

Effects of Topical O24 Essential Oils on Patients with Fibromyalgia Syndrome: A Randomized, Placebo Controlled Pilot Study

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ABSTRACT

Objectives: To review the literature on topical pain management in fibromyalgia [FMS] and to report on effective treatment with topical O24 essential oils.

Methods: Following a literature review of MEDLINE and EMBASE for published randomized controlled trials on topical therapies for FMS pain treatment, a double-blinded placebo controlled trial was carried out in outpatient clinics on 153 subjects meeting the American College of Rheumatology criteria for FMS using topical O24 essential oils for a treatment period of one month. Main outcome measures were pain visual analog scale ratings, a diary, the Fibromyalgia Impact Questionnaire, Jamar grip strength, pressure algometry measurements of tender point [TeP] pain threshold, and seven-point Lanier scale rating of treatment.

Results: In the 133 participants with complete data, improvements were noted in the visual analog scale night pain rating [$P=0.018$], Jamar grip strength [$P<0.001$], number of TePs [$P<0.001$] and average TeP pain threshold [$P<0.001$], and the Lanier scale [$P=0.001$] with topical O24 over the placebo.

Conclusion: This pilot randomized controlled trial suggests that FMS patients may be effectively managed for pain with topical O24. This would need to be confirmed with larger and longer randomized controlled trials. The topical O24 essential oils appear to have a clinically important effect in FMS.

KEY WORDS: Essential oils, fibromyalgia, chronic pain syndrome, trigger point, low back pain, naturopathy, alternative medicine

INTRODUCTION

By the American College of Rheumatology [ACR] definition, fibromyalgia syndrome [FMS] is a syndrome of widespread muscle pain [over three months] and stiffness with 11 or more characteristic tender points [TePs] on palpation.¹ It affects two percent of the population, predominantly females, with the most common age at presentation of 40 to 50 years.²

Fibromyalgia patients are high consumers of complementary/alternative medicine [CAM] interventions.^{3 4 5} In our survey of 116 physiatrists [rehabilitation medicine specialists] in Ontario, Canada, 55 percent of respondents agreed that FMS is a "real disabling condition." When asked what type of alternative therapy works, 14 different types were mentioned; the top three were acupuncture, biofeedback, and chiropractic.⁶ In one survey of 72 FMS participants, the use of topical analgesic rubs was rated the highest in CAM products tried.⁷ Few studies have been published on the use of topical agents in FMS. This includes an uncontrolled, short follow-up [20 minutes] study of topical camphor, methyl salicylate, and menthol lotion.⁸ Another double-blind study used topical capsaicin for chronic neck pain. Of those patients, 35 percent had FMS.⁹ To date, there has been no published high quality randomized controlled trial on topical agents for FMS pain.

In September 2004, we were approached to coordinate a clinical trial for FMS using a novel agent for pain. This patented over-the-counter topical was named O24 and consisted of a proprietary blend of six essential oils: rosemary, peppermint, camphor, eucalyptus, aloe vera, and lemon/orange.

METHODS AND MATERIALS

Males and females were included and all subjects were at least 18 years of age. Subjects were recruited from newspaper advertisements and Internet communication to FMS support groups. Telephone respondents who agreed to be seen for a pre-study assessment were assessed at clinics held in different cities around and including the greater Toronto area. The clinical diagnosis was confirmed by medical evaluation, pain diagram, and TeP evaluation. Note was made of previous rheumatologists' evaluations and diagnoses. All subjects were assessed and excluded for a history of connective tissue disease [scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, mixed connective tissue disease, etc.], endocrine disease [hypothyroidism, diabetes mellitus], hematologic disease [blood dyscrasia, paraproteinemias], and neuromuscular disorders [demyelinating disease]. Individuals with multiple chemical environmental sensitivities and peppermint allergy were also excluded. Use of cigarettes, alcohol, and caffeine was recorded. Medication use including opioids, antidepressants, anti-inflammatories, anticonvulsants, and other analgesic adjuvants was recorded. Other topics were documents, including use of herbal products and supplements. Treatments with physiotherapy, biofeedback, etc., were noted. Patients were instructed and educated to not change any physical therapies, exercises, or use of adjuvant medications; otherwise they would be disqualified from the study. Pregnant females were excluded.

The study protocol and consent form for participation were approved by the university-based teaching hospital's ethics committee. All subjects provided written informed consent to their participation in the study.

TREATMENT

Topical O24 essential oils were supplied to half of the participants who were instructed by a blinded consultant [a registered nurse] as to appropriate use. Instructions included application every four hours as needed for pain and avoidance of the oils on the mucosal membranes, eyes, genitalia, or any open wounds. Placebo oils [peppermint oil] identical in smell and appearance to the active oils were supplied to the other half. If subjects encountered any side effects while using the product, they were instructed to notify study personnel immediately. Participants were issued one bottle [30 ml] of the appropriate product [treatment or placebo] by the study nurse. They could gradually increase frequency and quantity of applications as they found benefit. Participants could get as much of the product as they wanted, provided they ran out of their initial product, or were given a defective bottle. Subjects were advised to report their replacement needs in advance [approximately one week] so that the appropriate product could be sent to them promptly. In total, seven participants [four active, three placebo] required replacements. They were issued immediately by same-day or next-day delivery. Allocation to a treatment group [active versus placebo] was carried out by assigning the subject the next available randomization number from a computer generated list in the sequence given to the clinic.

STUDY DESIGN

The study consisted of one block of four to six weeks. The first subjects were recruited and assessed in December 2004. Two weeks later those subjects were called via phone to encourage compliance. Subjects were then reassessed in January 2005. The assessments were done consistently by the same registered nurse [including dolorimetry measurements]. The treatment and follow-up periods were double blind.

CLINICAL OUTCOME VARIABLES

All subjects were required to complete a pain diagram, numerical rating scales for pain over the past week, and the Fibromyalgia Impact Questionnaire. Each subject was assessed pre- and post-treatment by the one trained nurse. Measurements included Jamar grip strength [the average of three trials with each hand was used] and TeP assessments with the Fischer algometer [pain threshold and number of active TePs]. There were no concerns about variability in the Fischer algometer use as only one assessor [a blinded trained registered nurse] did all the assessments.

At the pre-treatment evaluation, height and weight were recorded and the body mass index calculated. Blood pressure and pulse were recorded. At the post-treatment evaluation, subjects also rated their response to treatment using the seven-point Lanier scale. This scale was scored as follows: 1= markedly worse, 2= moderately worse, 3= mildly worse, 4= no change, 5=mildly better, 6=moderately better, 7=markedly better.

Mean weekly outdoor temperatures were determined for each subject from data provided by the local meteorological center. Subjects were asked to wait about 30 minutes at room temperature. Testing dates and times were noted.¹⁰

Test-retest reliability for several of the outcome measures had been previously published in a similar study for Raynaud's Syndrome.¹¹ The intraclass correlation coefficients were extremely high for the pain scales and Jamar average grip strength.

TOLERABILITY AND SAFETY

Subjects were asked during the follow-up phone call and the post-treatment assessment to report any adverse events. Forty-three subjects complained of smell sensitivity; 19 were from the placebo group and 24 were from the active group. In addition, two subjects, one from the placebo group and one from the active group,

complained of skin irritation. One subject from the placebo group also noted that the research therapy may have triggered her asthma on a single occasion. However, this subject was committed to several other treatment plans and was uncertain as to whether the research therapy had a direct effect on her asthma. There were otherwise no serious side effects reported. A previous human patch study demonstrated no evidence for allergic contact dermatitis with prolonged application [72 hours] in normal subjects.

STATISTICAL ANALYSIS

Statistical methods followed an intention-to-treat principle. There was no significant missing data requiring use of a regression equation to minimize bias. Analyses were performed using Statistical Analysis Software routine and were conducted by independent statisticians at the Institute of Clinical and Evaluative Sciences.

RESULTS

Out of a total of 325 telephone respondents, 153 agreed to be seen for a pre-study assessment. Of those 153 subjects, 133 [87 percent] completed the necessary forms and followed through with the post-treatment evaluation. Over the one month, 65 subjects used active treatment and 68 subjects used placebo treatment. Of the 20 who did not complete the study, 10 were on active treatment and nine were on placebo treatment. One individual [from the active group] was also excluded as her course was complicated by a leg fracture requiring crutches [she was unable to attend the follow-up session].

The demographic characteristics of the subjects were similar in the treatment and placebo groups [Table 1].

TABLE 1

Normal body mass index is classified as 18 to 25. On average, our subjects were above this range. For the likelihood ratio chi-square, there were also no significant

differences between the two groups for smoking, alcohol, caffeine use, or analgesic medications. The FIQ breakdown also did not demonstrate any significant differences for sleep or functional activities between active and placebo groups. Baseline outcome measures were similar between the two groups prior to treatment as listed [Table 2].

TABLE 2

Before and after treatment outcome measures are listed for each group below [Table 3]. Treatment results which were statistically significant for the active group are asterisked [*]. The corresponding result for the control group is also listed below the active values.

TABLE 3

CONCLUSION

These findings indicate that topical O24 essential oils are superior to placebo in the management of FMS. Significant improvements were documented in both subjective surveys of pain/dysfunction and in objective measures of algometry and hand dynamometry.

The Lanier scale rating for placebo was 3.9 and for the active group 5.6. The P-value was highly significant at $P < 0.0001$. The subjective rating of the Lanier scale suggests that the active group had mild-to-moderate improvement whereas the placebo group noted no significant change. A breakdown of the Lanier scale ratings is shown below [Table 4a and 4b].

TABLE 4a and 4b

DISCUSSION

The most common medications taken by FMS patients are the five As: Advil [ibuprofen], acetaminophen, amitriptyline [by prescription only], aspirin, and antacids.¹²

Such medications are often complicated by adverse effects. Nonsteroidal anti-inflammatory drugs are linked with gastric ulcers and deaths.¹³ Cox-2 inhibitors through the inhibition of prostacyclin have been associated with higher rates of cardiovascular disease. Even acetaminophen, shown to be ineffective for FMS pain¹⁴, is associated with gastric deaths as well as hepatotoxicity and nephrotoxicity [with chronic use].¹⁵

One recent review on pharmacological therapies concluded that the best supported medications to date are the low dose tricyclic antidepressants, but the benefits are short-term and have not been shown to be superior to placebo at six months of study^{16 17}. Selective serotonin reuptake inhibitors are generally ineffective for pain^{18 19}. Hence there is a need for safer and effective alternative therapies for pain control.

Compared to other topical products, topical O24 is unique in incorporating well studied botanicals without alcohol, glycerin, synthetics, or preservatives. Its ingredients are derived from best-sourced botanicals. Each active ingredient, camphor oil²⁰ from Japan, eucalyptus oil²¹ from Australia, aloe vera oil²² from Mexico, peppermint oil²³ from India, rosemary oil²⁴ from Spain, and lemon and orange oils²⁵ from the United States, has been studied for pain.

The primary mode of action is as a counterirritant for pain sensation. By stimulating large A-beta sensory fibers, there is inhibition of pain [A-delta, C] fibers at the dorsal horn of the spinal cord. Local effects from the ingredients include inhibition of pain transmitters such as bradykinin, histamine, and prostaglandins [see Appendix]. Increased skin and muscle temperatures and cutaneous bloodflow have been shown to occur following similar topical counterirritant use²⁶.

Topical O24 appears safe when applied topically in recommended amounts. Its safety in pregnancy and lactation has not been studied or established. Currently, it is

recommended that it not be used in pregnancy [when taken orally, rosemary oil may stimulate uterine contractions]. It should also not be used by individuals with severe liver, kidney, or gastrointestinal diseases or with brittle diabetes. It should not be applied in the face, nasal, or chest areas of babies and infants. It is contraindicated in individuals with true peppermint allergy or sensitivity.

Limitations to this study include the short duration and the lack of more advanced measures of impairment and function, such as the ARCON functional capacity evaluator. Future studies would be helpful in documenting response over a longer period of time [six months] and with a larger number of subjects. These studies should also consider monitoring done more closely. Plans are now underway to conduct such a multi-center trial.

FUNDING

Swiss Medica provided the funds for this pilot study. This included the costs of patient recruitment, hiring of nursing staff, and use of measuring devices and statistical analysis [completed by Marko Katic with the Institute of Clinical and Evaluative Sciences]. Special thanks to Donald Breault for overseeing the study and ensuring completion of surveys and assessments.

CONFLICT OF INTEREST DECLARATION

None. Drs. Ko, Hum, Traitses, and Berbrayer received no direct or indirect funds for this clinical study.

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Table 1. Demographic comparison of placebo and active groups.

Demographics	Placebo	Active	Statistical Significance
Gender			
Male	4	3	
Female	64	62	P=0.74
	Likelihood ratio chi-square		
Average age [years]	55.5	53.7	P=0.27
	T-test with unequal variance		
Body Mass Index	28.0	29.1	

Table 2. Pre-treatment baseline outcome measures in both groups.

Outcome measures	Placebo	Active	P-value [statistical measure]
VAS Best Pain	3.9	3.6	0.356 [f-test]
VAS Worst Pain	9.3	8.8	0.007 [f-test]
VAS Night Pain	6.6	6.6	0.251 [f-test]
FIQ	60.8	62.7	0.357 [t-test]
Active TePs [N]	16.1	16.4	0.569 [t-test]
Average pain threshold [kg]	1.9	1.6	0.407 [t-test]
Average Jamar grip strength [kg]			
Left	18.8	17.8	0.44 [t-test]
Right	18.8	17.2	0.275 [t-test]

VAS = visual analog scale, FIQ = Fibromyalgia Impact Questionnaire, TePs = tender points, N = number

**Table 3. Before-and-After Outcome Measures: Active versus Control
[Group or Treatment x Time Analysis of Variance on Selected Dependent
Variables]**

Outcome Measures	Before Treatment	After Treatment	P-value [Statistical Seasure]
PVAS Worst Pain* [active]	8.8	8.1	0.05
[control]	9.3	9.1	
PVAS Best Pain [active]	3.6	3.8	0.997 [f-test]
[control]	3.9	4.1	
PVAS Night Pain [active]	6.6	5.8	0.18 [f-test]
[control]	6.6	6.7	
PVAS Activity Pain [active]	7.0	6.3	0.097 [f-test]
[control]	7.0	6.8	
FIQ [active]	62.8	61.9	0.989
[control]	60.8	60.0	
Active TePs [N]*	16.4	16.2	<0.0001
[control]	16.1	17.1	
Average pain* threshold [kg]	1.6	2.0	<0.0001
Control	1.9	1.5	
Average Jamar left grip strength [kg]*	17.8	23.0	<0.0001
Control	18.8	18.9	
Average Jamar right grip strength [kg]*	17.2	24.1	<0.0001
Control	18.8	21.1	

PVAS = pain visual analog scale, FIQ = Fibromyalgia Impact Questionnaire, TePs = tender points, N = number

Table 4a. Lanier Scale Ratings for Placebo Group [Group Average=3.9]

Lanier scale rating	Subjects [N]	Subjects [%]
1	1	2
2	2	3
3	6	9
4	54	79
5	5	7
6	0	0
7	0	0

Table 4b. Lanier Scale Rating Breakdown for Active Group [Group Average=5.6]

Lanier Scale Rating	Subjects [N]	Subjects [%]
1	0	0
2	0	0
3	0	0
4	6	9
5	23	35
6	18	28
7	16	25

N = number, % = percent

Appendix A

Each of these botanicals have been studied in detail, with effects summarized as follows [for detailed references, please refer to the natural medicines comprehensive database at www.naturaldatabase.com].

Aloe vera: studies suggest topical use is effective in psoriasis, burns, frostbite, genital herpes, radiation-induced skin toxicity [delayed onset]. The aloe gel is found in the inner portion of the aloe leaf. Its active constituents include aloe emodin anthrone, dithranol, chrysarobin and allantoin. Pain producing transmitters such as [1] bradykinin is inhibited by the carboxypeptidase and salicylate components; [2] histamine inhibited by magnesium lactate component. Another component C-glucosyl chromone reduces topical inflammation. It may also inhibit a potent vasoconstrictor thromboxane A₂ and thus increase microcirculation to prevent ischemia in the wound area and speed the healing of burns and frostbite. Antibacterial and antifungal properties have also been documented. Potential adverse effects/ interactions include lowering of blood glucose [when taken orally].

Eucalyptus: studies suggest effectiveness in inflammation of respiratory tract mucous membranes, rheumatic complaints and nasal stuffiness. The oil contains 40-85 percent eucalyptol [1,8-cineole] which by stimulating saliva production, will activate the swallowing reflex and suppress an impending cough. As a topical, it works as a mild counterirritant and may inhibit prostaglandin synthesis. Potential adverse effects/interactions with oral use include nausea, vomiting, diarrhea. The ingestion of 3.5 ml of the oil alone can be fatal [delirium, convulsions]. Inhibition of cytochrome P450 1A₂/ 2C₁₉/ 2C₉/ 3A₄ may increase drug levels but this has not been reported yet in humans. It's oral use is contraindicated in gastrointestinal and bile duct inflammation, severe liver disease, kidney inflammation and hypotension.

Rosemary: studies suggest effectiveness for preventing baldness, alopecia areata, toothache, eczema, myalgia, sciatica, intercostals neuralgia and as an insect repellent. The dried leaves contain 1-2.5 percent essential oil which consists primarily of cineole, borneol, camphor and pinenes. The oil has a spasmolytic effect on smooth muscle and may also have a positive inotropic effect on the heart. Topical use may irritate the skin and increase blood flow. It also has antibacterial, antifungal and antioxidant properties. Potential adverse effects/ interactions with topical use include photosensitivity, erythema and dermatitis. Occupational asthma has also been reported. With oral use, it may stimulate uterine and menstrual flow and is therefore not recommended in pregnancy.

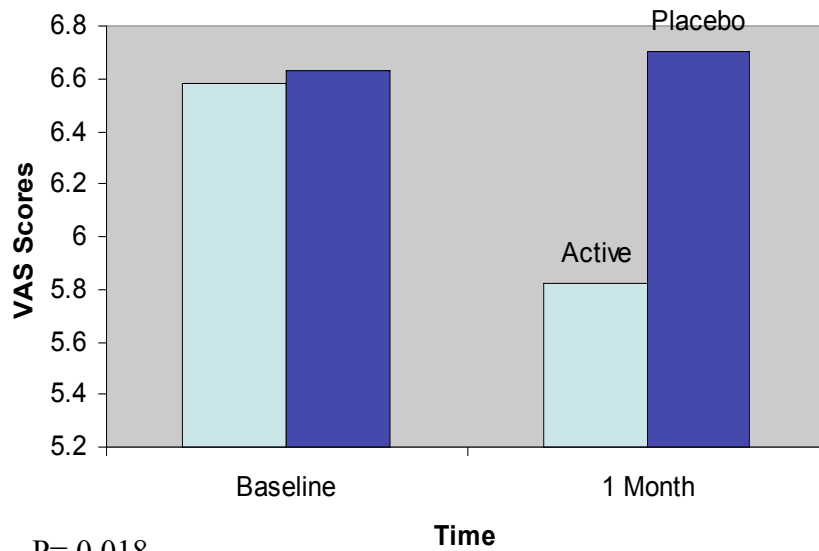
Camphor: studies on topical use suggest usefulness in osteoarthritis, warts, cold sores, hemorrhoids. It is used topically as an analgesic and antipruritic. It is also used in inhalation therapy as an antitussive and orally as an expectorant, antifatulent. It is safe when used in low concentrations 0.1-11 percent for topical use on intact skin. The applicable part of camphor is the wood distillate. Its counterirritant action is due to vasoconstriction which leads to the activation of reflex mechanisms resulting in improved local circulation. Adverse effects occur with improper oral use. Significant toxicity [respiratory failure, status epilepticus] has been documented with as little as two grams in

adults and 700 mg in children. Topical use is therefore not recommended in infants and should not be applied around the mouth. Oral use is not recommended as well in adults.

Peppermint: studies indicate topical usefulness in headache, myalgia, post-herpetic neuralgia, toothache, oral mucosa inflammation, pruritis, urticaria and as an antibacterial, antiviral agent for repelling mosquitoes. Orally, the oil is used for colds, coughs, irritable bowel syndrome, dyspepsia, dysmenorrhea. The oil is obtained by steam distilling the fresh above ground parts of the flowering plant. It contains 28-28 percent menthol, 20-31 percent menthone and 3-10 percent methyl acetate. Its topical action is as a counterirritant. It has in vitro antibacterial and antiviral effects. It also increases salivation, thus inhibiting the cough reflex and orally, via direct smooth muscle relaxing effects, it works as an antispasmodic. Adverse reactions from topical use include skin irritation and contact dermatitis. Application to the face, nasal, chest areas of babies, small children can cause laryngeal and bronchial spasms leading to respiratory collapse. Potential interactions including inhibiting CYP1A2, 2C9, and 3A4 enzymes [not yet documented in humans].

Appendix B: Graphs

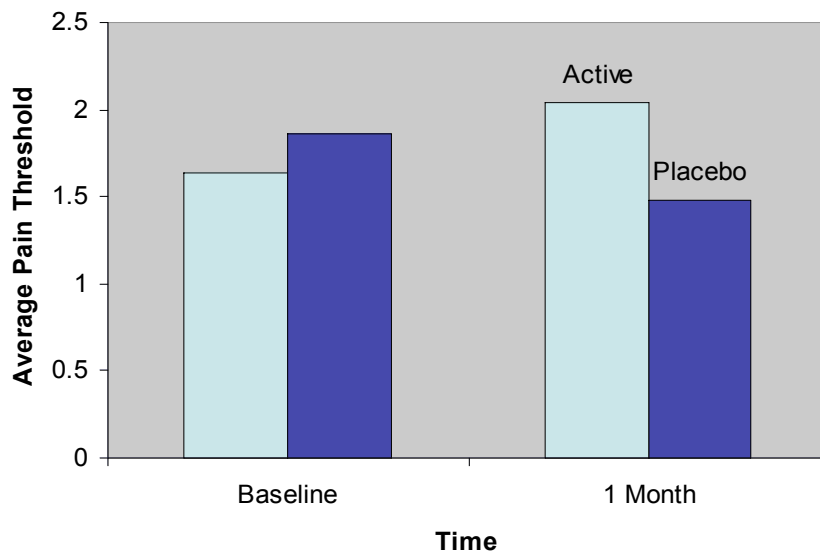
VAS Night Scores



P= 0.018

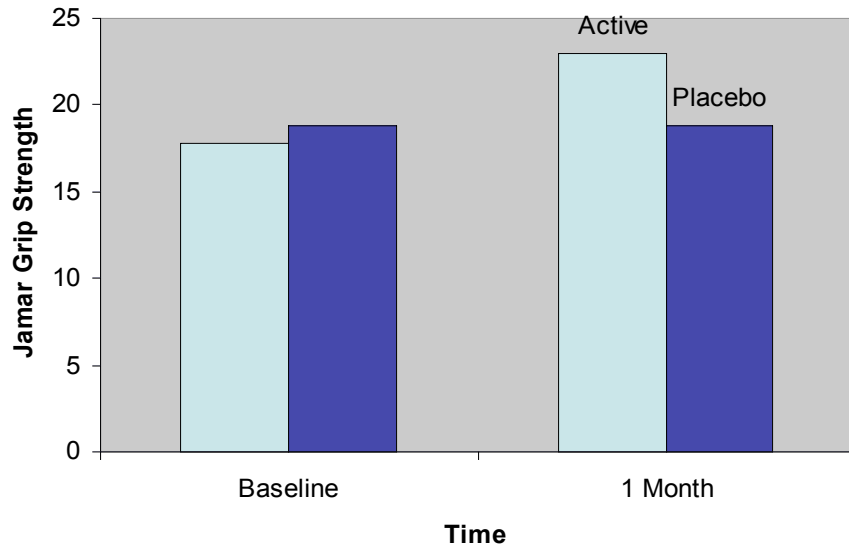
VAS = visual analog scale

Average Pain Threshold



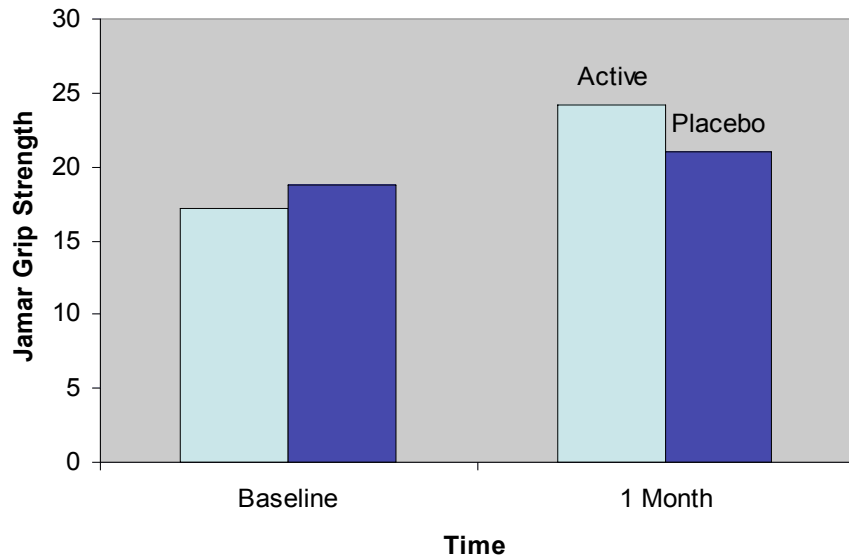
P<0.0001

Jamar Grip Strength [Left]



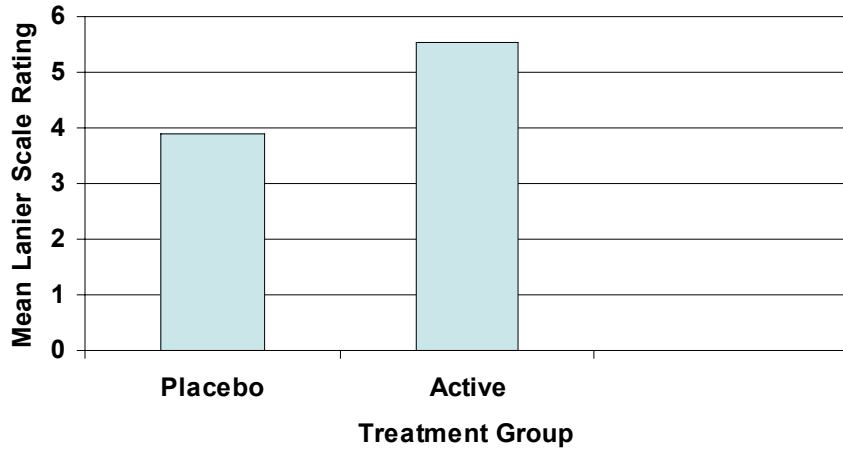
P<0.0001

Jamar Grip Strength [Right]



P<0.0001

Lanier Scale Rating



$P < 0.0001$

REFERENCES

- ¹ Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. *Arthritis Rheum* 33: 160-172, 1990.
- ² Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 38:19-28, 1995.
- ³ Fitzcharles MA, Esdaile JM: Nonphysician practitioner treatments and fibromyalgia syndrome. *J Rheumatol* 24: 937-940, 1997.
- ⁴ Nicassio PM, Schuman C, Kim J, Cordova A, Weisman MH: Psychosocial factors associated with complementary treatment use in fibromyalgia. *J Rheumatol* 24: 2008-2013, 1997.
- ⁵ Dimmock S, Troughton PR, Bird HA: Factors predisposing to the resort of complementary therapies in patients with fibromyalgia. *Clin Rheumatol* 15: 478-82, 1996.
- ⁶ Ko GD, Berbrayer D: Complementary and alternative medicine: Canadian physiatrists' attitudes and behavior. *Arch Phys Med Rehabil* 81: 662-667, 2000.
- ⁷ Jokic M. University of Toronto, 4th year Human Biology HMB499 Research Project report. April 12, 2004. pp.23-26.
- ⁸ Romano TJ, Stiller JW: Usefulness of topical methyl salicylate, camphor, and menthol lotion in relieving pain in fibromyalgia syndrome patients. *Amer J Pain Management* 4: 172-174, 1994.
- ⁹ Mathias BJ, Dillilingham TR, Zeigler DN, Chang AS, Belandres PV: Topical capsaicin for chronic neck pain: a pilot study. *Am J Phys Rehabil* 74: 39-44, 1995.
- ¹⁰ Bellamy N, Sothorn RB, Campbell J: Aspects of diurnal rhythmicity in pain, stiffness, and fatigue in patients with fibromyalgia. *J Rheumatol* 31: 379-389, 2004.
- ¹¹ Ko GD, Berbrayer D: Effect of ceramic-impregnated "thermoflow" gloves on patients with raynaud's syndrome: Randomized placebo-controlled study. *Altern Med Rev* 7: 327-334, 2002.
- ¹² Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, Yunus MB: A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum* 40: 1560-1570, 1997.
- ¹³ Schoen RT, Vender RJ: Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. *Amer J Med* 86: 449-458, 1989.
- ¹⁴ Russell J, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA: Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol* 6: 250-257, 2000.
- ¹⁵ Forel CM, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, Lipworth L, Elinder CG, Blot WJ, McLaughlin JK, Zack MM, Nyren O: Acetaminophen, aspirin, and chronic renal failure. *NEJM* 345: 1801-1808, 2001.
- ¹⁶ Clauw DJ, Crofford LJ: Chronic widespread pain and fibromyalgia: What we know, and what we need to know. *Best Practice & Clin Rheumatol* 17: 685-701, 2003.
- ¹⁷ Tofferi JK, Jackson JL, O'Malley PG: Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 51: 9-13, 2004.
- ¹⁸ Norregaard J, Volkmann H, Danneskiold-Samsøe B: A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain* 61: 445-449, 1995.

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- ¹⁹ Wolfe F, Cathey MA, Hawley DJ: A double-blind placebo controlled trial of fluoxetine in fibromyalgia. *Scand J Rheumatol* 23: 255-259, 1994.
- ²⁰ Cohen M, Wolfe R, Mai T, Lewis D: A randomized, double-blind, placebo-controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol* 30: 523-528, 2003.
- ²¹ Gobel H, Schmidt G, Soyka D: Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algometric headache parameters. *Cephalalgia* 14: 228-234; discussion 182, 1994.
- ²² Davis RH, Rosenthal KY, Cesario LR, Rouw GA: Processed Aloe Vera administered topically inhibits inflammation. *J Am Podiatr Med Assoc* 79: 395-397, 1989.
- ²³ Davies SJ, Harding LM, Baranowski AP: A novel treatment of postherpetic neuralgia using peppermint oil. *Clin J Pain* 18: 200-202, 2002.
- ²⁴ Hay IC, Jamieson M, Ormerod AD: Randomized trial of aromatherapy. Successful treatment for alopecia areata. *Arch Dermatol* 134:1349-1352, 1998.
- ²⁵ Calabrese V, Scapagnini G, Randazzo SD, Randazzo G, Catalano C, Geraci G, Morganti P: Oxidative stress and antioxidants at skin biosurface: A novel antioxidant from lemon oil capable of inhibiting oxidative damage to the skin. *Drugs Exp Clin Res* 25: 281-287, 1999.
- ²⁶ Hong CZ, Shellock FG: Effects of a topically applied counterirritant [eucalyptamint] on cutaneous blood flow and on skin and muscle temperatures: A placebo-controlled study. *Am J Phys Med Rehabil* 70: 29-33, 1991.