Symptom Management for Distal Sensory Peripheral Neuropathy in T2DM: A Preliminary RCT using Moxibustion

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ABSTRACT

Distal sensory peripheral neuropathy (DSP) is a chronic, painful condition in the lower limbs of many individuals with Type 2 Diabetes (T2DM). DSP is the most prevalent complication of T2DM. Moxibustion, a traditional Chinese medicine therapy, offers a non-invasive and promising treatment for DSP pain. This study examined Traditional and Smokeless Moxibustion in a prospective, randomized, placebo-and waitlist-controlled, subject-and evaluator-blinded, parallel-group clinical trial. Participants received twice weekly moxibustion treatments for three weeks and were followed for two months. Participants in this preliminary study completed symptom diaries, Gracely Pain Scale (GPS), Subjective Peripheral Neuropathy Scale (SPNS), and Clinical Global Impression Scale (CGIS) patient-rated outcomes. In both Traditional and Smokeless Moxibustion groups, not control groups, GPS symptom severity decreased from baseline to end of treatment, and the benefit was sustained for two months post-treatment, p< 0.001. In treated groups, all three SPNS characteristics (pain, pins/needles, numbness) decreased by >3 severity levels at the end of treatment and were unchanged from baseline in control groups, p <0.001. Traditional and Smokeless Moxibustion show promise as a non-invasive and non-pharmacologic therapy in DSP symptoms associated with T2DM. Standards for Reporting Interventions in Controlled Trials of Acupuncture-Moxibustion (STRICTA-M) guided the development and design of this study.

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Introduction

Distal sensory peripheral neuropathy (DSP) is a prevalent, distressing, chronic condition that causes debilitating pain in the lower limbs and feet of individuals with Type 2 Diabetes (T2DM), affecting their quality of life (QOL) [1-2]. In the US, 23 to 45 million individuals suffer from DSP, the most prevalent complication of Type 2 diabetes mellitus (T2DM). T2DM has become a global burden, with 536.6 million adults living with T2DM as of 2021 and an estimated 783.2 million by 2045 [3-6]. By ten years into the diagnosis, at least 50% of T2DM patients develop some form of neuropathy, the majority experiencing lower limb peripheral neuropathy [4-5]. Patients with DSP experience a range of distressing symptoms (e.g., pain, allodynia, paresthesia) in a bilateral stocking-and-glove distribution, contributing to sleep disruption, mood disorders, loss of protective sensation, impaired balance, falls, ulceration, amputations, loss of mobility, and disability [7-10]. To date, no therapies have been shown to reverse DSP progression; the goal of treatment, therefore, is symptom management. Conventional medical options for managing

DSP pain include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, and sodium channel blockers [11]. However, DSP patients treated with oral medications report low satisfaction rates, as oral agents have limited efficacy and commonly cause troublesome side effects (e.g., dizziness, nausea, drowsiness, insomnia, dry mouth), particularly among individuals with pre-existing comorbidities [8, 11]. Implanted stimulation devices are not well tolerated, and serious adverse events have been reported: infection, dural puncture, subdural hematoma, and death [12]. Given DSP prevalence and the limits of available treatments, noninvasive, nonpharmacological therapies for DSP symptom management hold great appeal. Traditional Chinese medicine (TCM)—comprising acupuncture, moxibustion (moxa), herbal therapies, and lifestyle interventions—has been used to prevent, manage and treat disease in the East for over 3000 years and is increasingly used in Western medical practice to manage pain [13-14]. Less well known in the West, moxa is a noninvasive TCM therapy that involves burning a dried herb Artemisia vulgaris, rolled into a cigar-shape, called

'pole moxa or 'moxa stick' over acupoints. Acupoints are specific point locations on which are stimulated with the lighted moxa stick using the *indirect technique* [13-14]. Animal studies suggest that moxa may work by restoring the balance between nuclear factor-2 (Nrf2) and nuclear factor-kappa B (NFκB) protein expression in nerve tissues, thus reducing neuroinflammation and neuropathic pain [15]. While moxa is commonly used as an adjuvant therapy to acupuncture, moxa may also be administered as a monotherapy, stimulating acupuncture point(s) without needles. Moxa has the advantage of excellent tolerability and high patient acceptance, including among those with a fear of or an aversion to needles [16-18]. The procedure for delivering moxa is such that, with training, some patients might be able to self-administer at home, which might, in theory, improve convenience, access, and treatment adherence and reduce costs. Moxa is available in traditional and "smokeless" forms (which inhibits smoke formation) and is particularly well suited for clinical practice and research but has never been evaluated in the same study. Well-designed clinical trials of moxa are rare. To address this gap, our team designed and conducted a preliminary study to establish the feasibility, methods of participant recruitment, retention, and protocol design and to estimate the effects of moxa for DSP lower extremity pain in persons with T2DM for a future study [19].

Materials and Methods
Study Design
Forty-four adults with T2DM who experienced a '*moderate*' level of DSP pain were randomized to one of four groups in a randomized, controlled, participant-and evaluator-blinded RCT. Study procedures and methods details were published previously [19]. In brief, participants who met the eligibility criteria and averaged moderate pain or greater on a 1-week symptom diary (SD) using the Gracely Pain Scale (GPS) were randomized to one of four groups:

- Traditional Moxa,
- Smokeless Moxa,
- Placebo Moxa (control), or
- Waitlist (control).

Treatment assignments were concealed and placed in sequentially numbered, sealed, opaque envelopes. The study coordinator, neurology nurse practitioner, data manager, and statistician were blinded to group allocation until the final data analysis. Participants in active treatment groups (1 and 2) and Placebo moxa control (group 3) received six treatments (twice weekly treatments for three weeks). Those randomized to group 4 received usual care over an equal period but did not receive true or placebo moxa intervention. Groups 1, 2, and 3 participants were followed for eight weeks following the last treatment. Followups were included to assess group differences after treatment had stopped. Participants received $10 and a round-trip MetroCard valued at $5.50 for each completed study session. The study received institutional review board approval before the start of the study, and informed consent was obtained from all study participants.

Participants
The inclusion criteria were adults 18-75 years of age, diagnosed with T2DM, bilateral lower limb DSP and experiencing *moderate* pain and symptoms (numbness, tingling, burning) for a minimum of three months or more, achieved a score of 24 or better on the *Mini-Mental State* questionnaire, stable analgesic regimen (drug, dose, and frequency) for at least three weeks, and committed to maintaining stable medications for the duration of the study. Medication changes during the study were recorded. We obtained written verification from the primary care provider of T2DM,

DSP diagnosis, and medical history consistent with the eligibility criteria. Individuals were excluded if they had acute conditions requiring medical care (e.g., severe heart disease, uncontrolled hypertension, lung disease, renal failure, foot lesions, sores, ingrown nails, infection); current use of topical medication(s) applied to the lower extremities/feet; allergic to smoke; alcohol and/or substance dependence; current use of injectable corticosteroids and use of other complementary therapies for treating foot pain (e.g., herbs, massage, acupuncture); pregnancy and inability to attend all planned study sessions and/or recording daily symptom diary (SD) information.

General Procedures
Licensed acupuncturists trained in TCM performed the moxa procedures for groups 1, 2, and 3 (Traditional moxa, Smokeless moxa, and Placebo moxa). Before the start of the study, the acupuncturists received training and passed both a written and practical exam consisting of point location and applications specific to the study protocol [20]. The acupuncturists were also trained to administer the placebo moxa. Conversations during treatment sessions were scripted and focused on participant instructions. Participants in study groups 1, 2, and 3 were blindfolded during each treatment session to minimize the secondary effects of visual cues associated with the moxa procedure. A neurology nurse practitioner conducted the neurologic and sensory testing (NST) to establish a baseline assessment of DSP, which involved motor pathways, sensory pathways, gait, coordination, and reflexes. The Medoc Q-Sense© was also used to test the thermal sensitivity of small nerve fibers for warm, cool, and heat-pain thresholds. It is a validated quantitative sensory testing (QST) device for evaluating neuropathic sensory function and detecting small fiber damage among people with T2DM [21- 22]. The neurologic assessments were conducted at sessions 1 and 7.

Study Protocol
Design Consideration
An important consideration in designing this study is including a Placebo Moxa control and a WaitList control. We incorporate a Placebo condition, designed and tested to be indistinguishable from active Moxa, to control for effects potentially attributable to attention and moxa administration and/or the odor associated with the true intervention. Our team has experience delivering and monitoring the fidelity of these double-masked control protocols that we developed, tested, and published [23]. We incorporate a WaitList control to estimate the naturally occurring changes in DSP pain that occur over time.

Protocol Point Selection
The selection of protocol points for this study was conducted carefully, considering several factors. Our primary objective was to identify a fixed set of points effective for T2DM DSP pain when using moxa therapy. To achieve this, we considered the descriptions of pain and discomfort characteristics associated with DSP in patients with T2DM (pattern differentiation in TCM) and the location of pain and related symptoms in the lower limb and feet. The points chosen were specifically aimed at promoting the movement of qi and blood, unblocking stagnation, and assisting in the restoration of energy. Furthermore, we incorporated the current understanding that acupuncture meridians (or channels) stimulation is propagated along these planes [24]. We also selected points that lie on large planes of fascial tissue in the body that would benefit DSP. In addition to efficacy, practicality was also an important consideration. We identified points on the lower limbs and feet that could be easily implemented in various clinical settings. This has the potential to eliminate the need for patients

to fully undress, allowing for the possibility of implementing the protocol in settings furnished with chairs instead of traditional treatment tables. This approach has the potential to significantly impact the management of lower limb DSP pain in T2DM, benefiting a larger population.

Protocol Schedule

To further support our selection of points, we conducted expert consensus panel meetings and informational sessions (with TCM providers, neurology/diabetes specialists, and patients with DSP T2DM) to receive advice and feedback. These studies provided important information on clinical and patient acceptance toward the development of this study. The schedule consisted of one screening/eligibility session, six treatment sessions (twice-weekly for three weeks) and followups at 8, 12 and 16 weeks.

Protocol Points*

GB-34, ST-40, SP-6, GB-40, SP-4, LV-3, KI-1

*All points are bilateral; the point functions/rationale and specific sequencing and timing of points cited elsewhere [19].

Groups

Group 1: Traditional Moxibustion

Participants received the indirect moxa technique as described in the classic text, Chinese Acupuncture & Moxibustion [14]. The aim is to provide point stimulation by moxa, to move and smooth the flow of qi, provide warmth, nourish points, channels, organ systems and relieve pain (points listed above). Moxa sticks (cigar-shaped) made from the herb *Artemisia vulgaris* were lit and held approximately one inch over the traditional points. The moxa stick is moved in a clockwise circular motion directly over the point for 2 minutes or until the skin around the area of the point becomes pink. The participant can also give feedback about how hot the area is during treatment.

Group 2: Smokeless Moxibustion

Participants received smokeless moxa. The aim, points, and moxa administration procedure are the same as for Group 1, using the dried leaves of *Artemisia vulgaris* in a Smokeless Moxa formulation. This type of moxa looks similar in shape (moxa stick/pole, cigar-shaped); however, the moxa pole is densely compressed by the manufacturer, inhibiting smoke formation. We included smokeless moxa in our design because smoke from the traditional moxa type may not be permitted in offices or clinical facilities, thus limiting the use of an important therapy to manage pain. Incorporating this in our study may address this challenge and allow a broader range of treatment settings.

Group 3: Placebo Moxibustion (Control)

Participants received Placebo Moxa. A burning moxa stick is held approximately *eight inches above*, two to three centimeters *away* from the true point location for two minutes (points listed above). The acupuncturists are trained and instructed to administer this procedure that does not generate any heat sensation. The acupuncturist intermittently places their hand close to the participant's skin to assess heat sensation. This method allows the 'moxa-naïve' blindfolded participants to experience the smell, although not the heat of the burning herb. At the end of the study, participants were offered moxa treatments.

Group 4: Waitlist (Control)

Participants were provided with an experience of an equal time commitment as that of a moxa treatment session. Participants

randomized to the control group experienced all aspects of study participation except for exposure to moxa (during the study). They underwent all screening and eligibility assessments, attended study visits, submitted and review their SD updated concomitant medication and adverse event data, completed assessment instruments, and received NST assessments and compensation. In all respects, participants in the control group receive the same concern as participants assigned to the other groups. At the last study visit, participants were offered moxa sessions.

Outcome Measures
DSP pain

DSP pain was evaluated using daily SD that incorporated the **Gracely Pain Scale (GPS)** (the primary outcome) and the **Subjective Peripheral Neuropathy Screen (SPNS)**. The GPS measures the sensory components of pain using a 13-point Likert scale and records the average and worst pain experienced over a 24-hour period [25]. Each of the 13- word descriptors correspond to a log-scaled value of psychometrically validated "just-notice-able-difference" levels of pain intensity ranging from 0.00 to 1.77 (*nothing, faint, very weak, weak, very mild, mild, moderate, barely strong, slightly intense, strong, intense, very intense, extremely intense*). The weekly average of the daily rated log scores was used for the primary analysis. The SPNS was used to determine DSP pain severity [26-27]. A description of the pain symptom (*aching/burning, pins and needles, or numbness*) is first selected, and the severity of the pain symptom is rated on a 10-point scale. The Average Severity Score (SPNS Average) and Clinical Severity Grade (SPNS Grade) were computed for the analysis. The SPNS Average is the mean daily symptom severity score ranging from mild (1) to most severe (10), and the SPNS Grade is the highest symptom severity score of any symptom (aching/burning, pins and needles, or numbness).

Clinical Global Impression Scale (CGIS)

This scale was administered pre-intervention and post-intervention, measuring illness severity separately from global improvement on Likert-type scales with seven descriptors. The global severity of symptoms scale measures the participant's level of discomfort with their DSP, from no discomfort (0) to *very severe discomfort* (6) [28-31]. The global improvement scale measures the level of change after receiving an intervention, from *no improvement at all* (0) to *great improvement* (6). The score allows for the integration of a disparate group of symptoms into a single global clinical rating. CGIS was administered at pre-intervention and post-intervention. The CGIS is recognized as a 'well-known, cross-culturally valid measure' with test-retest reliability > 0.70 and suitable convergent, discriminant, and criterion validity; and ROC AUC + SE against gold-standard assessments of global improvement of 0.84 + 0.06 (95% CI 0.72 – 0.97) [29].

Credibility Assessment

Credibility Assessment is a tool to assess participants' rating of the 'credibility' of treatment in a research study. The tool was adapted from an acupuncture credibility assessment scale developed by Borkovec and Nau [32-33]. The instrument measures the *level of confidence* that they received the true moxa treatment rather than the placebo. Scores ranged from *very confident* (1) *to not at all confident* (6). Only participants in Groups 1, 2 and 3 completed this.

Safety Measures

Study staff collected and recorded adverse-event information at every session using a scripted adverse-event elicitation form. In

addition, a symptom checklist form was used to monitor health status information and any side effects associated with the moxa treatments if they occurred.

Statistical Analysis
We planned a data reduction analysis prior to inferential testing: if a comparison of the Placebo and Waitlist groups tested with a p-value difference larger than 0.50, those groups would be combined in subsequent comparisons; otherwise, group 3 (placebo) would serve as the control comparator. We would first estimate the combined Traditional and Smokeless Moxa groups difference from control, and then post hoc comparison of each moxibustion group with control and each other. Sample size calculations relied upon our prior study of acu/moxibustion treatment of DSP lower limb pain in patients with HIV. There, the GPS decreased from 1.30 + 0.20 to 1.12 + 0.40, and a reduction in the SPNS grade score from 7.32 + 1.00 to 6.31 + 2.35. The corresponding standardized effect size for the GPS is 0.90 and for the SPNS 1.01. A planned comparison of treated (Traditional and Smokeless) vs. control (Placebo and Waitlist), assuming 80% power, a two-tailed alpha of 0.05 using a simplifying T-test, was calculated to require 20 treated and 20 control participants.

Data Analytic Plan
Although a preliminary efficacy study, the planned statistical analysis followed accepted procedures for randomized clinical trials. All data was examined for completeness, accuracy of coding, reasonableness of values, distributions of continuous variables and category coverage of coded variables. Skewed distributions and poorly distributed counts across coded variable categories were transformed or collapsed, respectively, prior to analysis. The missing data mechanisms were explored, although the planned analysis did not require data imputation. Treatment group baseline characteristics were analyzed with Fisher's Exact Test for categorical variables and with Kruskal-Wallis one-way ANOVA test for continuous variables. The intent-to-treat analysis cohort was defined as all randomized participants who attended the second visit. The primary outcome intent-to-treat analysis of the between-group difference of the change in the GPS score from baseline to the endpoint of three weeks of twice-weekly treatment used an independent T-test of the change scores for comparing combined moxibustion groups to control and a three-group one-way analysis of variance (GLM) for traditional and smokeless moxibustion and control. Sheffé-adjusted post-hoc comparisons of means were used. Analysis of the secondary outcomes for SPNS-specific symptoms (pain, burning/tingling, numbness) and Clinical Global Improvement Scale scores were analyzed similarly. The primary and secondary outcomes were viewed as assessing qualitatively orthogonal dimensions of DSP lower limb neuropathy and therefore these analyses were not adjusted for multiple comparisons. Longitudinal follow-up data was analyzed with repeated measures analysis with baseline, three-week treatment endpoint and at the end of follow-up as fixed effect for time.

Results
Forty-four participants met eligibility criteria and were randomized to treatment, see CONSORT diagram Figure 1. See Table 1 for participant characteristics.
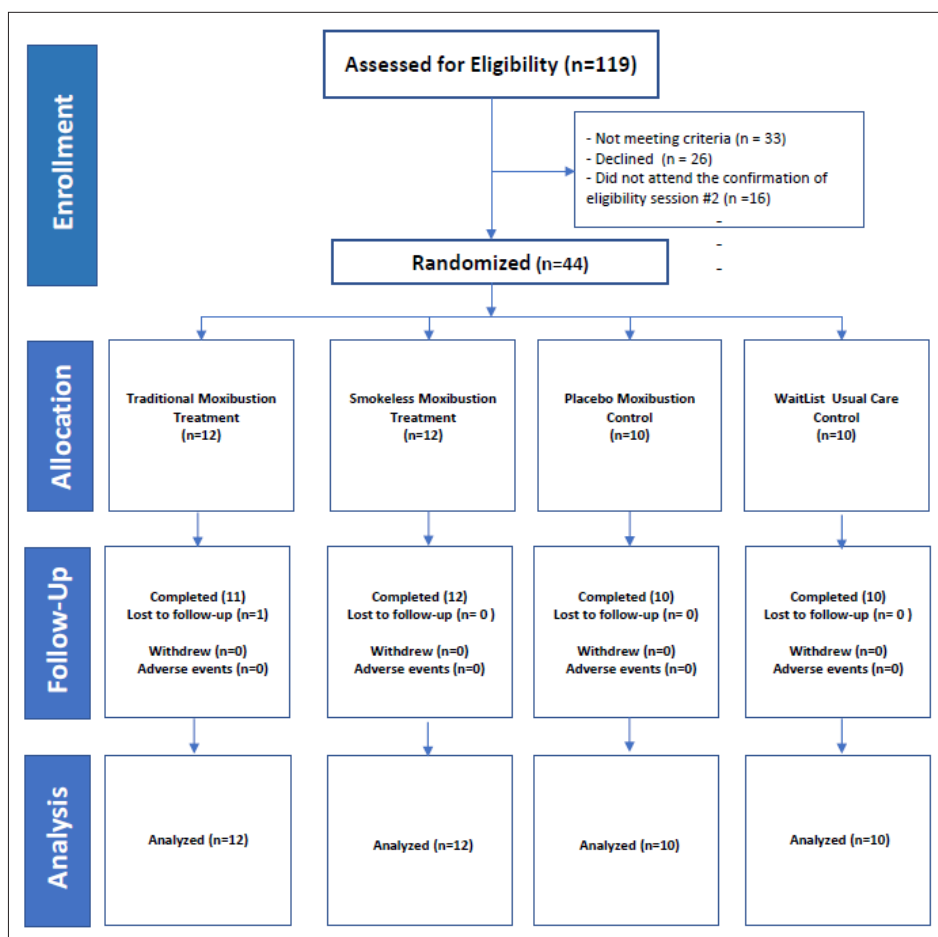
Figure 1: CONSORT

Table 1: Participant Characteristics and Clinical Presentation

Demographics	Traditional n=12	Smokeless n=12	Waitlist n=10	Placebo n=10	p-value [a]
Age (years)	66 (60 - 70)	65 (58 - 67)	63 (59 - 69)	65 (58 - 73)	0.99
Gender (n(%) female)	6 (50)	4 (33)	5 (50)	6 (60)	0.70
Race (n(%) White)	3 (25)	4 (33)	1 (10)	1 (10)	0.74
Race (n(%) Black)	5 (42)	5 (42)	6 (60)	6 (60)	
Race (n(%) Asian)	2 (17)	0 (0)	2 (20)	2 (20)	
Race (n(%) other)	2 (17)	3 (25)	1 (10)	1 (10)	
Ethnicity (n(%) Hispanic)	5 (42)	3 (25)	1 (10)	1 (10)	0.27
Height (inches)	64 (64-70)	65 (63-67)	65 (64-68)	66 (62-69)	0.94
Weight (pounds)	181 (156-206)	194 (165-207)	173 (154-212)	187 (139-236)	0.96
BMI	31 (26-32)	32 (28-34)	27 (30-38)	26 (27-31)	0.66
Hypertension	7 (58)	7 (58)	7 (70)	7 (70)	0.92
Medications:					
Diabetes meds.(eg. metformin)	10 (83)	9 (82)	4 (40)	6 (60)	0.13
Antihypertensives meds.	7 (58)	4 (36)	4 (40)	9 (90)	0.06
Cholesterol meds.	3 (25)	3 (27)	1 (10)	7 (70)	0.04
Pain meds (eg.duloxetin)	2 (17)	0 (0)	0 (0)	2(20)	0.30
[a] Four group comparison by Kruskal-Wallis one-way ANOVA or Fisher's Exact test.					

Outcomes

The baseline Gracely Pain Scale (0=nothing to 12= extremely intense) ratings of the *average* DSP symptom pain and the worst symptom pain for the seven days preceding initiation of treatment did not differ across randomized groups, $p < 0.55$ and 0.57, respectively, with means between "moderate" and "strong" pain severity, see Table 2. Figure 2 shows Gracely Pain Scale raw scores at baseline and end of treatment. In both Traditional and Smokeless moxa groups, symptom severity decreased statistically significantly from baseline to end of treatment and remained so through follow-up, p-value for group-by-time interaction < 0.001. Of importance, participants in the treated groups report improvement of *three or more GPS weekly average pain levels* at the end of treatment. In contrast, Placebo and Waitlist groups were unchanged from baseline at end of treatment and the Placebo group remained at or above baseline pain severity levels through follow-up. Table 2 highlights Traditional and Smokeless moxibustion each statistically better compared to Placebo and Waitlist and not statistically different from each other.

The daily SD captures the SPNS the presence or absence of a symptom and the severity of the symptom if present. Table 2 shows the SPNS data for *pain/aching/burning, pins and needles,* and *numbness* in feet and legs at each timepoint. In treated groups, all three SPNS characteristics (*pain, pins/needles, numbness*) decreased by >3 severity levels at end of treatment groups and unchanged from baseline in control groups, $p< 0.69$, with symptoms present about 6 of 7 days, $p < 0.79$ at a severity of 6 on a scale of 0 to 10, $p < 0.78$, again averaging about 6 days per week, $p < 0.35$, and with an average severity slightly below 6, $p < 0.71$. Numbness was reported by 37 of 44 participants, $p < 0.77$, on average 6.5 days per week, $p < 0.39$, with a wide-ranging severity from 4.8 to 7.3, $p < 0.21$ across groups. The proportion of participants who report experiencing all three symptoms in the same week was high: Traditional Moxa 67%, Smokeless Moxa 92%, Placebo 90% and WaitList 80%, $p < 0.47$ across groups.

The CGI scale of pre-treatment symptom ratings (*0 - none to 6 - very severe*) of overall DSP pain severity were "moderate" or greater with more than half of participants rating severity as "*severe*" or "*very severe*". CGI severity ratings for the individual symptoms of pain, *pins and needles or numbness* were the same as the overall DSP pain severity rating. The CGI symptom improvement scale, at end of treatment, showed greater than 2/3rds of moxa-treated groups reporting "*quite a bit*" to "*great*" improvement, and control groups all reported "*none*" or "*minor*" improvement in overall symptoms, pain, pins & needles, and numbness, all p-values by Fisher's Exact Test < 0.01.
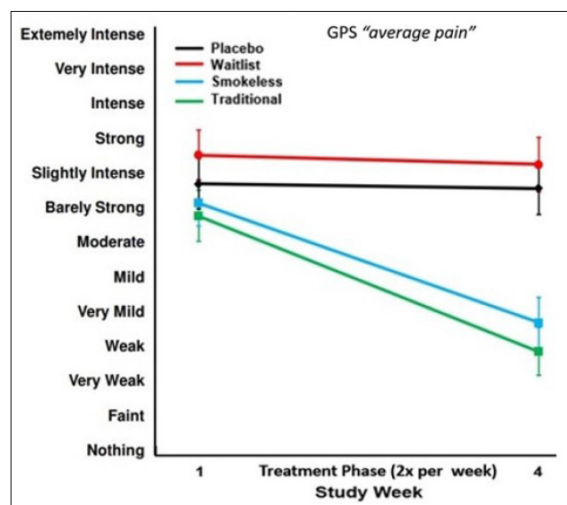

Figure 2: Gracely Pain Scale at baseline and end of treatment

Table 2: Gracely Pain Scale (GPS) and SPNS Symptom Severity

	Baseline/Screening Session 1/ Week 1	End of Treatment Session 7/ Week 4	Follow-up Week 8	Follow-up Week 12	Follow-up Week 16	p-value[1]
Traditional Moxibustion (n=12)						
GPS Average Pain	6.92 ± 5.25	**3.34 ± 4.60** [a]	**3.48 ± 4.71** [a]	**4.12 ± 4.60** [a]	**4.54 ± 4.94** [a]	0.001
GPS Worst Pain	7.47 ± 5.10	**3.56 ± 4.46** [a]	**3.77 ± 4.58** [a]	**4.40 ± 4.46** [a]	**4.50 ± 4.79** [a]	0.001
SPNS Pain/Aching/Burning	4.68 ± 5.72	**2.39 ± 5.14** [a]	**2.53 ± 5.55** [a]	3.14 ± 5.40 [a]	3.35 ± 5.81 [a]	0.019
SPNS Pins & Needles	4.90 ± 6.42	**2.23 ± 5.85** [a]	**2.90 ± 6.24** [a]	3.36 ± 6.11 [a]	3.53 ± 6.54 [a]	0.012
SPNS Numbness	3.94 ± 6.49	**1.48 ± 5.89** [a]	**2.10 ± 6.30** [a]	2.93 ± 6.16 [a]	3.19 ± 6.60 [a]	0.210
Smokeless Moxibustion (n=12)						
GPS Average Pain	7.27 ± 4.20	**4.10 ± 5.59** [b]	**4.10 ± 4.36** [b]	**4.69 ± 4.87** [b]	**5.35 ± 5.44** [b]	
GPS Worst Pain	7.53 ± 4.06	**4.30 ± 5.49** [b]	**4.57 ± 4.23** [b]	**5.09 ± 4.74** [b]	**5.49 ± 5.29** [b]	
SPNS Pain/Aching/Burning	5.98 ± 4.93	**2.61 ± 6.68** [b]	**3.46 ± 5.13** [b]	**3.92 ± 5.75** [b]	**4.06 ± 6.42** [b]	
SPNS Pins & Needles	5.72 ± 5.60	**2.31 ± 7.31** [b]	**3.81 ± 5.80** [b]	**4.37 ± 6.44** [b]	**4.40 ± 7.18** [b]	
SPNS Numbness	5.96 ± 5.64	**3.23 ± 7.41** [b]	**3.63 ± 5.85** [b]	**4.01 ± 6.50** [b]	**4.56 ± 7.26** [b]	
Placebo Control (n=10)						
GPS Average Pain	8.35 ± 4.60	8.28 ± 6.09 [ab]	8.40 ± 4.60 [ab]	8.17 ± 4.77 [ab]	8.50 ± 4.60 [ab]	
GPS Worst Pain	8.76 ± 4.45	8.20 ± 4.98 [ab]	8.60 ± 4.45 [ab]	8.36 ± 4.62 [ab]	8.90 ± 4.45 [ab]	
SPNS Pain/Aching/Burning	6.93 ± 5.94	7.01 ± 7.27 [ab]	7.40 ± 5.40 [ab]	7.50 ± 5.61 [ab]	7.40 ± 5.40 [ab]	
SPNS Pins & Needles	5.71 ± 5.60	6.24 ± 7.96 [ab]	5.80 ± 6.13 [ab]	5.89 ± 6.34 [ab]	6.10 ± 6.13 [ab]	
SPNS Numbness	6.42 ± 6.18	6.27 ± 8.07 [ab]	6.30 ± 6.18 [ab]	6.40 ± 6.39 [ab]	6.30 ± 6.18 [ab]	
Waitlist Control (n=10)						
GPS Average Pain	8.35 ± 4.50	8.00 ± 6.57 [ab]				
GPS Worst Pain	8.76 ± 4.51	8.07 ± 6.62 [ab]				
SPNS Pain/Aching/Burning	6.93 ± 5.68	7.03 ± 8.69 [ab]				
SPNS Pins & Needles	5.71 ± 6.79	6.06 ± 10.30 [ab]				
SPNS Numbness	6.41 ± 6.54	6.47 ± 10.14 [ab]				

GPS – primary outcome
Bolded value statistically different from baseline
Groups sharing the same superscript statistically differ at that timepoint
[1]Overall p-value for group-by-time interaction linear mixed model for repeated measures

Safety
No adverse events were reported during the course of this study.

Credibility Assessment
Eighty-eight percent of the participants in groups 1, 2, and 3 reported they were confident they received "true Moxa." These findings support that the treatment masking was effective.

Discussion
All participants began with GPS symptom severity at *or above level 6*, "*moderate*" or greater weekly average pain severity. In this preliminary study of 3 weeks of twice-weekly treatment with Traditional Moxa or Smokeless Moxa, over two-thirds of treated participants responded with a clinically meaningful reduction of more than three or more pain levels. Analysis of post-treatment follow-up GPS scores show benefit achieved at the end of treatment and during the following two months. The SPNS rates pain severity in each of the pain/discomfort, *pins/needles/tingling and numbness* characteristics of DSP in T2DM. Similar to the treatment benefit shown by the GPS, all three SPNS characteristics are statistically improved in the moxa treated groups and superior to the unchanged pain levels in the control groups. Also, the control groups remained at or above their baseline symptom severities throughout the treatment and followup phases. This is the first

study to examine the benefits of Traditional and Smokeless moxa in a single RCT. Here, we report the two moxa groups improved and did not differ on the GPS, the SPNS or the CGI.

More than one in three US adults will develop diabetes in their lifetime, making it among the largest and most consequential public health crises of the 21st century. [1,6] Diabetes' most common complication is DSP; a progressive, distressing, debilitating disorder associated with high personal and societal costs. [2,3] Direct and indirect healthcare costs related to DSP and complications of DSP are more than 10 billion dollars in the US annually. As there is no known cure, DSP management is largely supportive with the goal of reducing symptoms, managing pain, preventing disability, and improving quality of life [1]. Patients with DSP cite pain relief, symptom relief, and the chance to live normal, independent lives as chief concerns and drivers for seeking care. Satisfaction with pharmaceutical options is generally low due to limited efficacy, unpleasant side effects, and also for the risk of addiction with opioid analgesics.

Methodologically, acupoint selection, placebo, waitlist design, and other aspects of protocol development were informed by past learnings as well as traditional TCM texts, published reports of related clinical trials, consultations with TCM practitioners,

endocrinologists, neurologists, pain specialists provided insights into DSP in T2DM symptoms, evaluation and management. TCM practitioners who administered study treatments including placebo treatments underwent training and assessment for all aspects of their role, including participant interaction (a verbal script), acupoint and nonacupoint location, moxibustion technique, protocol adherence, and proper documentation [19, 20].

Our results indicate that in this preliminary study, both traditional and smokeless forms of moxa significantly reduce neuropathic pain, numbness, and paresthesia among patients with DSP pain compared with controls in T2DM. Our results indicate that the efficacy of smokeless moxibustion is comparable to traditional moxibustion and may be a preferred method for further study and in clinical practice.

Limitations
This preliminary study was aimed at providing valuable information on study logics, sample, methods, moxa dosage, participant acceptability, statistics etc. to inform a larger RCT; as with smaller-scaled studies the generalizability is limited. With a limited sample size we were unable assess statistical differences in gender, race, concomitant medications etc. A future larger study will address these limitations.

Summary
Moxibustion is noninvasive, affordable, and well-received by patients. The presented findings support the feasibility of clinical research in the use of moxa, both Traditional and Smokeless, to reduce moderate or greater lower limb neuropathic pain in individuals with T2DM. While this was a preliminary study, we employed a rigorous, randomized, evaluator- and participant-blinded, placebo, waitlist-controlled methodology. The study design was guided by the Consolidated Standards of Reporting Trials (CONSORT) and The Standards for Reporting Intervention in Controlled Trials of Acupuncture, with an extension for moxa (STRICTA-M) [34]. The results are encouraging and lay solid ground for performing larger-scale investigations using the same design, moxa protocol, acupoint sequence, and study procedures. Given the urgent clinical need, moxa, a highly tolerable and affordable solution to the current deficit in DSP symptom management options Traditional and Smokeless Moxibustion show promise as a non-invasive and nonpharmacologic therapy in lower-limb pain and neuropathic symptoms associated with T2DM.

Author Contributions
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Writing, reviewing, editing – JKA, BC, LH, MN, ND, DJM
Methodology - JKA, BC, DJM
Analysis-DJM
All authors have read and agreed to the published version of the manuscript

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Institutional Review Board Statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of NYU Langone Medical Center – Protocol No. i17-008929).

Informed Consent Statement
Informed consent was obtained from all participants included in this study.

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