subjects receiving OMT, posttreatment DRS scores increased significantly for the cannabimimetic descriptors *good, high, hungry, lightheaded,* and *stoned,* with significant score decreases for the descriptors *inhibited, sober,* and *uncomfortable.* Mean posttreatment AEA levels (8.01 pmol/mL) increased 168% over pretreatment levels (2.99 pmol/mL), mean OEA levels decreased 27%, and no changes occurred in 2-AG levels in the group receiving OMT. Subjects in the sham manipulative treatment group recorded mixed DRS responses, with both increases and decreases in scores for cannabimimetic and noncannabimimetic descriptors and no changes in sera levels. When changes in serum AEA were correlated with changes in subjects' DRS scores, increased AEA correlated best with an increase for the descriptors *cold* and *rational,* and decreased sensations for the descriptors *bad, paranoid,* and *warm.* The authors propose that healing modalities popularly associated with changes in the endorphin system, such as OMT, may actually be mediated by the endocannabinoid system.

Osteopathic principles and philosophy are based on an appreciation of human beings' triune unity (body, mind, and spirit), the interrelationship between structure and function, and the body's ability to heal itself.[1] Osteopathic physicians employ the entire therapeutic armamentarium of traditional Western medicine while maintaining a "holistic" or patient-centered approach. Osteopathic physicians augment standard medical interventions with osteopathic manipulative treatment (OMT), the skillful and dexterous use of the hands.

The founder of osteopathic medicine, Andrew Taylor Still, MD, DO, originally intended the discipline to be a drugless school of medicine. In his autobiography (1897), Still wrote, "Man should study and use the drugs compounded in his own body."[2] Still hypothesized that manipulative treatment stimulated the production of endogenous compounds that promoted homeostasis and healing.

Candace B. Pert, PhD, the biochemist who discovered the endorphin receptor in 1972, suggested that massage and manipulation trigger a release of neuropeptides in patients.[3] However, three subsequent studies tested whether OMT augmented neuropeptide levels (enkephalins and β-endorphins) and found no effects.[4–6] Although one chiropractic study reported an increase of plasma β-endorphin in patients after spinal manipulation,[7] two later studies failed to confirm these findings.[8,9]

Investigators have begun studying the relationship between OMT and the endocannabinoid system.[10] The endocannabinoid system, like the better-known endorphin system, consists of neuroreceptors (cannabinoid receptors) and their endogenous ligands (endocannabinoids).

The best-known endocannabinoids are anandamide (arachidonylethanolamide) (AEA) and 2-arachidonoylglycerol (2-AG). Oleylethanolamide (OEA), a natural analogue of AEA, does not bind to cannabinoid receptors; instead, it

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Dr McPartland presented results from this study at the plenary session of the 2005 Symposium on the Cannabinoids of the International Cannabinoid Research Society in Clearwater Beach, Florida, on June 25, 2005, under the title "Cannabimimetic effects of elevated serum anandamide levels from osteopathic manipulation." Study results were also reported by Dr McPartland at the annual convocation of the American Academy of Osteopathy in Reno, Nevada, on March 19, 2005, and titled "The endocannabinoid system and osteopathic manipulative treatment."

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binds to the peroxisome-proliferator-activated receptor (PPAR-α), a nuclear receptor that regulates several aspects of lipid metabolism, and regulates satiety and body weight.[11] In rodent studies, the administration of AEA induced changes in locomotor activity, antinociception, hypothermia, and catalepsy, known as the "cannabimimetic tetrad."[12]

Anandamide is mimicked by an exogenous plant compound, Δ9-tetrahydrocannabinol (THC). The effects of THC and AEA substantially overlap in rodent behavioral studies.[13] Anandamide has not yet been clinically tested in humans, so its effects are unknown; but THC's well-known effects on humans include anxiolysis, easement of suffering, increased sense of well-being, and euphoria,[14,15] which are sensations not easily measured in rodent studies. In human subjects, the effects of THC have been measured with a neuropsychological questionnaire, the 67-item Drug Reaction Scale (DRS).[16]

Osteopathic manipulative treatment has long been reported to induce psychotropic changes that resemble the aforementioned reactions induced by THC.[17–19] Recently, it has been proposed that OMT generates these reactions by stimulating the release of AEA.[19,20] A small, uncontrolled clinical trial (n=1, 5 replications) showed that OMT elicited cannabimimetic effects that were measurable when the DRS was administered.[10]

A conceptually related study demonstrated that the subjective sensation of "runner's high" in humans correlated with a rise in serum AEA levels.[21] Runner's high has commonly been attributed to changes in serum β-endorphin levels, but recent studies have not confirmed this hypothesis.[22]

We hypothesized that OMT and other healing modalities associated with the endorphin system—such as acupuncture, chiropractic, massage, and meditation—may actually be mediated by the endocannabinoid system.

The purpose of the current study is twofold: (1) to assess the cannabimimetic effects of OMT by measuring subjects' DRS responses and serum AEA levels in a dual-blind, randomized controlled trial, and (2) to correlate changes in serum AEA levels with changes in subjects' results on the DRS.

Methods

Subjects

The institutional review boards at Unitec (Auckland, New Zealand) and the University of Texas (San Antonio) approved the study protocol prior to subject recruitment. All subjects provided written informed consent. All work was conducted in accordance with the Declaration of Helsinki.[23]

Inclusion criteria required subjects to be: (1) in good health, (2) aged 18 to 80 years, (3) able to read the DRS, its accompanying information sheet, and the informed consent statement in English, and (4) have previous experience with OMT as a treatment modality. Subject exclusion criteria were: (1) previous adverse effects from OMT, (2) currently receiving OMT in the treatment of acute or chronic conditions, or (3) contraindications to blood sampling, including fear of needles.

Sample size was based on a power analysis conducted by one of the present study's authors (A.G.) for a previous experiment using similar analytical methods.[21]

Subjects were 31 volunteers who were recruited and enrolled within one month of the experiment by convenience sampling from the patient population of one New Zealand osteopath (J.K.). Subjects were selected to reflect clinical realities (ie, a generalizable patient population), and were not restricted (homogenized) to a specific demographic group by age or sex.

In addition, although risks associated with OMT are minimal,[24] safety was given a high priority during the design phase of the study. Therefore, as noted in the exclusion criteria, we recruited subjects who had previous experience with OMT but had no history of adverse effects with that treatment modality. Finally, as noted, no subjects were undergoing treatment for acute or chronic conditions at the time of the experiment.

Subjects were unpaid volunteers. The only incentive to participate in this study was one free session of OMT (NZ $60–$100 value).

Some osteopathic manipulative (OM) and sham manipulative techniques used in this study involved prolonged handling of the top of the head—an area of the body considered *tapu* (ie, sacred) by New Zealand's native Maori people. Consistent with these cultural considerations regarding the cranial area of the body, and as delineated by the Treaty of Waitangi,[25] all potential subjects were informed of this aspect of the study and were reminded of their ability to withdraw from the study at any time should they so desire.

Interventions

Subjects received OMT (n=16) or control (sham manipulative) treatment (n=15), randomized by assignment of sealed envelopes with a numeric coding sequence that was concealed until interventions were assigned.

To enhance blinding of subjects, we used a calculated deception protocol. As noted, all subjects were recruited from the patient population of a New Zealand osteopath (J.K.) who regularly uses direct OM techniques such as myofascial release; muscle energy; joint articulation; and high-velocity, low-amplitude thrust. Subjects were unfamiliar with a new, indirect OM technique called *biodynamic osteopathy in the cranial field* (BOCF).[19,26]

The experiment was described to subjects as a four-arm trial: direct OM techniques, indirect BOCF, sham direct OM techniques, and sham indirect BOCF. In actuality, only two arms were executed: OMT using direct OM techniques or sham indirect BOCF. Direct OM techniques used in this study were: myofascial release; muscle energy; joint articulation; and high-velocity, low-amplitude thrust. These direct OM techniques are described in precise detail elsewhere.[27]

The practitioner administering direct OM techniques (J.K.)

Table 1
Cannabimimetic Effects of Osteopathic Manipulative Treatment: Characteristics of Study Subjects (N=31)

Characteristic	Osteopathic Manipulative Treatment Group, n=16 No (%)*	Sham Manipulative Treatment Group, n=15 No (%)*
■ **Age, y (mean)**	**40.6**	**39.9**
■ **Sex**		
□ Men	9 (29)	8 (26)
□ Women	7 (23)	7 (23)

* Percentages reported were rounded for each study group by characteristic. Therefore, the sum of these percentages may not equal 100%.

had 9 years' clinical experience using these techniques. The practitioner administering sham BOCF techniques (E.S.) had 14 years' clinical experience. Both study protocols were administered in separate rooms at one clinical site and took 20 minutes for their respective practitioners to perform.

Direct OM techniques were delivered in an osteopathic diagnostic paradigm known as the common compensatory pattern (CCP) model.[28] Diagnosis following this model addresses specific somatic dysfunctions (eg, at spinal segments, using TART [tenderness, asymmetry, restricted range of motion, and tissue texture changes] criteria[27]) as well as generalized dysfunctions (eg, fascial and fluid patterns in the body).[29] The CCP protocol calls for physician administration of individualized treatment plans based on physical findings; it can also be effective as a preventive treatment plan for people with no manifest disease or musculoskeletal complaints—such as the subjects in this study.[28,29]

In a previous study, treatment based on the CCP model elicited beneficial physiologic changes in "normal" subjects, such as decreased heart and respiratory rates, increased tidal volume, and decreased skin resistance.[30]

Sham BOCF techniques were delivered with subjects lying supine on the treatment table while the practitioner (E.S.) used light manual contact to "treat" subjects' heads. The practitioner's attention and "healing intention" were diverted by silently reciting "subtract serial seven" calculations.[31,32]

Outcomes Measures

■ **Drug Reaction Scale**

Outcomes measures included the DRS questionnaire and serum endocannabinoid levels.

The DRS measures changes in 67 descriptors, such as *good*, *optimistic*, and *irritated*, categorized into indicators of perception, emotion, cognition, and sociability.[16] The DRS has been validated for internal consistency and test–retest reliability; it has sensitively discriminated between cannabimimetic drugs and noncannabimimetic drugs.[33,34] Administration of cannabimimetic drugs (THC, marijuana) positively correlated with increased incidence of the DRS descriptors *high*, *lightheaded*, *stoned*, and *hungry*, and negatively correlated with DRS descriptors *sober* and *alert*.[33]

In the present study, the DRS was administered twice to each subject, immediately pretreatment and posttreatment. Subjects were asked to score each DRS descriptor on a scale of 1 (not feeling that descriptor at all) to 11 (the strongest feeling ever).

Prior to distribution of the surveys to study subjects, however, investigators labeled all DRS questionnaires with a numbering system to preserve subject anonymity. Once the surveys were completed by study subjects, all completed questionnaires were shipped to Middlebury, Vermont, for analysis by personnel who were blinded to treatment assignments (R.M., *see also Acknowledgments section*). Numerical means were then calculated for each DRS descriptor, tallied from the active treatment group and the control group (both preintervention and postintervention), and differences between means were statistically analyzed with a 2-tailed paired *t* test.

■ **Blood Serum Testing**

Peripheral blood samples (10 mL) were collected twice via antecubital vein suction in EDTA (ethylenediamine tetra-acetic acid) tubes by a certified laboratory technician using standard sterile techniques. Blood samples were drawn once after subjects completed each DRS questionnaire they were administered, approximately 10 minutes pretreatment and 20 minutes posttreatment.

Prior to sampling, investigators labeled all EDTA tubes with a numbering system to preserve subject anonymity. Immediately after sampling, EDTA tubes were centrifuged for 10 minutes at 800 × *g*. The serum layer was transferred to nonsiliconized glass vials, stored at −80°C, and shipped on dry ice to the University of Texas for analysis. Under the direction of a fully blinded study investigator (A.G.), laboratory personnel performed endocannabinoid measurements also fully blinded to treatment assignments—as were laboratory personnel who performed DRS calculations.

Table 2
Cannabimimetic Effects of Osteopathic Manipulative Treatment: Pre- and Posttreatment Mean Drug Reaction Scale Scores and Correlations (*r* Values) in Changes Between Scores and Changes in Serum Levels

Drug Reaction Scale	Osteopathic Manipulative Treatment Group Mean (SD)		Sham Manipulative Treatment Group Mean (SD)		Serum*	
					Anandamide	Oleylethanolamide
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	*r*=ΔAEA	*r*=ΔOEA
Active	6.4 (2.6)	5.6 (1.7)	4.7 (2.7)	5.2 (2.6)	0.008	0.059
Anxious	3.3 (2.3)	2.2 (2.1)	3.0 (2.4)	2.4 (1.7)	−0.228	−0.022
Bad	2.9 (2.4)	2.4 (2.1)	2.6 (2.6)	2.0 (1.7)	−0.399†	0.080
Careless	3.1 (2.4)	3.3 (2.4)	1.4 (0.7)	2.1 (1.4)	0.293	0.010
Cautious	4.0 (2.2)	4.0 (2.4)	4.5 (2.0)	3.9 (3.4)	0.141	−0.013
Coherent	8.1 (2.2)	7.6 (2.2)	7.3 (2.9)	7.5 (2.3)	0.198	0.223
Cold	4.3 (2.9)	3.6 (2.1)	4.2 (3.1)	3.6 (2.7)	0.473†	−0.313
Confused	2.5 (2.3)	2.3 (1.4)	3.1 (3.1)	1.6 (1.1)	−0.028	−0.104
Consistent	5.0 (2.4)	6.5 (1.8)	7.1 (2.9)	6.2 (2.6)	0.307	−0.151
Creative	5.6 (2.5)	5.9 (1.6)	4.8 (2.8)	5.2 (2.6)	−0.044	0.038
Depressed	2.7 (2.5)	1.7 (1.1)	2.2 (1.6)	1.6 (1.2)‡	0.020	−0.255
Distractible	5.5 (3.3)	4.2 (2.5)‡	4.1 (2.8)	3.8 (2.3)	−0.300	−0.244
Dizzy	2.3 (1.9)	2.5 (2.2)	.7 (1.7)	1.9 (1.8)	−0.157	0.050
Drunk	1.8 (1.4)	1.7 (1.1)	1.1 (0.3)	1.8 (1.9)	−0.169	−0.096
Elated	5.3 (1.9)	5.7 (2.1)	4.5 (2.2)	5.2 (2.0)	0.139	−0.128
Euphoric	4.1 (2.1)	4.9 (2.3)	4.2 (2.3)	4.8 (2.3)	0.006	−0.173
Fast	4.9 (2.9)	4.1 (2.3)	5.4 (2.4)	3.9 (2.3)‡	0.277	−0.065
Focused	6.0 (2.6)	6.1 (2.8)	5.9 (2.9)	5.3 (2.5)	0.217	−0.407
Forgetful	4.6 (2.7)	3.9 (2.8)	3.9 (2.4)	3.7 (2.6)	−0.149	0.219
Free	6.8 (2.6)	7.1 (1.9)	5.9 (2.5)	6.1 (2.1)	0.265	−0.035
Gentle	6.7 (2.1)	6.7 (2.1)	7.2 (2.7)	7.5 (1.8)	0.094	−0.026
Good	7.0 (1.0)	8.3 (1.5)§	6.7 (1.1)	7.8 (1.8)‡	0.058	0.108
Happy	7.8 (2.0)	8.7 (1.3)‡	7.5 (1.7)	8.0 (1.9)	0.244	0.020
Heavy in the Arms	3.3 (2.7)	2.9 (2.3)	2.5 (2.2)	2.3 (2.0)	−0.201	0.060
High	4.6 (2.5)	5.7 (2.7)§	4.2 (3.1)	3.5 (3.2)§	0.120	−0.260
Hot	3.3 (2.3)	4.1 (2.2)	2.0 (1.3)	2.4 (1.6)	−0.354†	−0.240
Hungry	3.9 (2.6)	5.0 (2.5)‡	2.7 (2.7)	3.0 (3.0)	0.187	−0.233
Impatient	3.7 (3.2)	3.3 (2.3)	3.2 (2.5)	2.1 (1.9)‡	−0.037	−0.401
Incapable	1.8 (1.6)	1.6 (0.7)	2.6 (2.6)	1.8 (1.4)	−0.046	−0.329
Inept	2.7 (2.5)	2.6 (2.0)	1.9 (1.2)	1.9 (1.5)	−0.060	−0.080
Inhibited	2.7 (2.0)	2.1 (1.5)‡	3.9 (2.9)	3.2 (2.8)	−0.159	−0.181
Insensitive	3.4 (2.1)	2.5 (1.6)	2.1 (1.6)	1.9 (1.5)	0.345	0.145
Irritated	2.8 (2.0)	2.1 (2.0)	2.4 (2.3)	1.3 (0.6)	−0.132	−0.201
Light Bodied	3.7 (2.1)	4.7 (2.5)	3.1 (2.2)	4.8 (3.1)‡	−0.077	−0.136

(Continued)

* Pearson correlation coefficient (*r*) between changes in Drug Reaction Scale (DRS) descriptor ratings (scale: 1 to 11) pre- and posttreatment, and changes in serum anandamide and serum oleylethanolamide levels pre- and posttreatment.
† Significant Pearson correlation between change in DRS descriptor and change in serum anandamide or serum oleylethanolamide.
‡ Significant difference between mean DRS descriptor ratings pre- and posttreatment ($P<.05$).
§ Significant difference between mean DRS descriptor ratings pre- and posttreatment ($P<.005$).

Extraction and quantification of AEA, 2-AG, and OEA were performed by chemical ionization gas chromatography/mass spectrometry using deuterium-labeled AEA, 2-AG, and OEA as internal standards, similar to methods described previously.[21] Changes in AEA, 2-AG, and OEA measured pretreatment and posttreatment were subjected to a 2-tailed paired *t* test with post hoc analysis using the Tukey test. Correlations between changes in endocannabinoids and

Table 2 (Continued)
Cannabimimetic Effects of Osteopathic Manipulative Treatment: Pre- and Posttreatment Mean Drug Reaction Scale Scores and Correlations (*r* Values) in Changes Between Scores and Changes in Serum Levels

Drug	Osteopathic Manipulative Treatment Group Mean (SD)		Sham Manipulative Treatment Group Mean (SD)		Serum*	
					Anandamide	Oleylethanolamide
Reaction Scale	Pretreatment	Posttreatment	Pretreatment	Posttreatment	*r*=ΔAEA	*r*=ΔOEA
Light Headed	2.8 (1.9)	4.9 (2.5)§	2.7 (2.4)	2.8 (2.4)	−0.049	−0.184
Lucid	6.7 (2.5)	6.7 (2.8)	6.9 (3.1)	6.7 (2.3)	0.060	0.130
Nauseous	1.9 (1.7)	1.6 (1.2)	1.5 (1.3)	2.0 (2.7)	−0.101	−0.561†
Optimistic	6.2 (1.9)	6.7 (2.8)	7.9 (1.4)	6.9 (2.9)	0.262	0.262
Paranoid	1.7 (1.2)	1.6 (0.9)	1.1 (0.5)	1.1 (0.3)	−0.357†	−0.043
Pessimistic	2.9 (2.3)	2.5 (2.1)	2.4 (2.1)	2.5 (2.1)	−0.012	−0.254
Quiet	5.4 (2.0)	5.9 (3.0)	6.5 (2.6)	5.7 (3.2)	0.096	−0.449†
Rational	8.3 (2.2)	7.7 (1.8)	8.1 (2.5)	6.9 (3.0)	0.489†	0.431†
Relaxed	6.0 (1.7)	6.8 (3.0)	5.6 (1.7)	8.4 (1.2)§	0.164	0.357
Rested	5.8 (1.5)	7.1 (2.7)	5.0 (1.6)	8.0 (1.4)§	0.019	0.483†
Rough	3.4 (2.8)	3.3 (2.9)	2.1 (1.8)	1.5 (1.2)	0.039	−0.440†
Sad	2.2 (1.7)	1.5 (0.6)	2.3 (2.2)	1.9 (1.9)	−0.076	−0.125
Secure	8.1 (2.2)	7.9 (1.9)	7.5 (3.1)	7.0 (2.9)	−0.054	−0.132
Seeing Details	5.5 (3.1)	4.3 (1.8)	5.3 (2.5)	5.7 (3.1)	0.218	0.095
Sensitive	5.4 (1.6)	5.6 (2.4)	6.3 (2.0)	5.8 (3.1)	0.167	−0.305
Sexy	4.1 (2.5)	5.1 (2.8)	3.2 (2.5)	3.3 (2.6)	0.144	−0.300
Silly	2.8 (2.5)	2.8 (2.1)	2.6 (2.6)	1.6 (1.6)	0.090	−0.286
Sleepy	4.9 (3.3)	5.7 (3.2)	4.1 (3.1)	5.1 (3.3)	0.153	0.004
Sober	8.7 (2.3)	5.7 (3.3)‡	9.9 (1.2)	8.5 (3.3)	0.128	0.061
Stoned	1.2 (0.4)	2.1 (1.6)‡	1.3 (0.6)	1.8 (1.6)	0.109	−0.10
Straight	7.5 (2.7)	7.5 (1.6)	7.9 (3.6)	6.4 (3.6)	0.184	−0.181
Stupid	3.0 (2.8)	2.4 (2.0)	1.7 (1.1)	1.4 (0.9)	0.073	−0.203
Sweaty¶	2.7 (2.7)	2.0 (1.5)	1.9 (1.8)	1.6 (1.1)	0.020	0.202
Talkative	6.1 (1.8)	5.6 (2.9)	5.7 (1.9)	4.8 (2.6)	0.062	−0.169
Tense	3.7 (2.7)	2.5 (2.4)	3.7 (2.3)	3.0 (3.0)	−0.036	−0.157
Thirsty	6.6 (2.7)	6.4 (2.8)	3.8 (2.0)	4.0 (3.0)	−0.019	−0.174
Tingling	2.5 (1.3)	2.1 (2.0)	1.9 (1.8)	2.0 (1.9)	−0.535†	0.034
Tired	5.9 (2.7)	5.7 (3.1)	6.3 (3.2)	5.9 (2.5)	−0.186	−0.004
Uncomfortable	3.7 (2.8)	2.5 (2.1)‡	2.6 (1.8)	2.0 (1.7)	−0.045	−0.028
Unfriendly	2.9 (3.1)	1.7 (1.3)	2.1 (2.1)	1.3 (0.6)	0.134	0.134
Uninhibited	5.1 (2.5)	5.3 (2.8)	6.4 (2.1)	5.5 (3.1)	−0.029	−0.377
Useful	7.2 (2.2)	6.7 (2.1)	7.3 (2.4)	7.0 (1.5)	0.109	0.204
Warm	6.3 (2.0)	6.0 (2.0)	4.7 (2.3)	6.1 (2.2)	−0.295	0.273

* Pearson correlation coefficient (*r*) between changes in Drug Reaction Scale (DRS) descriptor ratings (scale: 1 to 11) pre- and posttreatment, and changes in serum anandamide and serum oleylethanolamide levels pre- and posttreatment.
† Significant Pearson correlation between change in DRS descriptor and change in serum anandamide or serum oleylethanolamide.
‡ Significant difference between mean DRS descriptor ratings pre- and posttreatment ($P<.05$).
§ Significant difference between mean DRS descriptor ratings pre- and posttreatment ($P<.005$).
¶ The Drug Reaction Scale descriptor *sweaty* was used twice to check internal validity. For the second use of the descriptor *sweaty*, the pre- and posttreatment scores for patients receiving osteopathic manipulative treatment were 2.7 (2.4) and 2.7 (2.7), respectively; for patients receiving sham manipulative treatment, 1.9 (1.8) and 2.0 (2.1), respectively. Serum anandamide levels were −0.110; serum oleylethanolamide levels were −0.127.

changes in DRS descriptors were tested with the Pearson product moment correlation coefficient coupled with the Bartlett χ^2 test for statistical comparisons.

Results

The two study groups shared similar demographic characteristics (*Table 1*) and can be generalized to a mixed white-Maori population. No subjects withdrew from the study and

Table 3
Cannabimimetic Effects of Osteopathic Manipulative Treatment: Serum Levels of Anandamide, 2-Arachidonoylglycerol, and Oleylethanolamide Among Study Subjects

	Osteopathic Manipulative Treatment Group Mean (SD)		Sham Manipulative Treatment Group Mean (SD)	
Serum Level, pmol/mL	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Anandamide	2.99 (5.39)	8.01 (16.22)	2.26 (4.31)	2.65 (4.38)
2-Arachidonoylglycerol	0.92 (3.31)	0.85 (2.96)	ND*	0.003 (0.012)
Oleylethanolamide	15.58 (35.95)	11.43 (30.69)	13.90 (25.40)	14.27 (29.51)

* *ND* indicates not detected. No serum levels of 2-arachidonoylglycerol were detected within the limits of the assay.

none were unavailable during follow-up.

Subject blinding using the dual-blinding method was partially successful. The success of blinding precautions were assessed by investigators at the end of each study group treatment sequence by asking subjects about their perceptions regarding whether they thought they had received active OMT or sham manipulative treatment. At this time, subjects were informed of the calculated deception protocol and the actual two-arm trial design. When queried as to which procedure (ie, active or control) subjects thought they had received, 12 (75%) of the 16 participants in the OMT group believed that they had received active treatment, whereas 4 (25%) believed they had received the control treatment. Among subjects in the sham manipulative treatment group, 6 (40%) believed they had undergone the active treatment procedure, whereas 9 (60%) believed they had received control.

Subjects who received OMT experienced cannabimimetic effects, as measured by changes in their DRS descriptor scores (*Table 2*). These included highly significant increases in incidence of the descriptors *high* and *light-headed*, and significant increases in *hungry* and *stoned*, with significant decreases in *sober*, *inhibited*, and *uncomfortable*.

Subjects who received sham manipulative treatment experienced mixed effects, with significant changes in the incidence of the noncannabimimetic descriptors *good*, *rested*, *impatient*, *depressed*, and *fast*; a significant decrease in the cannabimimetic descriptor *high*; and significant increases in the cannabimimetic descriptors *light-bodied* and *relaxed* (*Table 2*).

In the OMT group, mean posttreatment AEA levels increased 5.02 pmol/mL over pretreatment levels (*Table 3*). Surprisingly, this 168% increase did not reach statistical significance (P=.14) because of large standard deviations.

In the sham manipulative treatment group, changes in AEA levels were negligible with a pretreatment to posttreatment increase of 17% (P=.64). Mean 2-AG levels did not change between pretreatment and posttreatment measurements in either group (*Table 3*). Mean OEA levels decreased 27% in posttreatment OMT subjects (P=.07), whereas no change was seen in control subjects (*Table 3*). Post hoc Tukey testing revealed no differences in AEA, 2-AG, or OEA levels between the two groups before treatment. Changes in AEA, 2-AG, and OEA levels did not correlate with subject age or differ based on sex.

Changes in AEA and OEA significantly correlated with nine DRS scores (*Table 2*). Increases in serum AEA correlated best with increased feelings of *rational* (r=+0.49, P=.007) and *cold* (r=+0.47, P=.01), and decreased sensations of *paranoid* (r=−0.357, P=.05) and *bad* (r=−0.40, P=.04). Decreases in serum OEA best correlated with increased feelings of *nausea* (r=−0.56, P=.003), *rough* (r=−0.44, P=.03), *quiet* (r=−0.44, P=.01), and decreased feelings of *rested* (r=+0.48, P=.02) and *rational* (r=+0.43, P=.04).

Comment

This experiment utilized a dual-blind, randomized controlled trial design, which is difficult to perform in clinical OMT studies. Osteopathic manipulative treatment is notoriously difficult to blind in controlled studies.[35,36] The novel approach to subject blinding that we chose to use in our study (ie, dual-blinding) required that we use a calculated deception protocol. In this protocol, we described our two-arm study to subjects as a four-arm study. We found this approach to be somewhat effective, as reported.

As noted, the standard methodology for use in randomized controlled trials is termed "double blinding" in the majority of publications. However, we feel that the most appropriate and accurate terminology when investigating the clinical effectiveness of OMT and certain other treatment modalities (eg, surgery, psychotherapy, acupuncture, and chiropractic) is better described as "dual-blind" to reflect the

inability of researchers and clinical investigators to blind practitioners and caregivers working in these modalities.[37]

Blinding subjects in the control intervention (sham BOCF) group was more effective than blinding subjects in the OMT group. Sham manipulative treatment, in this case sham BOCF, may be intrinsically easier to blind, because the sham BOCF practitioner applies a very light touch and follows the subject's inherent rhythms (eg, respiratory excursions), so no movement in the practitioner may be perceived by the subject.[19] Thus, sham BOCF can be quite plausible.

Control interventions must be plausible to the subject yet remain clinically ineffective (ie, carry little or no therapeutic effect). Sham manipulative treatment is notoriously difficult to render ineffectively because even the slight application of human touch and attention may evoke physiologic responses in subjects.[32,35]

Rather than conduct an uncontrolled study to maximize the physiologic effects of OMT, we chose to conduct a controlled study with sham manipulative treatment—with the known pitfall of potentially diminishing the differences between OMT and sham manipulative treatment. We chose this option as preferable to the known pitfalls of conducting an uncontrolled study, which is vulnerable to detractors as it is not considered evidence-based medicine.

Laboratory personnel who performed the DRS evaluations and the endocannabinoid measurements were fully blinded. As noted, blinding practitioners who delivered OMT and the sham manipulative treatment protocols was not possible.

Osteopathic manipulative treatment elicited changes in subjects' responses to the DRS questionnaire, especially in cannabimimetic descriptors previously linked with THC administration, such as *high*, *light-headed*, *hungry*, and *stoned*.[16,33,34] These psychotropic alterations may explain why OMT, like THC, has been used to treat depression,[38] to improve appetite,[39] and to treat anxiety and provide an improved sense of health and well-being.[18,19]

Control subjects recorded a mix of DRS responses, with a decrease in score for the cannabimimetic descriptor *high*, and an increase in score for the noncannabimimetic descriptors *rested* and *relaxed*. The latter descriptors seemed to reflect effects of the control intervention itself (ie, lying comfortably on a treatment table in a warm, quiet room).

Although the serum endocannabinoid assays fell short of statistical significance ($\alpha < .05$) because of large variances, data trends suggested that OMT selectively increased AEA levels and decreased OEA levels, rather than influence a general elevation of circulating endocannabinoid concentrations. Serum AEA levels more than doubled in post-OMT subjects, and OEA levels decreased 27% in post-OMT subjects.

Aspects of the experimental design may have biased toward a beta error: a small study population was used and there was insufficient homogenization of subjects (ie, too wide an age range and use of both male and female subjects).

Additionally, the fact that we obtained serum samples from 8:30 am to 7:30 pm may have been a confounding variable in light of recently discovered circadian fluctuations in AEA and 2-AG.[40] Interestingly, a previous OMT study based on the CCP model showed greatest physiologic changes in subjects who underwent OMT during the late afternoon.[30] Anandamide has a short half-life in the serum, so small differences in collection and processing of samples could result in large variations between samples.

The effects from AEA administration have not been measured in humans. In rodent studies, administration of AEA[13] or metabolically stable AEA analogs[41,42] produced subtly different effects than THC.[13] If post-OMT changes in DRS scores are assumed to be the result of elevations in AEA, then AEA's effects on subjects' DRS scores were different than THC's effects on subjects' DRS scores, as reported in previous DRS studies.[16,33,34] Increased AEA levels correlated best with an increase in subjects' DRS scores in the *rational* and *cold* descriptors, and with decreased subject-reported scores among the descriptors *paranoid*, *bad*, and *warm*. Increased subject DRS scores in *cold* and decreased subject scores for *warm* were similar to physiologic results in rodent studies, where AEA produced hypothermia.[12,43]

The increase in subject scores for *rational* and the decrease in subject scores for *paranoid* were intriguing because increased AEA levels have correlated with decreased psychotic symptoms in schizophrenic patients.[44] Osteopathic manipulative treatment has long been noted to show improvements in patients with schizophrenia,[45] and an increase in AEA levels could conceivably provide a therapeutic mechanism for this patient population. Osteopathic manipulative treatment decreased serum OEA levels, and this result correlated with decreased feelings of the descriptor *rational*. Thus, the effects of OMT on AEA and OEA may produce additive effects to subjects in the *rational* category. Paradoxically, decreases in OEA correlated with increases in incidence of *nausea* as well as *hunger*, although the correlation with *nausea* was twice as strong as that with *hunger*.

As OMT has long been noted to improve appetite,[17] a decrease in OEA could conceivably provide a mechanism for decreasing the sense of satiety.[11]

The common mechanism by which OMT maintained health, according to Dr Still, was improved cardiovascular circulation, "The rule of the artery must be absolute, universal, and unobstructed, or disease will be the result. I proclaimed that all nerves depended wholly on the arterial system for their qualities...."[2] Salamon et al[46] lend additional support to Still's principle by suggesting that OMT augments blood flow and vasodilatation by stimulating the release of nitric oxide. Anandamide causes release of nitric oxide from vascular endothelial cells,[47] thus OMT's release of AEA links OMT to Salamon et al's nitric oxide hypothesis.

We plan to extend our investigations of AEA with

nitric oxide, using a larger, more homogenized subject population. Measuring AEA in cerebrospinal fluid, which is more sensitive than measuring serum levels,[44] has been considered. Perhaps OMT's effects on endocannabinoids are amplified in symptomatic subjects or correlate with somatic dysfunctions documented in specific body regions. Testing different OM techniques would be interesting (eg, indirect myofascial release versus direct high-velocity, low-amplitude thrust), and perhaps more than one treatment with OMT is needed to generate significant differences.

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