

GORDON D. KO, MD CCFP (EM) FRCPC, FAAPM&R, N.MD, CIME
“EMG studies and multidisciplinary Rx of back pain, fibromyalgia, muscle pain”

July 11, 2005

Dr. I. Jon Russell MD PhD
Journal of Musculoskeletal Pain, Editor
Dept of Medicine
University of Texas Health Science Center at San Antonio
Mail Code 7868, 7703 Floyd Curl Drive
San Antonio, TX 78229 3900 USA

Dear Dr. Russell

Re: “Effects of topical O24 essential oils on patients with fibromyalgia syndrome: a randomized, placebo controlled pilot study.

Please find enclosed our **full-length research article**. The manuscript has been typed to conform to the uniform requirements. We attest that this paper is **original** and has not been published or submitted for publication elsewhere. We also report that there are no potential conflicts of interest to be disclosed.

We believe it is suited best for publication in the Journal of MSK Pain for the following reasons:

1. Fibromyalgia affects at least 2% of the population and is one of the major chronic pain conditions that is poorly treated and most excellently reviewed in your journal.
2. This paper follows in timely fashion upon the growing interest in alternative therapies in fibromyalgia.
3. This paper should stimulate much debate and interest in further clinical research and review publications.

Peer review suggestions include:

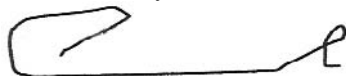
Dr. Veronica Kekosz MD FRCPC • Psychiatrist in Etobicoke, Ontario • Tel: 416-231-6166 • Fax: 416- 480-6885
Dr. JD Chen MD FRCPC • Rheumatologist in Toronto, Ontario • Tel: 905-771-9807 / 416-222-0660 •
Fax: 905-471-4348
Dr. Rida Baruni MD FRCPC • Psychiatrist in Vancouver, British Columbia • Tel: 604-737-6340 •
Email: barunirs2000@yahoo.ca

The corresponding author is: Dr. Gordon Ko MD FRCPC
5 Blencathra Hill, Markham, Ontario, Canada L6C 1G3
Email: drgordko@rogers.com
Telephone: 905-471-9355 Cell phone: 416-576-5915
Fax: 905-471-4348

The co-authors are: Dr. Annie Hum MD, Dr. George Traitses DC, Dr David Berbrayer MD FRCPC

The total numbers in the main body of this article (excluding the abstract and references) is 22 pages.
We look forward to your comments/ approval of this paper and to hearing from you soon.

Yours sincerely,



Dr. Gordon Ko MD CCFP (EM) FRCPC
Medical Director, Fibromyalgia Treatment Clinic (Sunnybrook)
Diplomat of the American Boards of Physical Medicine & Rehabilitation and of Pain Medicine

www.MusclePainRelief.ca

Canadian Centre for Integrative Medicine
12 Main St. North Markham, L3P 1X2
(905) 471-9355 Fax: (905) 471-4348

Sunnybrook & Women' Health Sciences Centre
University Of Toronto UG-25, 2075 Bayview Ave
M4M 3M5 (416) 480-4069 Fax (416) 480-6885

Title Page

- a) **Title:** “ Effects of the topical O24 essential oils on patients with fibromyalgia syndrome: a randomized, placebo controlled pilot study.

- b) **Authors:**
Gordon D. Ko, MD, CCFP (EM), FRCPC, University of Toronto
Annie Hum, MD, CAFCI, Canadian Centre Integrative Medicine
George Traitses, DC, Canadian Centre Integrative Medicine
David Berbrayer, MD, MCFP, FRCPC, University of Toronto

- c) **Affiliations:**
Department of Rehabilitation Medicine, Sunnybrook and Women’s College Health Services Centre, University of Toronto, Ontario, Canada
Canadian Centre for Integrative Medicine, Markham, Ontario, Canada

- d) **Disclaimers:** none

- e) **Corresponding author:** Dr. Gordon Ko
5 Blencathra Hill
Markham, Ontario L6C 1G3
Email; drgordko@rogers.com

- f) **Reprint requests:**
Dr. Gordon Ko
Suite UG-25, Fibromyalgia Treatment Clinic
Sunnybrook and Women’s College Health Sciences Centre
2075 Bayview Ave, Toronto, Ontario, Canada M4N 3M5

- g) **Sources of support:** none

Abstract and Key Words

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 using topical O24 essential oils.

Study Design: Double blind, placebo controlled study.

Study Setting: Outpatient clinics

Participants: One hundred and fifty three subjects meeting the “ACR” criteria for fibromyalgia syndrome.

Intervention: Treatment period of 1 month with use of topical O24 essential oils.

Main outcome measures: Primary end points: Pain visual analogue scale ratings AND DIARY, Fibromyalgia Impact Questionnaire (FIQ). Secondary end points: Jamar grip strength, Pressure algometry measurements of tender point threshold. Seven point Lanier scale rating of treatment.

Results: In the 133 participants with complete data, improvements were noted in the visual analogue scale night pain rating ($p=.018$), Jamar grip strength ($p<.001$), number of tender points ($p<.001$) And average tender point average threshold ($p<.001$), and the Lanier scale ($p=.001$) with topical O24 over the placebo.

Conclusion: This pilot RCT 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 O24 topical essential oils appear to have a clinically important effect in fibromyalgia syndrome.

Key words: essential oils, fibromyalgia, chronic pain syndrome, myofascial trigger point, lower back pain, naturopathy, alternative medicine.

Introduction:

By the American College of Rheumatology (ACR) definition, fibromyalgia is a syndrome of wide spread muscle pain (over 3 months) and stiffness with 11 or more characteristic tender points on palpation.¹ It affects 2% of the population, predominantly females, with the most common age at presentation of 40 to 50 years.²

FMS patients are high consumers of complementary/alternative medicine (CAM) interventions.³ ⁴⁵ In our survey of 116 physiatrists (rehabilitation medicine specialists) in Ontario, Canada, 55% of respondents agreed that FMS is a “real disabling condition”. When asked what type of alternative therapy works, 14 different types were mentioned with the top three being acupuncture, biofeedback and chiropractic.⁶ In one survey 72 of the 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 un-controlled, short follow up (20 minute) study of topical camphor, methyl salicylate, and menthol lotion.⁸ Another study, which was double blind, used topical capsaicin for chronic neck pain. Of those patients, 35 had FMS.⁹ To date, there has been no published high quality randomized controlled trial (RCT) 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 propriety blend of 6 essential oils. These consist of rosemary, peppermint, camphor, eucalyptus, aloe vera and lemon/orange.

Participants and Methods:

Subjects were recruited from newspaper advertisements and Internet communication to FMS support groups. Out of a total of 325 telephone respondents, 153 agreed to be seen for a pre-study assessment. These subjects were assessed at clinics held in different cities around the and including the greater Toronto (Ontario, Canada) area. The clinical diagnosis was confirmed by medical evaluation, pain diagram and tender point evaluation. Note was made of previous rheumatologist’s 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, anti-depressants, anti-inflammatories, anticonvulsants and other analgesic adjuvants was recorded. Subjects were also documented including use of herbal products and supplements. Treatments with physiotherapy biofeedback were noted. Males and females were included and all subjects were at least 18 years of age. Pregnant females were excluded. The study protocol and consent form for participation was 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 (registered nurse) as to appropriate use. Instructions included application every 4 hours as needed for pain and avoidance of the oils on the mucosal membranes, eyes, and genitalia or any open wounds. Placebo oils (peppermint only) identical in smell and appearance

to the active oils were supplied to the other half. If subjects encountered side effects while using the product, they were instructed to notify study personnel immediately.

Participants were issued one bottle of the appropriate product (treatment or placebo) by the study nurse. Participants could get as much of the product as they wanted provided they ran out of the initial product, or were given a defective bottle. Subjects were advised to report their replacement needs in advance (approx. 1 week) so that the appropriate product could be sent to them promptly. In total, 7 participants (4 active, 3 placebo) required replacements. They were issued immediately by same day or next day delivery. Allocation to a treatment group (active vs. placebo) was carried out by assigning the subject the next available randomized number (computer generated list) in the sequence given to the clinic.

Study Design:

The study consisted of one block of 4 to 6 weeks. The first group were recruited and assessed in December 2004. A phone call 2 weeks later was done 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 the following: Pain diagram, numerical rating scales for pain over the past week, fibromyalgia impact questionnaire (FIQ). Each subject was assessed and pre and post-treatment by the one trained nurse. Measurements included: Jamar grip strength (average of the tender point of each hand), Tender point assessments with Fisher algometer (pain threshold and number of active tender points).

At the pretreatment evaluation, height and weight were recorded and the body mass calculated. Blood pressure and pulse were recorded.

At the pretreatment evaluation, subjects also rated their response to treatment using the 7-point Lanier scale. Mean weekly outdoor temperatures were determined for each subject from data provided by the local meteorological center (Toronto). 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 outcomes measures had been previously published in a similar study for raynaud's.¹¹ The intraclass correlation coefficients were extremely high for the pain scales, 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. 43 subjects complained of smell sensitivity, out of which 19 were from the placebo group and 24 were from the active group. In addition, 2 subjects, one from the placebo group and one from the active group, complained of skin irritation. One subject from the placebo group noted that the research therapy might have triggered her asthma on a single occasion. However, this subject was committed to several other treatment plans and was uncertain to whether the research therapy had a direct effect on her asthma. There were otherwise no serious

side-effected reported. A previous human patch study demonstrated no evidence for allergic contact dermatitis with prolonged application (72hours) in normal subjects.

Statistical Analysis:

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

Results:

Of the 153 subjects initially assessed, 133 (87%0 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 and 9 were on placebo. One individual (active group) was also excluded as her course was complicated by a leg fracture requiring crutches (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:

Demographics		Placebo	Active	Statistical Significance
Gender	Male	4	3	p = 0.74
	Female	64	62	
Likelihood ratio chi-square				
Age average in years		55.5	53.7	p =0.27
T-test with unequal variances				
Body Mass Index		28.0	29.1	

Normal body mass index is classified as 18 to 25. Our subjects on average fell above this range. For the likelihood ratio chi-square, there were also no significant differences between the two groups for smoking and alcohol, caffeine use, analgesic medicines.

Baseline outcome were similar between the two groups prior to treatment as listed (table 2):

Table 2:

Outcome measures	Placebo	Active	p-value (Statistical Measure)
VAS Best Pain	3.9	3.6	0.346 (f-test)
VAS Worst Pain	9.3	8.8	0.007 (f-test)
VAS Night Pain	6.6	6.6	0.251 (f-test)
VAS Active Pain	7.0	7.0	0.554 (f-test)

Fibromyalgia (FIQ)	60.8	62.7	0.357 (f-test)
Impact Questionnaire			
Number of active tender points (pain with <4kg pressure)	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)

Treatment results, which were **statistically significant** for the active group, **are asterisked* below** (table 3). The corresponding result for the control group is also listed below the active values.

Table 3:
(Group or Treatment x Time ANOVAS on selected dependant variables)

	Before	Active	p-value
VAS Worst Pain*	8.8	8.1	0.05
Placebo	9.3	9.1	
VAS Best Pain	3.6	3.8	0.997
Placebo	3.9	4.1	
VAS Night Pain*	6.6	5.8	0.018
Placebo	6.6	6.7	
VAS Active Scores	7.0	6.3	0.097
Placebo	7.0	6.8	
FIQ	62.8	61.9	0.989
Placebo	60.8	60.0	
Tender point count*	16.4	16.2	<.0001
Placebo	16.1	17.1	
Average pain threshold*	1.6	2.0	<.0001
Placebo	1.9	1.5	
Jamar left*	17.8	23.0	<.0001
Placebo	18.8	18.9	
Jamar right*	17.2	24.1	<.0001
Placebo	18.8	21.1	

Table 4:

	Placebo	Active	p-value
Lanier Scale Rating*	3.9	5.6	<.0001
Lanier scale rating was:	1 markedly worse		
	2 moderately worse		
	3 mildly worse		
	4 no change		
	5 mildly better		
	6 moderately better		
	7 markedly better		

Table 5:

Lanier Scale Rating Breakdown for Placebo Group:
(Group Average = 3.9)

Lanier Scale Rating	Number of Subjects	Percentage of Subjects
1	1	2
2	2	3
3	6	6
4	54	79
5	5	7
6	0	0
7	0	0

Lanier Scale Rating Breakdown for Active Group:
(Group Average = 5.6)

Lanier Scale Rating	Number of Subjects	Percentage of Subjects
1	0	0
2	0	0
3	0	0
4	6	9
5	23	35
6	18	28
7	16	25

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 subjective rating of the Lanier scale suggests that the active group had mild-to moderate improvement whereas the placebo group noted no significant change.

Discussion:

The most common medications taken by FMS patients are the five “A”s of: Advil (ibuprofen), Acetaminophen, Amitriptyline (by prescription only), Aspirin and Antacids.¹² Such medications are often complicated by adverse effects. Nonsteroidal anti-inflammatory (NSAID) drugs are linked with gastric ulcers and deaths. 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 pain¹³ is associated with gastric deaths as well as hepatotoxicity and nephrotoxicity (with chronic use).¹⁴

One recent review on pharmacological therapies concluded that the best supported medications to date are the low dose tricyclic anti-depressants, but that the benefits are short-term and have not been shown to be superior to placebo at six months of study.^{15 16}

SSRI’s are generally ineffective for pain.^{17 18} 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 has been studied for pain: camphor oil¹⁹ from Japan, eucalyptus oil²⁰ from Australia, aloe vera oil²¹ from Mexico, peppermint oil²² from India, rosemary oil²³ Spain. Lemon and Orange oils²⁴ from the USA. The primary mode of action is as counter-irritant for pain sensation. By stimulating large A-beta sensory fibres, there is inhibition of pain (A-delta, C) fibres at the dorsal horn of the spinal cord. Local effects from the ingredients include inhibition of pain transmitters such as bradykinin, histamine, prostaglandins (see appendix). Increased skin and muscle temperatures and cutaneous blood flow have been shown to occur following similar topical counter-irritant.²⁵

Topical O24 appears safe when applied topically in recommended amounts. Its safety in pregnancy and lactation has not been studied/established. Currently. It is recommended that it is not used in pregnancy (rosemary oil when taken orally may stimulate uterine contractions). It should also not be used in individuals with severe liver, kidney, and gastrointestinal diseases or with brittle diabetes. It should not be applied in the face, nasal, 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 (6 months) and with a larger number of subjects. Plans are now underway to conduct such a multi-centre 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 the 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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Appendix A:

Each of these botanicals has 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% 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 counter-irritant and may inhibit prostaglandin synthesis. Potential adverse effects/interactions with oral use include nausea, vomiting, diarrhea. The ingestion of 3.5ml 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. Its oral use is contraindicated in gastrointestinal and bile duct inflammation, severe liver disease, kidney inflammation and hypotension.

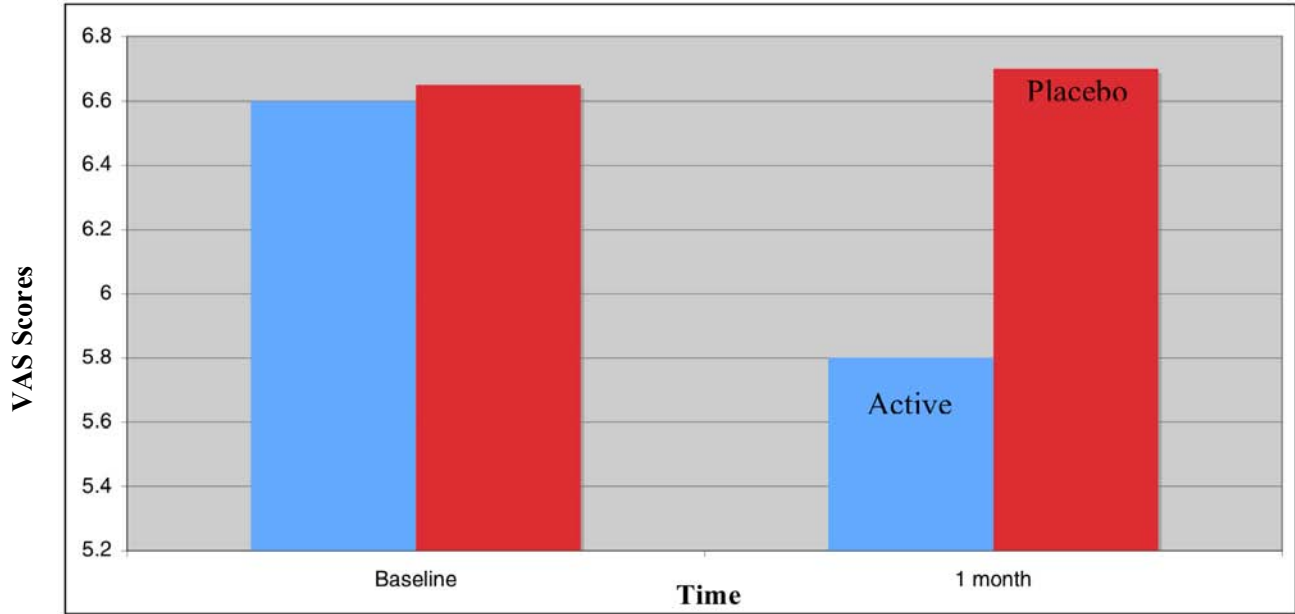
Rosemary: Studies suggest effectiveness for preventing baldness, alopecia areata, toothache, eczema, myalgia, sciatica, intercostals neuralgia and as an insect repellent. The dried leaves contain 1-2.5% essential oil, which consists primarily of cineole, borneol, camphor and pinenes. The oil has spasmolytic 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. In 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, and 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, antiflatulent. It is safe to use when used in low concentrations 0.1-11% for topical use on intact skin. The applicable part of camphor is the wood distillate. Its counter-irritant 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 2 grams in adults and 700mg in children. Topical use is therefore not recommended in infants and should not be applied around the mouth. Oral use is not recommended in adults as well.

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

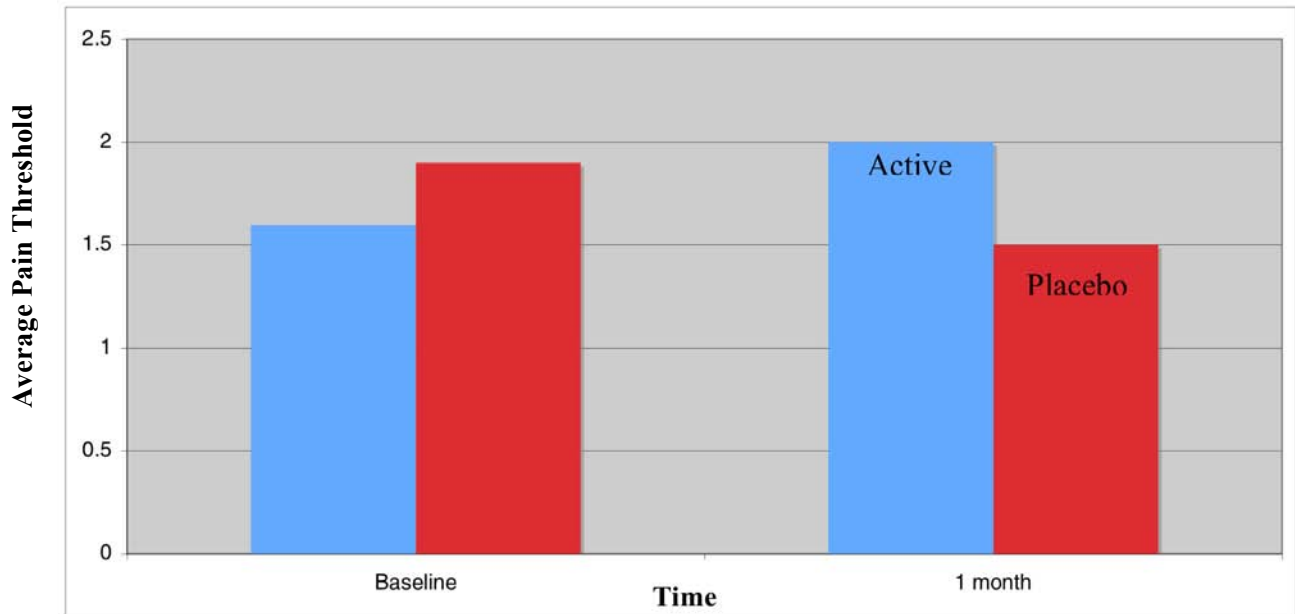
Appendix B: Graphs

VAS Night Scores



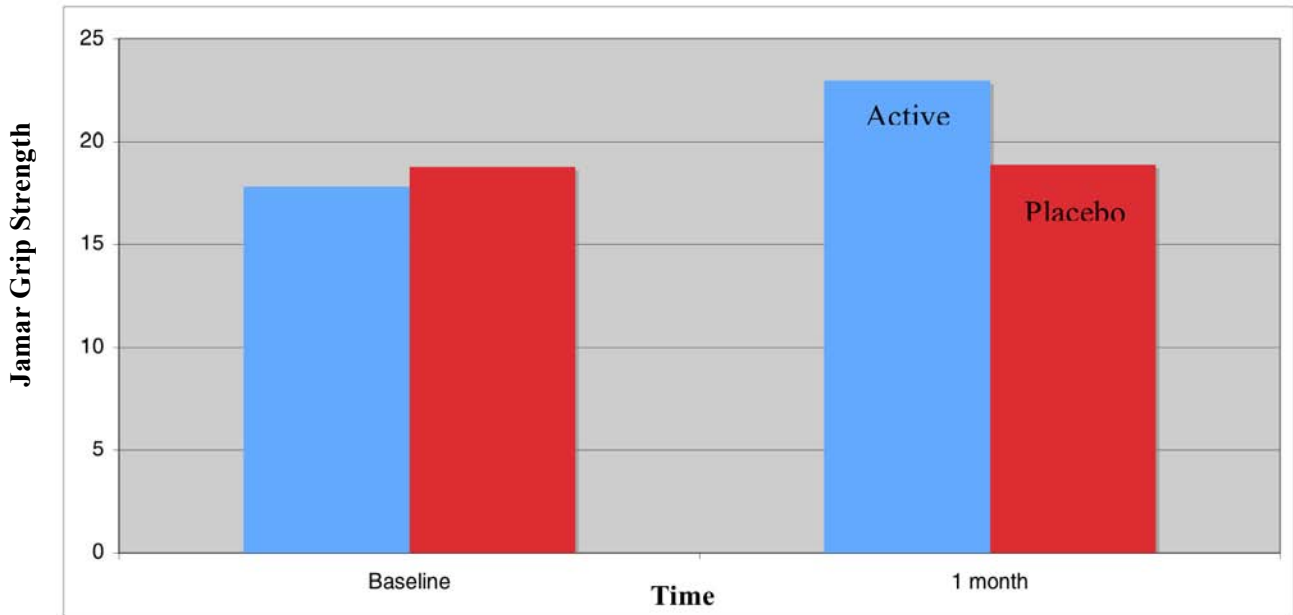
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Average Pain Threshold



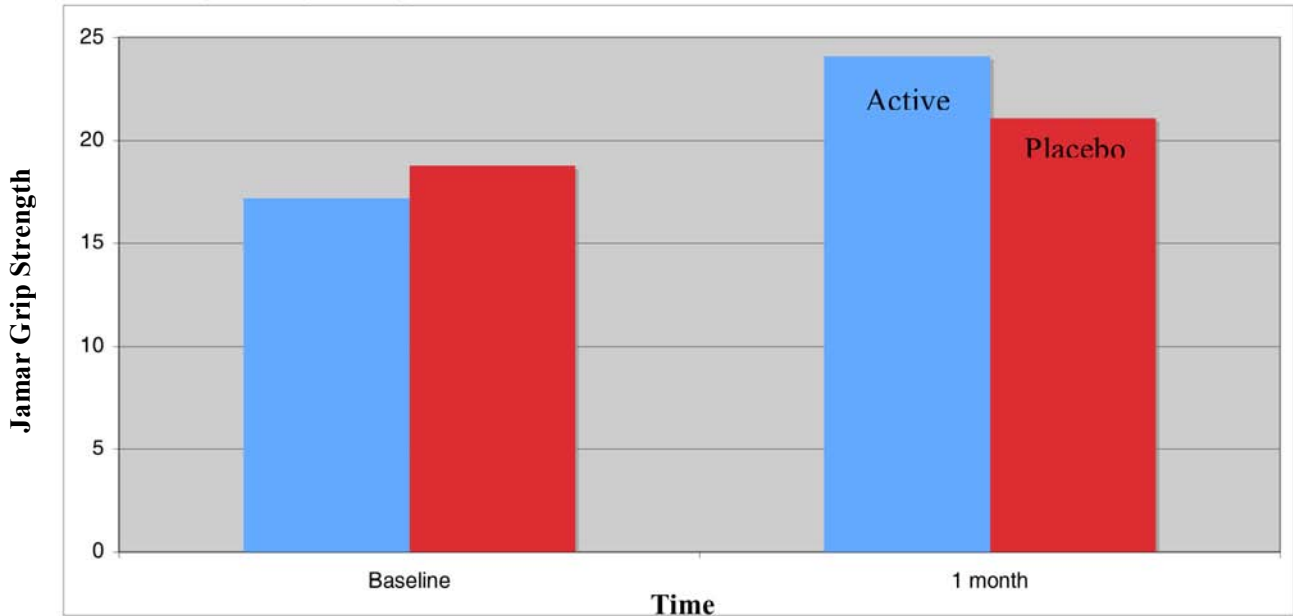
p-value=<.0001

Jamar Grip Strength (Left)



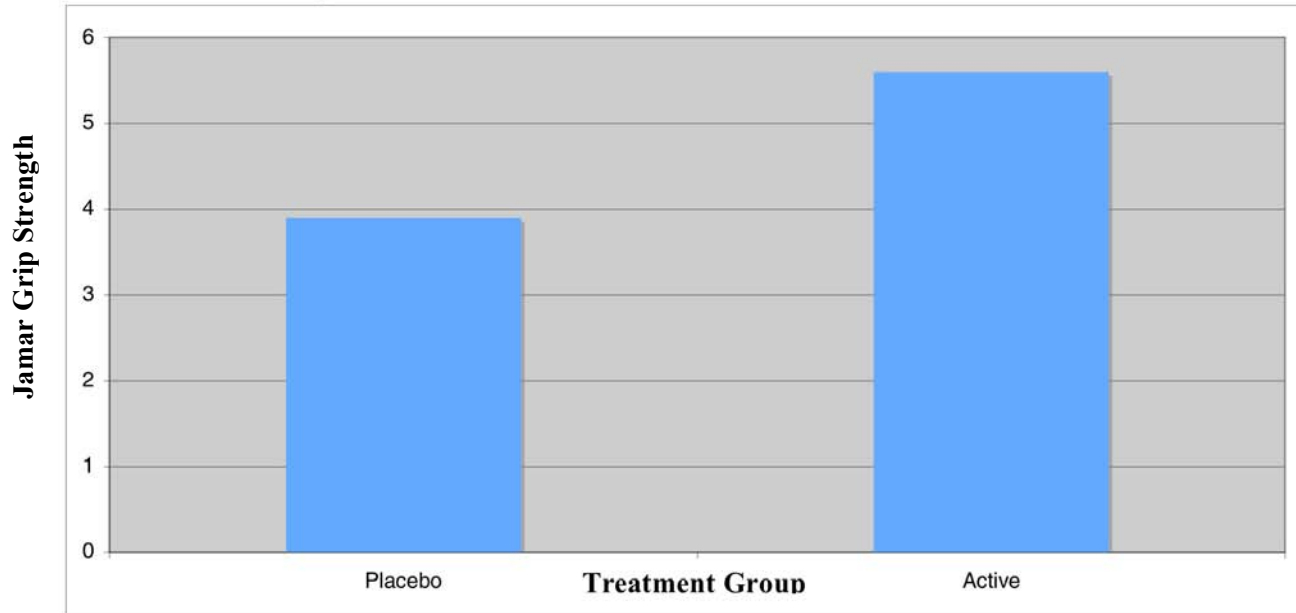
p-value=<.0001

Jamar Grip Strength (Right)



p-value=<.0001

Lanier Scale Rating



p-value=<.0001

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