Acupressure for Persistent Fatigue in Systemic Lupus Erythematosus

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1.0 BACKGROUND AND SIGNIFICANCE

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterised by involvement of multiple organs with a female to male ratio of 12:1 with the highest incidence reported in women of child bearing age (15-44 years).[1] In general, advances in diagnosis and management have led to significant improvements in outcomes.[2] However fatigue remains a challenging and prevalent issue for SLE patients.

1.1 Fatigue in lupus

SLE patients consider fatigue to be one of the most pervasive and disabling aspects of their disease. As many as 85% report significant levels of fatigue[3], a prevalence far in excess of that observed in the general population and most other chronic disorders. Moreover, its impact permeates all aspects of life as reflected by fatigue's strong association with impaired quality of life[4] and work disability[5]. Despite these profound consequences, there is a dearth of accepted therapies and in a meta-analysis of 32 studies in over 9,000 rheumatoid arthritis patients (who receive similar treatments to SLE and also suffer from significant fatigue) who received biological treatments found these medications, while effective for pain and disease activity, showed modest and mixed impacts on improving fatigue.[6]

The etiology of fatigue is likely to be complex and existing evidence supports a multi-dimensional origin. While many SLE patients describe cognitive features of fatigue (e.g. difficulties in concentrating), even more complain of physical aspects (e.g. needing to rest more)[7,8]. Physical fatigue is commonly attributed to problems with the skeletal muscle (indeed physical fatigue and muscle fatigue are synonymous terms). In fact, by measuring voluntary muscle contraction, others have observed significantly reduced skeletal muscle strength in SLE patients compared to healthy controls[9] – a difference which could be explained by pathological abnormalities within the muscles. In the past, muscle biopsy studies have identified microscopic abnormalities in the majority of patients, ranging from muscle fiber atrophy to lymphocytic vasculitis[10].

1.2 Acupressure

Self-administered acupressure is one possible safe, self-management technique for which may be effective for improving fatigue as well as physical and psychosocial functioning in several chronic disease populations.[11-13] Acupressure, a technique derived from acupuncture, is a component of Traditional Chinese Medicine (TCM) in which pressure is applied to specific acupoints on the body using a finger or small device, to treat disease. Our prior research demonstrated that acupressure, self-administered by women with breast cancer, significantly reduced clinically significant fatigue by approximately one-third in fatigued breast cancer survivors and was superior to standard therapies.[14] Moreover these self-rated improvements were maintained up to one month after treatment was discontinued.

However, impact on other chronic disease populations with fatigue is unknown. To explore this intervention in SLE, we propose to conduct a pilot randomized clinical trial in 72 SLE patients with established fatigue, through the following aims.

2.0 SPECIFIC AIMS

1. To determine the feasibility of recruiting and conducting acupressure in fatigued persons with lupus
2. To explore the effect of two distinct acupressure formulas (relaxing and stimulating) plus usual care versus sham acupressure plus usual care and usual care alone on severity and impact of chronic fatigue (as measured by the Brief Fatigue Inventory)
    a. Hypothesis: Both relaxing and stimulating acupressure are superior to sham acupressure and usual care, but relaxing acupressure is superior to stimulating acupressure

3. Secondary: To explore the effect of two distinct acupressure formulas (relaxing and stimulating) plus usual care versus sham acupressure plus usual care and to usual care alone on quality of life, sleep and pain
    a. Hypothesis: Both relaxing and stimulating acupressure are superior to sham acupressure and usual care, but relaxing acupressure is superior to stimulating acupressure

3.0 PRELIMINARY DATA

3.1 Study 1: Self-administered for Fatigue in Breast Cancer Survivors [14]

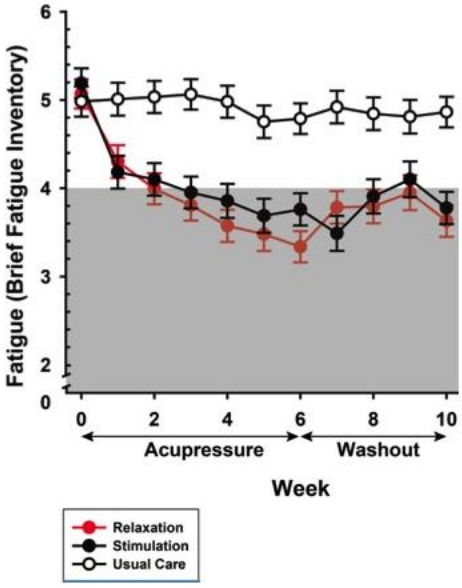


Figure 1. Effect of Two Types of Acupressure on Fatigue (Grey area represents normal fatigue levels <4 on BFI)

A total of 424 survivors of stages 0 to III breast cancer who had completed cancer treatments at least 12 months previously were screened, and 288 were randomized, with 270 receiving relaxing acupressure (n = 94), stimulating acupressure (n = 90), or usual care (n = 86). One woman withdrew owing to bruising at the acupoints. At week 6 (post-treatment), the percentages of participants who achieved normal fatigue levels (Brief Fatigue Inventory score <4) were 66.2% (49 of 74) in relaxing acupressure, 60.9% (42 of 70) in stimulating acupressure, and 31.3% (26 of 84) in usual care. At week 10, a total of 56.3% (40 of 71) in relaxing acupressure, 60.9% (42 of 69) in stimulating acupressure, and 30.1% (25 of 83) in usual care continued to have normal fatigue (see Figure 1). At neither time point were the 2 acupressure groups significantly different. Relaxing acupressure, but not stimulating acupressure, showed significant improvements in sleep quality compared with usual care at week 6, but not at week 10. Only relaxing acupressure significantly improved quality of life vs usual care at weeks 6 and 10.

Both acupressure arms significantly reduced persistent fatigue compared with usual care, but only relaxing acupressure had significant effects on sleep quality and quality of life. Relaxing acupressure offers a possible low-cost option for managing symptoms.

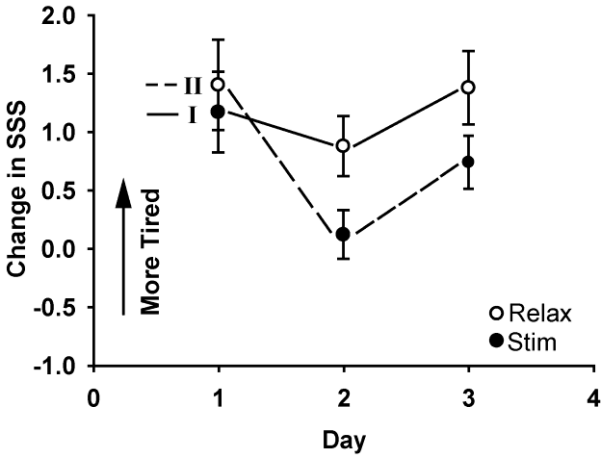
3.2 Study 2: Acupressure Modulates Sleepiness in the Classroom [15]

We conducted a single-blind randomized crossover study to determine whether self-administered acupressure has a significant effect on sleepiness in a population of healthy student participants in a prolonged lecture situation. Our study utilized 2 active acupressure treatments with hypothesized opposing effects, a relaxation treatment and a stimulation treatment, in a crossover design in which all participants received both treatments on different days. The study population consisted of thirty-nine subjects enrolled at the University of Michigan School of Public Health course on clinical research design and statistical analysis.

Methods: Acupressure regimens promoting mental stimulation or relaxation were utilized in a crossover design with subjects randomized to either Sequence I (day 1 stimulation – day 2 relaxation – day 3 relaxation) or Sequence II (day 1 relaxation – day 2 stimulation – day 3 stimulation). Each regimen was taught to all study participants by 2 members of the class who were previously trained in acupressure. Each regimen

consisted of a 15-minute self-administered session of acupressure at either 5 stimulatory or 5 relaxation points (3 minutes each). The stimulatory point formula consisted of *Si Shen Chong* and bilateral – Large Intestine 4 (LI 4), Stomach 36 (St 36), Kidney 1 (K 1), and Urinary Bladder 10 (UB 10). All points were stimulated using either the thumb or forefingers to massage in both clockwise and counterclockwise directions. The primary outcome was the difference between afternoon and morning scores on the Stanford Sleepiness Scale (SSS) (afternoon score – morning score).[16] The SSS was administered 2 hours prior to and 3 hours after each acupressure regimen. The 3 hour endpoint was chosen because this was the end of the class period where students were most likely to be fatigued. Data were analyzed using the PROC MIXED procedure of SAS (version 8.2). This model incorporated the fixed effects of sequence (I or II), period (day 1, 2, or 3), treatment (relaxation or stimulation), and other covariates, as well as the random effects of subject within sequence.

Results: A mixed model regression analysis using the change in SSS as the dependent variable was performed and the following variables were retained from the model: treatment (p=0.019), day (p=0.004), AM caffeine (p=0.083), hours of overnight sleep (p=0.042), and AM upsetting event (p=0.071). No significant carry over effects between days or treatments were detected. The least squares means for the stimulation and relaxation acupressure treatments were 0.570 and 1.127, respectively, with a significant difference in change in alertness scores between the 2 acupressure treatments. The mean difference between morning and afternoon SSS scores are presented by treatment, sequence, and day in Figure 2 above. Participants in the relaxation acupressure group took more naps (p=0.048) during day 1. Stimulating acupressure yielded a 0.56-point greater difference in score on the SSS, corresponding to less fatigue, compared to the relaxing acupressure treatment (p = 0.019). Day of study (p = 0.004) and hours of overnight sleep (p = 0.042) also significantly affected the change in SSS scores. Incorporating participants' beliefs as to which treatment they received did not significantly alter the observed treatment effect.



4.0 METHODS

We propose to perform a randomized, single-blind parallel clinical trial. This will be parallel design with four arms (relaxing acupressure plus usual care, stimulating acupressure plus usual care, sham acupressure plus usual care and usual care alone) for persistent fatigue in SLE. The study will be approximately 12 weeks in duration: **Screening** (up to 30 days in duration) consists of a phone call evaluation for study eligibility; **Treatment** (active treatment phase; 6 weeks in duration) will consist of random assignment to self-administered acupressure regiment plus usual care or usual care only daily for 6 weeks (outcomes will include fatigue, sleep, QOL, pain); and **Post-treatment follow-up** (4 weeks in duration) to evaluate the persistence of effects following 4 weeks of no treatment. We will allow up to +/- 2 weeks difference for study visits and the interim phone call in order to accommodate schedules.

4.1 Participants and Recruitment

Patients will be recruited from multiple University of Michigan Rheumatology Clinics including the Brighton Health Center and the Taubman Clinics at the University of Michigan Hospital. Both General Rheumatology and Lupus Specialty Clinics will be available for recruitment. Participants in other studies who have granted permission to be contacted about other research protocols (eg, MILES program or the Michigan Lupus Cohort),

will also be recruited. Lastly, we will recruit from the UMHealthResearch.org website and from the surrounding community through the use of fliers.

4.2 Eligibility Criteria.

4.2.1 Participant Characterization

Eligible participants will be patients with SLE, classified according to the 1997 American College of Rheumatology (ACR) criteria, attending General Rheumatology and Lupus Specialty Clinics at the University of Michigan. Participants will undergo a full clinical assessment including collection of core measures such as disease damage (SLAQ), disease activity (SELENA SLEDAI), organ involvement, disease duration, medication use, serological status and co-morbidities. Furthermore, information of factors which may be associated with the reporting of fatigue will be collected. Eligible participants that are not a part of the U of M health system will be determined by completing a connective tissue disease screening questionnaire (CSQ), if scoring positive on the CSQ these participants will be asked to complete a medical records release form. Once the study team receives the medical records they will conduct a medical record review to ensure the ACR criteria for SLE has been met. Additional eligibility criteria are listed in Table 2.0. During screening, identification of an untreated mood disorder or suicidal ideations will exclude the participant from the study. The study team will provide a list of resources for those with an untreated mood disorder and will follow study protocol for dealing with severe depression and suicidal ideations.

Table 2.0 Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
✓ Women aged 18 years and older ✓ Report chronic (>3months) clinically relevant fatigue, defined as a score of ≥4 on the Brief Fatigue Inventory (BFI) ✓ Have inactive disease, defined as SELENA SLEDAI ≤ 4, AND/OR no addition or increase in dose of corticosteroids, immunosuppressive agents, or antimalarial medications or hospitalization in the last 30 days ✓ Have no commonly recognized medical explanations for fatigue (a history of cancer in the previous 5 years –except for certain low risk cancer, unstable thyroid disease, moderate to severe chronic kidney disease, moderate to severe anemia) ✓ Baseline glucocorticoid dose equivalent of ≤10mg prednisone. ✓ No other planned intervention for fatigue other than current stable medication regimen	× Pregnant or breast feeding × Have a diagnosis of untreated mood disorder, e.g., bipolar or major depressive disorder × Have an initiation, a cessation or change of treatment of any chronic medications, dietary supplements, behavioral therapy, physical therapy etc., or any planned change of medications, supplements or therapies during the study × Acupuncture or acupressure receipt in past year

4.3 Randomization and Stratification.

Our randomization scheme will be created by our study statistician. Eligible patients will be randomized into one of four groups: once daily relaxing acupressure, once daily stimulating acupressure, once daily sham acupressure or usual care in a 1:1:1:1 ratio for a total of 72 participants with 18 randomized into each group.

4.4 Blinding.

The three acupressure formulas (relaxing, stimulating and sham) will be labeled acupressure set "A", set "B", and set "C". Acupressure educators, outcome assessors, study participants, and study investigators (who will not interact with any of the study participants) will be blinded as to acupressure allocation. Only after data analysis is completed will the randomization code be unblinded. Those randomized to usual care will know that they are not receiving acupressure.

4.5 Intervention Methods.

We will teach participants to perform acupressure on themselves, i.e., self-administered acupressure. The participants will be taught by acupressure educators who are study staff, and who will be trained by the study co-PI Richard Harris, a professional acupuncture practitioner. Training will include basic philosophy of TCM and acupressure, demonstration of acupressure points (relaxing, stimulating or sham points). He will designate the three sets of points as set "A", set "B", or set "C" so educators will be blinded as to which sets of points are the true versus the sham treatment. He will also ask the educators to demonstrate the correct location, pressure and stimulation techniques.

4.5.1 Testing Fidelity of the Intervention in Acupressure Educators

Dr. Harris will test the acupressure educators after their first two participants and thereafter once every three months. He will also ask them to identify each acupoint for both interventions, apply the correct amount of pressure and stimulation on a point on himself; and ask them how long to stimulate each point, and how often points should be stimulated. Incorrect answers will be addressed and corrected. Further, acupressure educators can request additional clarification and instruction at any time. Acupressure educators achieved a 92% fidelity score in our previous study.[17]

4.5.2 Teaching Participants the Acupoints

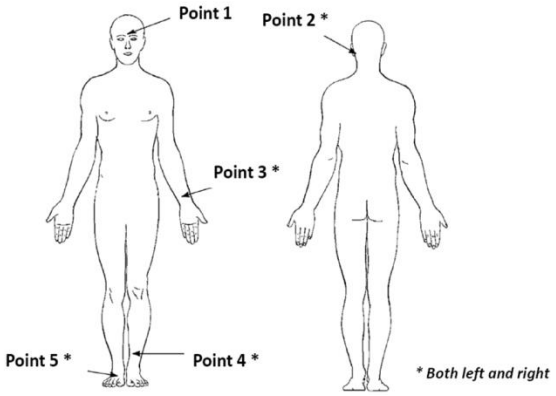
From our previous study[18] participants can be taught to perform their acupoints within 15 minutes. Acupressure educators will meet with each participant separately and demonstrate the location of each acupoint on themselves and on the participants. Participants will be given an illustration of acupoints along with a written description of where the points are located. At the end of the session participants will be tested to determine their acupressure fidelity by demonstrating the location of all their acupoints to the educator and appropriate adjustments will be made. Acupressure educators also demonstrate on the participant the appropriate level of pressure to apply and the correct motion. Participants are asked to stimulate points on the educator until it is determined that they are using the correct pressure. Participants may return at any time to be retrained or ask clarifying questions.

4.5.3 Relaxing Acupressure

There are 5 acupoints with 4 of the acupoints performed on both the left and right sides of the body (total of 9 points to stimulate; see Figure 3.0). Each of the 9 acupoints will be stimulated for 1 minute per point giving a total treatment time of 9 minutes daily. The relaxing acupoints are:

- *Point 1: Yin tang* (Unilaterally)
- *Point 2: Anmian* (EX17) (Bilaterally)
- *Point 3*: Heart 7 (HT7) (Bilaterally)
- *Point 4*: Spleen 6 (SP6) (Bilaterally)
- *Point 5*: Liver 3 (LV3) (Bilaterally)

Figure 3.0 Relaxing Acupressure



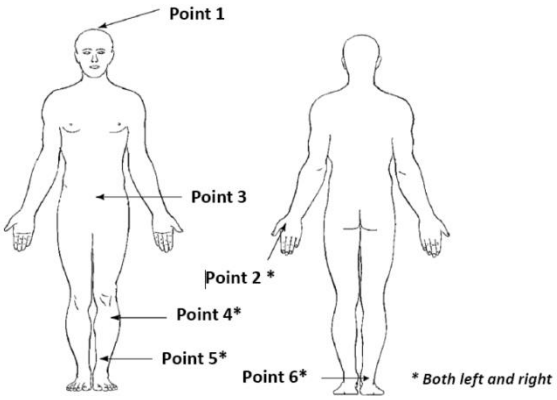
4.5.3.1 Justification for the Choice of Relaxing Acupressure Points. The "True Acupressure" points were chosen based on a TCM theory for treating insomnia, that these specific acupoints are commonly used for insomnia in clinical trials,[19] that previous studies using these 5 specific acupressure points found better results than other commonly used acupressure points for inducing sleepiness[18 15], and mechanistic studies indicating effects on sleep for the 4 of the 5 acupoints: HT-7; SP-6; LV-3; and *anmian*, which have demonstrated effects on sleep-related neurotransmitter systems and HPA axis activity in basic, human and animal studies.[20-30]

4.5.4 Stimulating Acupressure

Stimulating acupoints were chosen to increase daytime activity. There are 6 acupoints with 4 of the acupoints performed on both the left and the right sides of the body giving a total of 10 points to stimulate. Each of the 10 acupoints will be stimulated for 1 minute per point giving a total treatment time of 10 minutes done once daily. The acupoints are:

- *Point1:* Si Shen Chong (Unilaterally)
- *Point2:* Conception Vessel 6 (CV6)
- *Point 3*: Large Intestine 4 (LI4) (Bilaterally)
- *Point 4*: Stomach 36 (ST36) (Bilaterally)
- *Point 5:* Spleen 6 (SP6) (Bilaterally)
- *Point 6:* Kidney 3 (K3) (Bilaterally)

Figure 4.0 Stimulating Acupressure



4.5.4.1 Justification for the Choice of Stimulating Acupressure Points Acupoints were chosen by consensus of 4 acupressure practitioners and based on a previous study design in students with sleep disturbances as well as TCM theory for treating insomnia and fatigue.[15,31] Practitioners had all been in practice for at least 2 years actively seeing patients. They also had been trained as and received one of more of the following degrees; a Naturopathic Doctorate (ND), masters in TCM or Oriental Medicine and a license of acupuncture (L.Ac.) or a diploma in acupuncture (Dipl. Ac.). Practitioners were asked to choose a set of relaxing and stimulating acupressure points based on a Western diagnosis of fatigue that could be reasonably reached by participants,

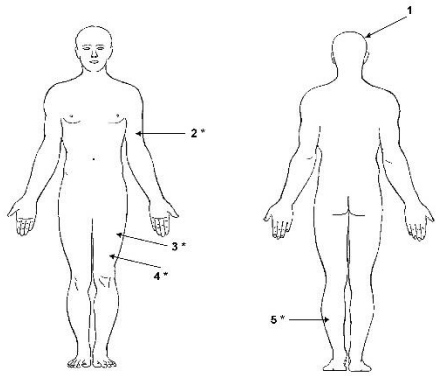
i.e., not the middle of the back, and not so many points that it would take an excessive amount of time to complete a treatment.

4.5.5 Sham Acupressure

Sham acupoints were chosen by Dr. Harris in locations where no known acupoints exists. There are 5 acupoints with 4 of the acupoints being performed bilaterally (Figure 5.0). None of these points are on meridians nor are they near actual points (at least one inch away from meridians). They were chosen to be in the same general body quadrant as the true points. Each of the 9 acupoints will be stimulated for 1 minute per point giving a total treatment time of 9 minutes daily. The sham acupoints are:

- Pressure Point #1 (Unilaterally)
- Pressure Point #2 (Bilaterally)
- Pressure Point #3 (Bilaterally)
- Pressure Point #4 (Bilaterally)
- Pressure Point #5 (Bilaterally)

Figure 5.0 Sham Acupressure



* = bilateral

4.5.6 Usual Care (UC)

Participants will be asked to continue following their healthcare providers' instruction for chronic SLE management. We anticipate that most women will be treated per the American College of Rheumatology clinical guidelines. Participants will be asked to continue any current treatment and not to start or stop treatments including acupuncture/acupressure over the course of the study. All treatments for pain will be recorded.

4.6 Study Schedule and Contacts

	SCREENING	***TREATMENT PHASE***				***FOLLOW-UP***
Week	**-2 to 0 (+/- 2 weeks)**	**0 (+/- 2 weeks)**	**1-6**	**2 (+/- 2 weeks)**	**6 (+/- 2 weeks)**	**10 (+/- 2 weeks)**
Activity	Participant Interaction #0	Participant Interaction #1 Baseline	Daily (Days 1 to 42)	Participant Interaction #2 Phone Call	Participant Interaction #3 Post-Treatment	Participant Interaction #4 Follow-up Call/Visit
Informed Consent		x				
Comorbidities	x					
Medication and Health History		x				
Sociodemographics	x					
Concomitant Medications		x			x	x
Lupus Activity (SLAQ)[1]	x	x			x	x
BFI[1]	x	x		x	x	x
CSQ[1]	x					
ARPHI[1]	x					
PHQ9 [1]	x					
Promis Fatigue 8 Item		x			x	x
RAND SF-36[1]		x			x	x
PSQI[1]		x			x	x

IPAQ		x				x
GAD7[1]		x			x	x
PANAS[1]		x			x	x
SWLS[1]		x			x	x
Fibromyalgia Survey Criteria		x			x	x
Perform Acupressure			x		x	
Assess Treatment Fidelity		x			x	
Assess Blinding					x	
Adverse Events				x	x	x
Adherence to Acupressure			x	x	x	
BPI[1]		x			x	x
Logbook			x			

1. SLAQ = Systemic Lupus Activity Questionnaire; CSQ – Connective Tissue Screening Questionnaire; ARPHI –Authorization for Protected Health Information; BFI = Brief Fatigue Inventory; PHQ9 = Patient Health Questionnaire 9-Item; PSQI = Pittsburgh Sleep Quality Index; IPAQ= International Physical Activity Questionnaire; GAD7 = Generalized Anxiety Disorder 7-Item; PANAS = Positive and Negative Affect Schedule; SWLS = Satisfaction With Life Scale; BPI = Brief Pain Inventory.

4.7 Study Visits

4.7.1 Screening- Participant Interaction #0 (to determine eligibility)

A screening phone call will be made to evaluate participant interest and eligibility including, comorbidities and ability to maintain a stable lifestyle over the course of the study. Sociodemographic and participant contact information will be collected. Fatigue will be assessed using the Brief Fatigue Inventory (BFI) and baseline depression and lupus disease activity status with the Patient Health Questionnaire 9 (PHQ-9) and the Systemic Lupus Activity Questionnaire (SLAQ). If a potential participant is not a part of the U of M health system they will complete the Connective Tissue Screening Questionnaire (CSQ) and will be sent an Authorization for Release of Protected Health Information form to complete and give to their health care provider.

4.7.2 Randomization/Baseline- Participant Interaction #1 (Week 0, +/- 2 weeks)

Written informed consent will be obtained at the beginning of the study visit. Medication and health history, concomitant medications, lupus disease activity and urine pregnancy test results will be collected if applicable. Participants will complete BFI, SLAQ, PROMIS Fatigue Short Form 8 (PROMIS Fatigue 8), RAND SF-36, Pittsburg Sleep Quality Index (PSQI), the Brief Pain Inventory (BPI), Generalized Anxiety Disorder 7 (GAD7), The Satisfaction With Life Scale (SWLS), Fibromyalgia Survey Criteria (FM Survey Criteria), International Physical Activity Questionnaire (IPAQ) and The Positive and Negative Affect Schedule (PANAS). Participants will be instructed in how to perform their acupressure and told to start their acupressure on the following day. Participants will complete the Acupressure Fidelity test after the acupressure instruction has been completed. A study logbook will be dispensed, to document conduct of acupressure and the time of day. The post-treatment visit will be scheduled for exactly six weeks from the start day and the follow-up visit for four weeks post termination of treatment.

4.7.3 Interim phone call- Participant Interaction #2 (within 2 weeks, +/- 2 weeks)

A phone call by study team will be conducted to assess adherence, AEs, BFI or to otherwise answer questions.

4.7.4 Post-Treatment- Participant Interaction #3 (Week 6, +/- 2 weeks)

Participants return to study site or we will conduct the interaction via BlueJeans or Skype. BFI, SLAQ, PROMIS Fatigue 8, RAND SF-36, PSQI, BPI, GAD7, SWLS, FM Survey Criteria, and PANAS will be conducted. Any adverse events or change in medication will be collected. Treatment fidelity and blinding will be assessed; study

logbooks will be collected and participants will be asked to stop performing acupressure. If participants choose to conduct the visit using BlueJeans or Skype they will email or mail their logbooks in and pressure will be assessed by observing nail blanching as an indicator of correct pressure.

4.7.5 Follow-up- Participant Interaction #4(4-weeks Post Acupressure; Week 10, +/- 2 weeks)
Participants return to study site or we will conduct the interaction via BlueJeans or Skype. BFI, SLAQ, PROMIS Fatigue 8, RAND SF-36, PSQI, BPI, GAD7, SWLS, FM Survey Criteria, IPAQ and PANAS will be administered. Any adverse events will be collected. All participants will have the option of being taught what study investigators consider to be the most effective acupressure technique.

4.8 Assessment Measures.

4.81. Disease Activity

Systemic Lupus Activity Questionnaire (SLAQ):[32] is a self-administered tool developed for screening and epidemiologic studies; it is not intended for clinical management or in place of physical examination. The SLAQ is based on items from a physician-scored activity index (SLAM) that are suitable for self-report. It includes 24 symptoms questions and a single numerical rating scale asking the patient to rate their disease activity over the past three months, based on their most active day during that time. While the SLAQ correlates well with physician tools, as with any measure that does not include laboratory measures, it will not detect abnormalities in laboratory findings among asymptomatic patients.

4.8.2 Fatigue (primary measure)

Brief Fatigue Inventory (BFI) consists of 9 items that are rated on a 0-10 rating scale where 0 represents “no fatigue or does not interfere” and 10 refers to “bad fatigue or completely interferes with activity/work.” The BFI has been validated in disease groups including rheumatologic populations.[33]

4.8.3 Fatigue (secondary measure)

The PROMIS Fatigue-Short Form 8[34,35] consists of 8 items that assess the impact and experience of fatigue in the past week. It uses a 5-point Likert-like scale with response options that range from “Not at all” to “Very much.” A raw score is calculated by summing scores across items then a conversion table is used to calculate T-scores with higher scores indicating greater fatigue.

4.8.4 Health-Related Quality of Life

The Rand SF-36 is a reliable and valid self-report questionnaire consisting of 36 items aggregated to score 8 subscales related to physical and mental health.[36] Subscales include Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Function, Role Emotional and Mental Health. The subscale scores are normalized for a mean of 50 with a standard deviation of 10 where higher scores indicate better health.[36]

4.8.5 Pain

The Brief Pain Inventory (BPI) is a 15-item self-report measure that has been validated for use in a wide variety of pain states.[37] The BPI assesses for the presence of pain, pain intensity (i.e., worst, least, average, current) and functional interference from pain. Broad validation of this measure in the context of assessing chronic pain in FM has been reviewed.[38]

4.8.6 Sleep

Pittsburgh Sleep Quality Index (PSQI) is a widely used, valid and reliable measure of global sleep quality and sleep-related symptoms.[39] The 19-items yield 7 component-scores that reflect common sleep problems such as subjective sleep quality, sleep disturbance and use of sleep medication. The components are summed to yield a global score (0 to 21) with poorer sleep quality associated with a higher score.

4.8.7 Depression

Patient Health Questionnaire 9-item (PHQ-9): The PHQ-9 is a 9-item multipurpose instrument that has utility for screening, diagnosing, monitoring, and measuring the severity of depression. Diagnostic validity has been assessed in studies of primary care and obstetrical clinics. Scores ≥10 have a sensitivity of 88% and a specificity of 88% for major depression. Scores of 5, 10, 15, and 20 have been associated with "mild" "moderate", "moderately severe," and "severe" classifications of depression.[40]

4.8.8 Anxiety

Generalized Anxiety Disorder 7-item (GAD-7). The GAD-7 is a 7-item measure of anxiety. It has good reliability, criterion, construct, and factorial validity. It has a sensitivity of 89% and specificity of 82% for generalized anxiety disorder. It can be completed in several minutes and administered longitudinally.[41]

4.8.9 Subjective Well-Being Scores

Theory and research suggest that subjective well-being has at least three components: positive affective appraisal, negative affective appraisal, and life satisfaction.[42,43] Composite scores for well-being will be calculated using scores obtained on the measures below. For each case, negative affect will be subtracted from positive affect and life satisfaction score will be added to that for a single global well-being score. Well-being scores derived in this manner have been shown to be sensitive to change.[43]

Well-Being – Affect: Positive and Negative Affect Schedule (PANAS). The PANAS consists of two mood scales with 10-items each rated on a 5-point scale for assessing positive (e.g., inspired, strong) and negative affect (e.g., guilty, scared).[44] Each scale has a range of 10-50 with higher scores indicating greater levels of affect. Both scales are internally consistent, uncorrelated, and stable over a 2-month time period; good convergent and discriminant validity have been demonstrated.[44,45]

Well-Being – Life Satisfaction: Satisfaction with Life Scale (SWLS). The SWLS is a global measure of life satisfaction consisting of 5 items rated on a 7-point scale.[46] The SWLS is a reliable and valid measure of life satisfaction showing large correlations with reports by family/friends of the person's life satisfaction, number of memories of satisfying experiences and other similar scales.[42,46,47]

4.8.10 Fibromyalgia Survey Criteria

The regional distribution of pain can help differentiate pain due to peripheral damage or inflammation (e.g., a few discrete regions) vs that seen in centrally-mediated syndromes such as fibromyalgia. A modified version of the Wolfe Regional Pain Scale[48] will be used that queries for the existence of pain in 19 bodily regions, using a checklist allowing for efficient scoring, along with the Wolfe Symptom Inventory (SI); a "fibromyalgianess" score can thus be calculated. The presence or absence of comorbid fibromyalgia (thought to occur in at least ~20% of SLE patients) is the largest predictor of pain, fatigue, and function in SLE[49]; across various rheumatic

diseases, SI scores are associated with greater severity of disease (including mortality) and sociodemographic disadvantage.[50]

4.8.11 Physical Activity

The International Physical Activity Questionnaire (IPAQ) assesses self-reported physical activity at 0 and 10 weeks via a validated 7-day recall measure in which time and frequency spent performing activities of different intensities are recorded and tallied[51,52].

4.8.12 Connective Tissue Screening Questionnaire (CSQ)

The Connective Tissue Screening Questionnaire (CSQ) is a validated self-report tool used to help identify connective tissue diseases (CTD) including SLE.[53] The CSQ is reproducible, sensitive, and "moderately specific instrument for screening subjects with potential" CTD and is used as a first step in identifying subjects with SLE. [53]

5.0 REPORTING ADVERSE EVENTS

5.1 Definition

An adverse event (AE) is any condition which appears or worsens after a participant is enrolled in an investigational study. An AE does not necessarily have a causal relationship with the study agent.

5.2 Assessment of Relationship of AE to Treatment

The possibility that the adverse event is related to study treatment will be classified as one of the following: not related, unlikely, possible, probable, definite.

5.3 Study Specific Adverse Event Reporting Plan

All Serious Adverse Events that are deemed related, probably related or possibly related will be reported to the IRBMED within 7 days, as per UM IRBMED guidelines (http://med.umich.edu/irbmed/ae_orio/ae_report_standard.htm).

All other non-serious, non-life-threatening adverse events will be reviewed by the PI and reported as per the following **Study Specific Adverse Event Reporting Plan:**

Reportable Events	**Timing of Report to IRBMED**
Unanticipated / unexpected problem involving risks to subjects or others	Serious - within 7 days Non-Serious - with scheduled continuation review
Any physical, social, or psychological harm attributable to participation in this research study (e.g. an injury occurring	Serious - within 7 days

during a study visit, bruising at the site of acupressure treatment)	Non-Serious - with scheduled continuation review
Death while on study	With scheduled continuation review
Loss of job or insurability due to breach or revelation of research records or participation.	Within 7 days of notification
Non-Reportable Events	
• Pregnancy, or birth-related complications • Hospitalizations and morbidity expected in population (e.g. surgery for removal of fibroid tumor) • Other serious or non-serious events deemed *not related* or *unlikely related* to the research	

Serious = an event requiring hospitalization, permanent disability, incarceration, significant familial disruption (e.g. separation, divorce), job loss

Non-Serious = an event requiring some medical, psychological, psychiatric or similar attention to resolve.

Scheduled continuation review = renewal application.

5.4 Follow-up of AEs

All AEs will be followed according to good medical practices, and documented as such.

5.5 AE Reporting and Data Elements

All participants will be questioned regarding adverse events during the follow up phone call and final visit. All participants will be instructed to contact the study coordinator via phone call or email at any time during the study if they have a concern.

All adverse events that occur after the informed consent is signed will be recorded on the adverse event case report form (CRF) whether or not related to study intervention.

The following information will be collected for all adverse events:

- AE reported date

- AE Verbatim Term
- CTCAE Term (v 4.03)
- Event onset date and event ended date
- Severity grade
- Attribution to study treatment (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study intervention
- Outcome of the event
- Comments

5.6 Severity of AEs

Severity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at [http://ctep.cancer.gov].

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as follows:

Grade	Severity	Description
1	Mild	• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • Intervention not needed
2	Moderate	• Minimal, local or non-invasive intervention indicated • Limiting age-appropriate instrumental activities of daily living
3	Severe	• Medically significant but not immediately life-threatening • hospitalization or prolongation of hospitalization • Disabling • Limiting self-care activities of daily living
4	Life threatening	• Life threatening consequences

		• Urgent intervention needed
5	Death	• Death related to Adverse Event

6.0 CONCOMITANT MEDICATION, EXERCISE, DIET AND SMOKING

6.1 Limitations on Medication, Exercise, Diet and Smoking

Concomitant prescribed medications are allowed except as listed in Exclusion Criteria. Participants will be asked to refrain from starting or stopping any new medications or supplements for the entire duration of the study. Acute medication will be allowed, defined as taking a medication for < 10 days over the course of a month with the intent to discontinue that medication.

Similarly participants will be asked to maintain their customary exercise, dietary and smoking habits during the screening, intervention and follow-up phase of the study. Participants will be asked to refrain from starting or stopping any new lifestyle modifications for the entire duration of the study.

6.2 Documentation of Medication

All chronic medications (prescription or OTC used for at least 14 days continuously), dietary supplements and/or herbal preparations taken by the participant during the study period will be documented on a CRF with information including:

- Type of medication
- Medication dosage/schedule
- Purpose for taking the medication, supplements or herbs (if available)

7.0 OFF-STUDY CRITERIA

7.1 Study Termination

The study will be terminated for an individual when a participant completes the full study, as defined as completing the week 10 visit (follow-up visit).

The Principal Investigator can decide to terminate a participant's participation in the study at any time. This decision could be based on factors such as unacceptable adverse events or for safety concerns. The reason for termination shall be documented in the case report form.

7.2 Premature Removal of a Participant

7.2.1 Personal reason

A participant may withdraw from the study at any time.

7.2.2 Lost to follow-up

Several attempts must be made by telephone and letter to determine the circumstances for loss to follow-up, since such loss may be related to the study intervention.

7.2.3 New illness or Medication

Participants, who are diagnosed with a new chronic illness, start a new prescribed chronic medication (taking medication continuously for longer than 10 days) or have an increase in medication dose during the study period, will be withdrawn from the study and replaced by another participant. Participants who experience an acute illness (less than 2 weeks) e.g., a cold or receive acute medications will have these documented but will remain in the study.

7.2.4 Death

Participants who die while on study will be replaced by another new patient.

8.0 DATA MANAGEMENT

8.1 Case Report Form Set

The CRF, a set of forms for each participant, provides a record of data generated according to protocol. These forms are to be completed on an ongoing basis during the study. The research chart is the source of verification of data. During the study, CRFs will be monitored for completeness, accuracy, legibility and attention to detail. The CRFs will be retained for review.

8.2 Data Entry, Data Management and Quality Control

Hard copies of the data are kept in folders in the project coordinators' office, where it will be available for the project coordinators to evaluate whenever overall protocol assessment is wanted or needed. The coded list of participants on the study is maintained in a locked cabinet by the PIs. Confidentiality will be maintained and information kept on each participant will be made available only to the project coordinator and identified investigators.

8.3 Additional Reporting Requirements

8.3.1 Protocol revisions and amendments

- The IRBMED must be notified of proposed protocol amendments to assess impact on trial safety and management of regulatory submission.
- A full copy of the amended protocol must be submitted to the IRBMED for review and approval prior to initiating the amended protocol.
- The revised or amended protocol document must be accompanied by a cover sheet detailing the protocol changes, rationale for change, impact on other areas of the protocol, and specific reference to the changed protocol sections.
- The protocol shall be clearly marked with the protocol version number or amendment number
- All protocol amendments must be approved by the IRBMED prior to activation.

9.0 STATISTICAL METHODS

Baseline sociodemographic and clinical characteristics will be analyzed by treatment groups, using means and standard deviations (SD), counts and percentages as appropriate. Comparisons between groups on baseline characteristics will be tested using an independent sample t-test for continuous measures or Pearson's Chi-square, for categorical variables. In all analyses, a p-value of ≤ 0.05 was considered statistically significant. All tests will be two-sided.

9.1 Primary and Secondary Aims

To investigate the change through time both within and between groups for fatigue (BFI), we will use linear mixed models (LMM). An advantage of LMM is that it acts as essentially an intent-to-treat (ITT) analysis as it uses all available data at each time point. For each LMM, a random subject intercept will be included to account for subject clustering; visit, group, and the interaction term (visit by group), will also be included as fixed effects. The models for BFI will be controlled for the fixed effects of any baseline variable such as age or lupus disease activity that is significantly different at baseline. Normality of the residuals derived from the LMM will be assessed using the Shapiro–Wilk test and q-q plots. For non-normal results a Box-Cox transformation will be utilized. The same methods will be employed to investigate secondary outcomes of interest pain (BPI severity sub-scale), sleep (PSQI global score) and quality of life (RAND SF-36).

9.1.2 Handling Missing Data.

The *linear mixed-effects* framework is an intent-to-treat framework in the sense that it uses all available data at all time-points. So if there are missing outcome values in any phase due to patient dropout, the usual analysis will still be valid. If the proportion of dropouts is substantial (20% or more) in either arm, then we shall also perform a weighted analysis with weights equal to the inverse of the probability of dropout. On the other hand, missing covariate values for the subject-level information will be imputed using multiple imputation methods. All missing values will be imputed using the chained equation method. The advantage of using this technique is its flexibility in allowing different types of variables (categorical and continuous) to be imputed together without requiring any multivariate joint distributional assumption. In this method, the missing values are sequentially updated using bootstrap or Markov Chain Monte Carlo based on multiple regression models with other variables as covariates. This procedure will be carried out for a number of repetitions or cycles, thereby constructing an 'imputed' dataset. Ten such 'imputed' datasets will be used for the final analysis, a number which is considered adequate for most applications. Finally we shall combine the results from the ten regressions with the imputed data using Rubin's formula. The multiple imputation method uses the assumption that the missing-ness conforms to a *missing at random* pattern which allows missing-ness in a variable X to depend on other covariates but does not allow it to depend on X itself. All analyses will be carried out in the statistical software SAS version 9.2.

9.2 Sample Size Justification

Power is computed via simulation using LMM with a group, week, group by week interaction, and a random subject effect. Mean BFI values at week 6 are taken to be 4, 3, 2 at the end-treatment point for usual care, stimulating acupressure, and relaxing acupressure. The between-subject variance is assumed to be 4 at all time-points; whereas the variance of the random subject component was also 4 with an intra-class correlation of 0.5.[31] For this configuration, power for detecting group differences is > 0.80 and power for detecting a significant week by group interaction is 0.62 with a sample size of 15 per treatment arm and 5% level of

significance. We assume a 16 to 17% drop-out rate based on previous studies and thus plan to recruit 18 per arm to ensure that 15 participants complete the entire 10-weeks of the study.

10.0 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Institutional Review Board (IRB) Approval

Prior to initiating the study, the PI must obtain written approval to conduct the study from the appropriate IRB. Should changes to study protocol become necessary, protocol amendments will be submitted electronically by the PI to the IRB for approval prior to implementation.

10.2 Informed Consent

All potential candidates for the study will be given a copy of the study informed consent to read. The investigator or their designee will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate decides to participate in the study, he/she will be asked to sign the informed consent document. Participants who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent document must be reviewed and approved by the IRB prior to study initiation. Any subsequent changes to the informed consent must be approved by the IRB for approval prior to implementation.

10.3 Data and Safety Monitoring

10.3.1 Guidelines

The purpose of the data and safety monitoring plan is to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical, and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include:

- Monitoring the progress of trials and the safety of participants
- Plans for assuring compliance with requirements regarding the reporting of adverse events (AE)
- Plans for assuring data accuracy and protocol compliance.

The known or expected risks associated with this study include:

- Risk of bruising at points of pressure; there is a very small chance (<1%) of having bruises at points of pressure if too much pressure is applied. This bruising should not continue or get worse. To minimize the risk of bruising study staff members will demonstrate the correct amount of pressure to apply at the start of the study. Additionally, a member of the research team will call participants during the study to evaluate their health and safety. During these conversations study team members will ask about any bruising.

- Risk of breach in confidentiality; there is a possible risk of the loss of confidentiality of participant medical information. The study team will try to protect participant privacy and the confidentiality of information.

10.3.2 Study-specific DSMP

The PI will review study progress weekly with study staff, and problems with or pertaining to study subjects will be communicated immediately. The entire research team will meet monthly to review progress and any problems encountered. The PI will be notified when an AE occurs and will determine the attribution and relatedness of each adverse event. All AE must be given to the PI within 48 hours if involving a death or life threatening event, or within one week, if serious (not-life threatening/death) or non-serious.

10.4 Record Retention

Clinical records for all participants studied, including CRFs, history and physical findings, laboratory data, and results of consultations, will be maintained by the Investigator in a secure storage facility and stored for at least five years after the study is closed.

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