Non-Pharmacological Interventions for the Treatment of Raynaud's Phenomenon: A Systematic Review

Farhan Mahmood[1], Helena Chase[2], Sandrine Soucy[2], Stephanie Perron[2] and Mohamad Ahmad[2], Peter Tugwell[3], Nancy Maltez[4]

[1]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[2]Faculty of Science, University of Ottawa, Ottawa, ON, Canada
[3]Department of Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[4]Department of Rheumatology, The Ottawa Hospital, Ottawa, ON, Canada

Date Submitted: January 15, 2022
Date Accepted: February 27, 2022
Date Published: July 19, 2024

DOI: https://doi.org/10.18192/uojm.v13i1.6175

Keywords: *Raynaud's phenomenon, non-pharmacologic interventions, rheumatology, dermatology*

ABSTRACT

Objective: The objective of this systematic review is to describe existing literature pertaining to the use of non-pharmacological interventions (NPIs) for the management of primary or secondary Raynaud's Phenomenon (RP) compared to placebo.

Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched from their inception to the present for randomized controlled trials and clinical trials for studies assessing the therapeutic effects of NPIs in primary or secondary RP. The studies were screened, and data were extracted by two reviewers. The major outcomes assessed included frequency (per week) and duration (minutes) of attacks and pain.

Results: We found 23 parallel or crossover RCTs, 5 of which were not discussed in this review. The categories of NPIs included acupuncture and other needling techniques (n=4), temperature biofeedback (n=4), lasers and electrotherapy (n=5), exercise therapy (n=2), gas therapy (n=1), therapeutic gloves (n=1), and ischemic preconditioning (n=1). Most studies demonstrated trends towards therapeutic benefit; however, there was substantial heterogeneity amongst the studies. Laser therapy had the most consistent evidence; 60% and 75% of the studies reported significant improvements in frequency of attacks per week and pain. Acupuncture therapies had minimal statistically significant benefits, and the data for temperature biofeedback were inconsistent and of low -quality. Exercise therapy is more recently being explored, showing a marked therapeutic benefit for pain.

Conclusion: The evidence is limited and inconsistent; however, the studies demonstrated trends towards therapeutic benefits, with laser and electrotherapy having the most consistent evidence. Further high-quality and multi-center RCTs are required.

RÉSUMÉ

Objectif: L'objectif de cette revue systématique est de décrire la littérature existante relative à l'utilisation d'interventions non pharmacologiques (INP) pour la gestion du phénomène de Raynaud (PR) primaire ou secondaire, en comparaison avec un placebo.

Méthodes: Le Registre central Cochrane des essais contrôlés, MEDLINE et EMBASE ont été consultés depuis leur création jusqu'à aujourd'hui pour des essais contrôlés randomisés et des essais cliniques pour des études évaluant les effets thérapeutiques des INP dans la PR primaire ou secondaire. Les études ont été sélectionnées et les données ont été extraites par deux examinateurs. Les principaux résultats évalués comprenaient la fréquence (par semaine) et la durée (en minutes) des crises et de la douleur.

Résultats: Nous avons trouvé 23 ECR parallèles ou croisés, dont cinq n'ont pas été examinés dans le cadre de la présente analyse. Les catégories d'INP comprenaient l'acupuncture et d'autres techniques d'aiguilletage (n=4), la rétroaction biologique sur la température (n=4), les lasers et l'électrothérapie (n=5), la thérapie par l'exercice (n=2), la thérapie par les gaz (n=1), les gants thérapeutiques (n=1) et le préconditionnement ischémique (n=1). La plupart des études ont montré des tendances vers un bénéfice thérapeutique; cependant, il y avait une hétérogénéité substantielle entre les études. La thérapie au laser est la plus cohérente; 60 % et 75 % des études ont fait état d'améliorations significatives de la fréquence des crises par semaine et de la douleur. Les thérapies par acupuncture n'ont apporté que des avantages minimes statistiquement significatifs, et les données relatives au biofeedback de température étaient incohérentes et de faible qualité. La thérapie par l'exercice a été explorée plus récemment et a montré des avantages thérapeutiques marqués pour la douleur.

Conclusion: Les preuves sont limitées et incohérentes; cependant, les études ont démontré des tendances vers des avantages thérapeutiques, le laser et l'électrothérapie ayant les preuves les plus cohérentes. D'autres ECR multicentriques de haute qualité sont nécessaires.

INTRODUCTION

Raynaud's phenomenon (RP) is characterized by the vasospasm of arteries or arterioles of the extremities leading to pallor, cyanosis, and/or redness and is associated with significant morbidity.[1,2] These morbidities include severe symptoms leading to tissue loss, digital ulcers, and amputations.[2] Primary RP is idiopathic, and it accounts for the majority of cases, with a median age of onset around 14 years of age. Secondary RP develops as a result of underlying disorders, including connective tissue diseases such as systemic sclerosis and systemic lupus erythematosus.[2] The latter type of RP has a later onset, with a median age of onset around 40 years. Common triggers of RP attacks include exposure to cold temperatures and emotional stress.[3] Primary RP is the most common type of RP, accounting for 80-90% of cases, compared to 10-20% of secondary RP. The prevalence of RP [primary and secondary] in the general population is around 3-5%,[4,5] being more common amongst women. Diagnosis of primary RP is based on patient history and ruling out the presence of underlying causes, whereas the diagnosis of secondary RP includes an older age of onset with more severe symptoms and laboratory tests that suggest an underlying connective tissue disease, in addition to microscopy of the nail folds indicating the presence of microvascular disease.[2]

The pathogenesis of RP has not been fully elucidated; it is hypothesized to be attributable to abnormalities in blood vessels, neural control of vascular tone, and intravascular mediators.[1] Vascular abnormalities are more severe in secondary RP.[1,2] This possibly explains the irreversible digital ischemia seen in RP secondary to systemic sclerosis spectrum disorders. Secondary RP is often associated with microvascular structural abnormalities, and RP has been postulated to be associated with hormonal factors.

These pathophysiologic differences are thought to explain, in part, the variability in responses to treatment amongst patients with RP. As such, reviewing the use of non-pharmacological interventions (NPI) would help summarize the alternative therapies that are available to manage RP. NPIs also have fewer adverse effects. Although several pharmacological interventions are well established as options for treatment of RP,[6-8] describing the role of NPIs is of interest to those interested in adjuvant therapies. There are no specific clinical guidelines pertaining to the use of NPIs for RP.[9]

NPIs are used to modify lifestyles and educate patients in recognizing reflex vasospasm and identify factors leading to attacks such as sudden temperature changes, digital trauma, smoking and drugs.[1,10] NPIs include behavioural therapies, skin temperature biofeedback, lifestyle changes such as managing stress and smoking cessation, and acupuncture/acupressure.[3,11-13] In our review, NPIs are defined as therapeutic modalities that exclude oral, subcutaneous, or intramuscular pharmaceuticals or oral supplements (e.g., vitamins, minerals, herbal extracts, diets etc.).

The primary objective of this systematic review is to describe existing literature pertaining to the use of NPIs for the management of RP in comparison to placebo. We hypothesize that NPIs are beneficial treatments for RP. The study will allow us to better understand the use of NPIs as potential adjuvants of pharmacological treatments and provide a basis for identifying those NPIs with the most promising potential to explore the synergies.

METHODS

This systematic review was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Intervention* guidelines.[14] Further details can be found in our study protocol, accessible through the University of Ottawa Journal of Medicine.

Eligibility Criteria

We included randomized controlled trials (RCTs) and controlled clinical trials (CCTs), including cross-over and parallel designs pertaining to any NPI's as compared to placebo for RP. There was no language restriction. The study subjects must have been >18 years of age with a diagnosis of primary or secondary RP.

Outcomes

We measured the following major outcomes:

1. Frequency of attacks (average number per week or change in frequency per week)
2. Duration of attacks (average duration in minutes)
3. Pain
4. Withdrawals (any withdrawals from studies due to adverse effects)
5. Serious adverse events (adverse effects leading to withdrawal from study and hospitalization or death)

The minor outcomes included:

6. Patient global assessment
7. Physician's global assessment (physician assessed measure of disability due to RP)
8. Healthcare assessment questionnaires

Electronic Searches

The search was conducted using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from their inception to the present. We screened the references of all primary and review articles for additional references. The search terms included: "*Raynaud Disease, Vasospasm, raynaud*" plus validated study design filters for RCTs for Medline and EMBASE. Details of the search strategies are available in Supplementary 1, which is a component of our study protocol.

Data Collection and Extraction

We dual-screened all abstracts and titles and full-text articles amongst the reviewers. One reviewer (F.M.) screened all abstracts, and four other reviewers (H.C., S.S., S.P., M.A.) screened the studies equally amongst themselves. We independently extracted data twice amongst the reviewers then combined. We resolved all disagreements and discrepancies in data collection through discussion amongst the reviewers and consulting a third reviewer (N.M. and P.T.).

For studies presenting the frequency of attacks per day, we multiplied the outcome by 7 to standardize the data to the frequency of attacks per week. We made other necessary adjustments to standardize the units for each outcome, and the standard deviation (SD) was imputed accordingly when necessary. For studies presenting the change in outcome from a baseline value, we subtracted the change from the baseline to compute the outcome post-treatment. For these data, we used the SDs from other similar studies and methodologies; a new SD was not computed. For studies presenting data only on figures/graphs without providing exact measurements, we extrapolated the data from these figures/graphs.

We have presented the data in forest plots (without a final total) to provide an overview of the size and direction of effects and the general trends. We used The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan),[15] version 5.4 software for the analyses.

Assessment of Risk of Bias in Included Studies

Two review authors independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*,[14] and we resolved the conflicts upon discussion. We used the following domains to make a judgement on the overall risk of bias: 1) random sequence generation: checking for possible selection bias, 2) allocation concealment: checking for possible selection bias, 3) blinding of participants and personnel: checking

for possible performance bias, 4) blinding of outcome assessment: checking for possible detection bias, 5) incomplete outcome data: checking for possible bias due to attrition and methods used to handle missing outcome data, 5) selective outcome reporting: checking for possible reporting bias, 6) other bias: checking for bias not covered through 1 to 5 above.

Metanalysis

Due to the heterogeneity of the populations, time ascertainment and methodologies of the articles, in addition to the limited amounts of high-quality articles, metanalysis could not be conducted (Supplementary 2 describes our plan for meta-analysis in our protocol).

RESULTS

We performed the search on June 8th, 2021, which yielded 6892 studies; there were 1617 duplicates (Figure 1). Out of 5275 articles, 86 articles underwent full-text review twice, out of which 23 articles were identified to be included in this review (12 articles either had an incorrect study design (i.e., not an RCT or CCT, or they were ongoing trials)).

Furthermore, 5 articles are not reviewed for the following reasons: The study by Junger et al.[16] could not be translated to English in a timely manner thus, it is not included in this review. We are waiting for an assessment for the other 4 studies, as we have emailed the authors for clarifications regarding their study design and data. The study by Guo et

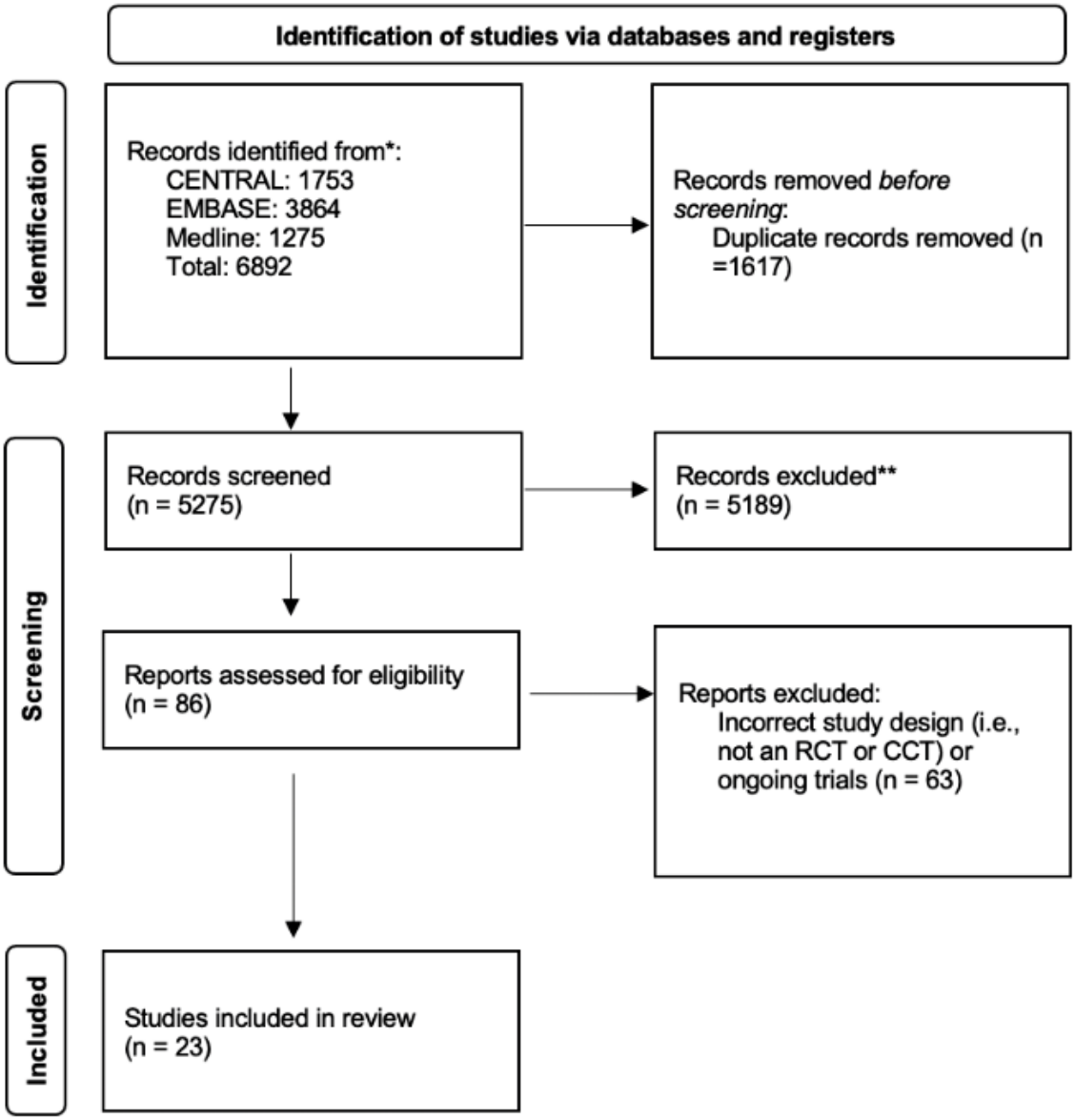


Figure 1. Flowchart of the Identification, Screening, and Inclusion of Studies

al.[17] was excluded as it is was unclear whether the authors differentiated patients with RP from patients with systemic scleroderma when reporting the outcomes. Freedman et al.[12] compared temperature biofeedback with electromyography. However, the pre-treatment frequency of attacks were markedly different (115.4 vs 13.1, respectively), and there was no clear description of the patient demographics in each group. Although Dabek et al.[18] discuss changes in pain and frequency of attacks after relaxation therapy, they do not provide the initial baseline values for these outcomes. Zhou et al.[19] was not discussed as it is unclear whether the data presented differentiated patients with RP from patients with diffuse systemic sclerosis.

The study characteristics and participant demographics are summarized in Tables 1 and 2. Out of the 18 studies discussed in this review, 3 are crossover RCT 20-22 and 15 are parallel RCTs. Four studies describe the use of acupuncture, acupressure, or warm needling as therapies, 4 studies use skin biofeedback temperature, 5 studies use lasers or electrotherapy, 2 studies assess the use of exercise/physical therapy as a NPI for RP, 1 study describes natural gas therapy, 1 study describes the use of thermal gloves, and 1 study assesses the role of ischemic preconditioning in treating RP. All but 2 studies include placebo or control interventions; Appiah et al.[11] and Sporbeck et al.[23] compared an acupuncture intervention group with a no treatment group.

The sample sizes range from 18 to 155 participants. The study by Raynaud's Treatment Study Investigators[24] had the largest sample size, including 81 participants in the intervention group and 74 participants in the control group. The age of the participants ranged from 24 to 69.6 years, and most of the studies had a predominance of female participants. The disease duration of RP ranged from 1.5 to 24 years. Seven of the 18 studies merely include participants with primary RP, whereas 5 studies include both primary and secondary RP (Table 2).

RISK OF BIAS

The risk of bias was assessed based on a variety of parameters regarding allocation, blinding, reporting. Each was judged based on high risk, low risk, or unclear. Most studies are detailed in their reporting and have low risks of bias. For example, 94% (17/18) of studies are at low risk for selective outcome reporting. In contrast, over half of the studies have an unclear risk or high risk of bias when evaluated regarding the blinding of participants. Due to the nature of the interventions, it is not always possible to keep them concealed. A 2018 study by Mitropoulos et al.[25] compared different types of exercises. In this situation, the participants cannot be blinded as they must perform actions based on assigned movements that will be known. In contrast, however, the study by Schmidt et al.[26] had a low risk of bias in most criteria as it kept the allocation concealed and the participants and outcome assessors blinded. The only personnel who knew which treatment group a patient was in, were those administering the intervention. The way this study was conducted eliminates most possibilities of bias. Al-Awami et al.[27] similarly conducted a high-quality study comparing low-level laser therapy to placebo therapy.

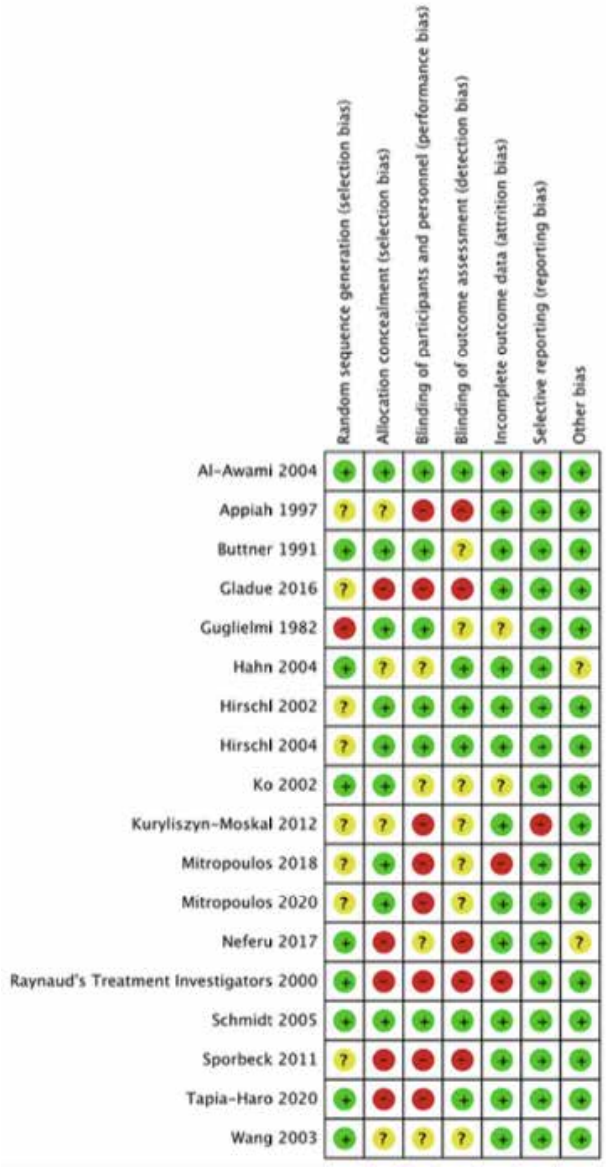


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

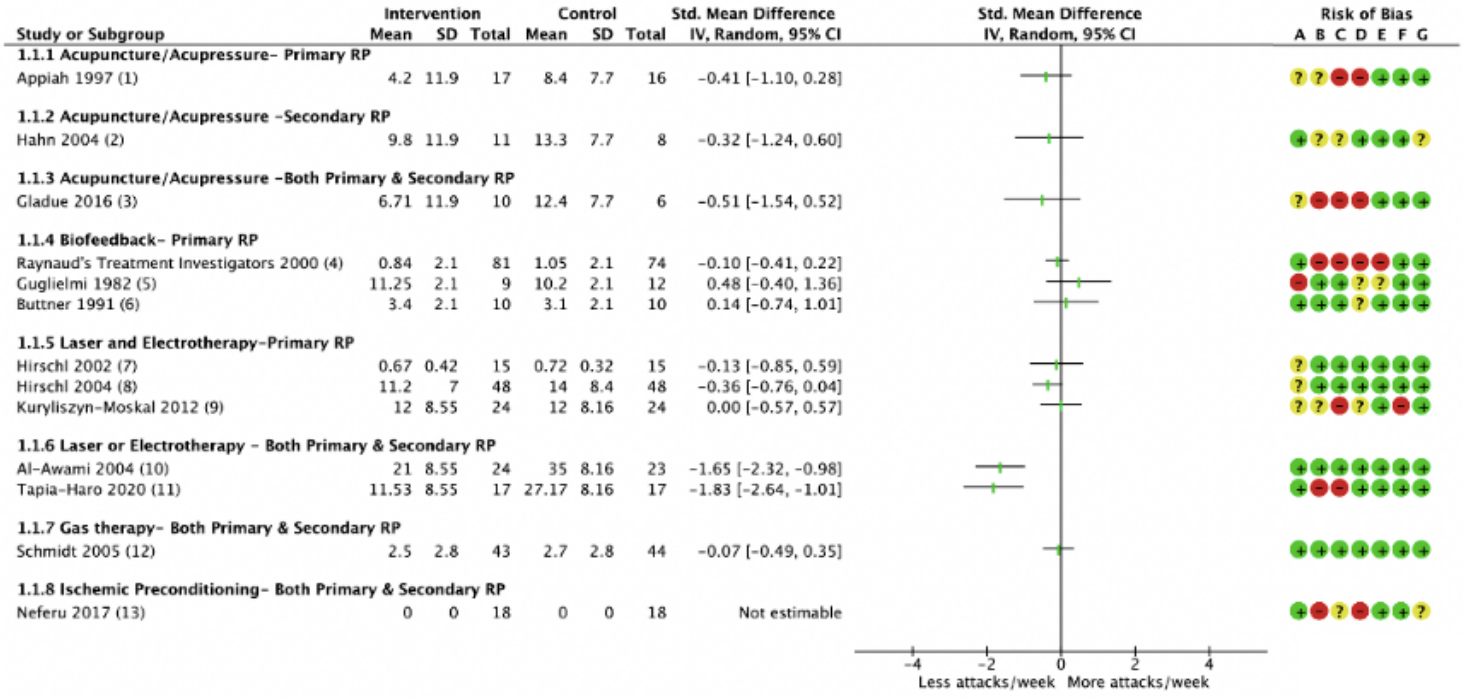
They clearly stated their blinding and randomization process, and clearly indicated that the patients and evaluators were not aware of the study protocol. In addition, the baseline characteristics of participants in the intervention and placebo groups were quite similar.

REVIEW AND ANALYSIS OF THE EFFICACY OF NON-PHARMACOLOGIC INTERVENTIONS

The forest plots (Figures 3, 4, and 5) summarize the data on major outcomes, including mean frequency of attacks per week, the average duration of attacks (minutes), and pain (scale 0 to 10) for the NPIs in treating primary or secondary RP. As a meta-analysis could not be completed, a total is not provided in the plots.

Acupuncture and Other Needling Therapies

Hahn et al.[28] compared 8 weeks of weekly acupuncture at 10 points with a sham acupuncture control in patients with secondary RP. They presented their frequency of attacks per day averaged over a 12-week period; when standardized, the acupuncture group had 9.8 (11.9) versus 13.3 (7.7) attacks per week in the placebo group. This difference was not statistically significant. Similarly, Appiah et al.[11] compared 7 sessions of acupuncture with moxibustion heat therapy with a no-treatment group in primary RP and found that the acupuncture group had fewer attacks per week (4.2 [11.9] vs 8.2 [7.7]) at 12 weeks. The overall reduction of attacks between the two groups was statistically significant (p=0.03). This was standardized from attacks



Footnotes
(1) Week 12. Means multiplied by 7. SD imputed from Hahn 2004.
(2) Week 12. Means multiplied by 7.
(3) Week 8. Change in mean subtracted from baseline; SD imputed from Hahn 2004.
(4) 2 month. Means multiplied by 7. SD imputed from Buttner 1991.
(5) Week 4. The data was provided in total period over 5 months, the means were divided by 20 weeks. SD imputed from Buttner 1991.
(6) Week 5.
(7) Week 3. RCT crossover.
(8) Week 3. Means multiplied by 7. RCT Crossover.
(9) Week 3. Data extracted from a graph, specific means were not provided. SD imputed from Tapia-Haro 2000, as this was most similar study.
(10) Week 6. Means multiplied by 7. SD imputed from Tapia-Haro 2000, as this was most similar study.
(11) Week 7.
(12) Day 19.
(13) RCT crossover. Mean difference was 1.6(10). The specific means for the intervention or control group were not provided.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 3. Forest plot of comparison—the Frequency of Attacks per Week in Non-Pharmacologic Intervention vs Control Groups for Primary and Secondary Raynaud's Phenomenon or Both Primary and Secondary.

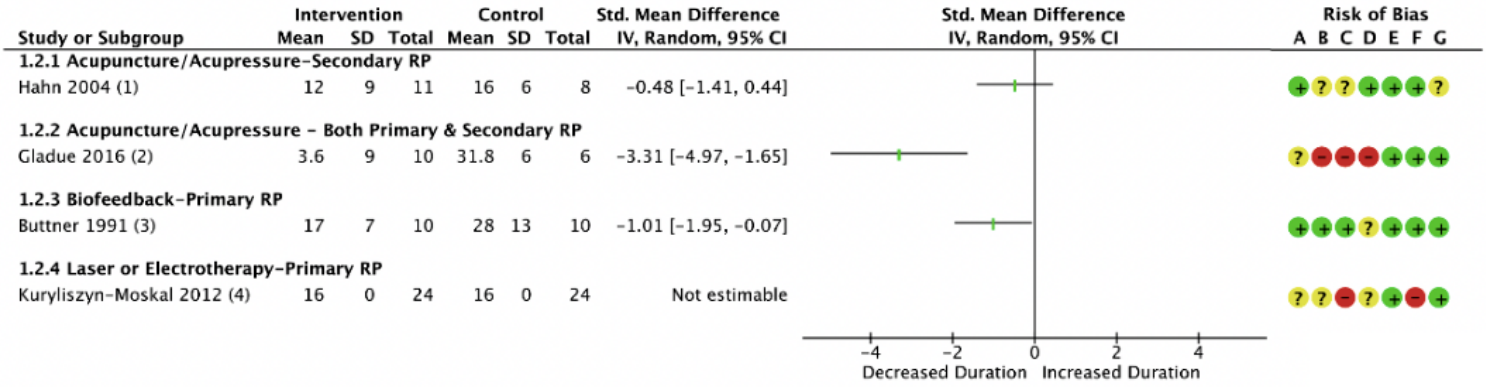
per day. Although Gladue et al.[29] did not use acupuncture as an NPI, they used two types of acupressure therapies, including vasodilation and relaxation acupressure. Their control group received an education package about Raynaud's. This study presented the combined data from the 2 acupressure groups and included both primary and secondary RP. The mean frequency of attacks in the acupressure versus control groups was 6.71 (11.9) versus 12.4 (7.7) at 8 weeks. The changes in baseline between the groups were not statistically significantly different (Figure 3).

Gladue et al.[29] also reported a reduction of 11.4 (19.9) minutes in the average duration of attacks in the acupressure groups versus an increase in the control group (0.8 [11.2]) from baseline. These changes and the difference between the groups were not statistically significant. Hanh et al.[28] similarly noted a statistically insignificant decrease in the mean duration of attacks before and after the acupuncture treatment (15[12] pre-treatment vs 12[9] post-treatment; Figure 4).

Gladue et al.[29] used a 0 to 100 visual analog scale (VAS) to measure pain and a patient VAS for the patient's assessment (0-10). There was a statistically significant reduction from the baseline VAS scores in the acupressure group (p=0.02; Figure 5). Wang et al.[30] also used a healthcare questionnaire developed in China to assess the efficacy of acupuncture with moxibustion for 15 days versus oral Betaloc tablets 50 mg twice a day for 15 days in primary RP. This criterion assessed symptoms resolution, tolerance to temperature, and nail fold microcirculation. The effective rate of the acupuncture group was statistically significantly higher than the control (x^2= 7.87; p<0.05).

Temperature Biofeedback

The Raynaud's Treatment Study Investigators[24] and Guglielmi et al.[31] compared skin temperature biofeedback with electromyography, whereas Sporbeck et al.[23] and Büttner et al.[32] used no treatment and hand exercises as control groups, respectively. These studies assessed primary RP; however, it is unclear if Sporbeck et al.[23] included secondary RP as well. The mean difference in the frequency of attacks per week for all the studies assessing primary RP ranged from -0.1 (-0.41, 0.22) to 0.48 (-0.4, 1.36) (Figure 3). The frequency of attacks per week was higher in the skin temperature biofeedback groups at 4[31] and 5 weeks[32] when compared to no treatment or hand exercises, respectively, but lower when compared to electromyography at 2 months.[24] The Raynaud's Treatment Study Investigators[24] noted up to a 32% reduction in attacks with biofeedback, but this was statistically insignificant. Büttner et al.[32] also reported a decrease in attacks from 4.8(2.9) to 3.4(2.1) in the biofeedback group and 3.9(1.9)



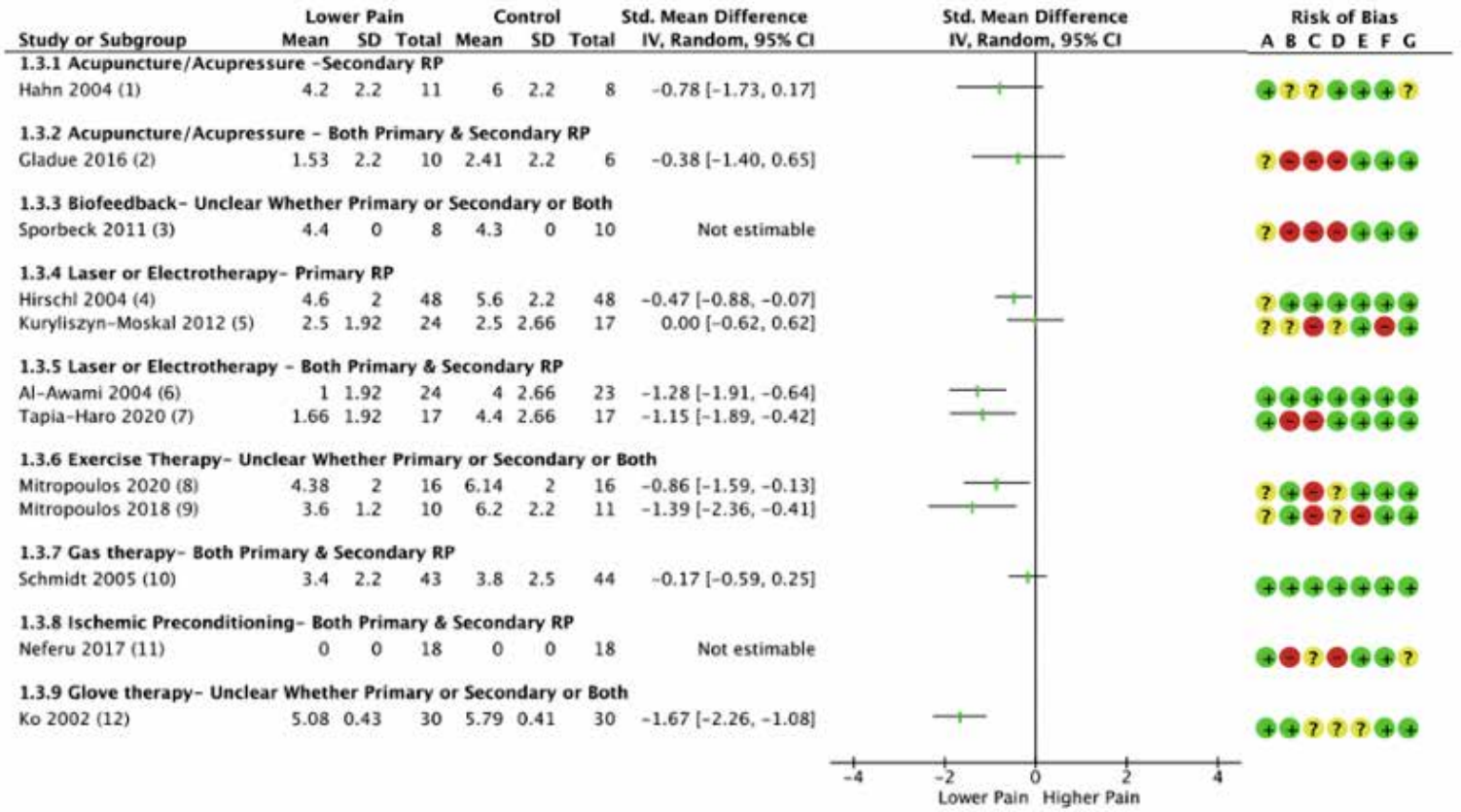
Footnotes
(1) Week 12.
(2) Week 8. The study only reports a change from baseline and baseline were not provided. Baseline values and SD imputed from Hahn 2004.
(3) Week 5.
(4) Week 3. Means were extracted from graphs.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4. Forest plot of comparison—the Duration of Attacks (minutes) in Non-Pharmacologic Intervention vs Control Groups for Primary and Secondary Raynaud's Phenomenon or Both Primary and Secondary.

to 3.1(2.1) in the placebo group; however, the reductions in both groups were not statistically significant. Büttner et al.[32] also found that the duration of attacks was significantly lower in the biofeedback group compared to the control at 5 weeks post-treatment (Figure 3 and 4).

Sporbeck et al.[23] used the Scleroderma VAS to assess pain. The absolute change from baseline at 12 weeks in the biofeedback groups was -0.5 and +0.5 in the control group (extrapolated from a graph); p=0.094 between the two groups (Figure 5). The baselines were 4.9 (8.6) and 3.8 (7.5) for biofeedback versus control. The Raynaud's Treatment Study Investigators[24] also reported clinical ratings of improvement in RP assessed by physicians, which included the severity, the impact of RP, improvement, and general health. At 1 year, there was no significant difference between the biofeedback and control groups, 49(57) versus 49 (65), respectively.



Footnotes
(1) Week 12. Means and SD multiplied by 2. This study used a severity scale out of 5 (0: only 1-2 fingertips, 5: entire hand).
(2) Week 8. Means divided by 10 and subtracted from the baseline means. SD used from Hahn 2004. VAS scale was 0 to 100.
(3) Week 12. Change from baseline extrapolated from graphs. Extracted values were subtracted from baseline means.
(4) Week 12. Means multiplied by 2. VAS scale ranged from 0 to 5.
(5) Week 3. VAS scores extracted from graph. The values were divided by 10 (VAS 0 to 100 used). SD imputed from Tapia-Haro 2000.
(6) Week 6. SD imputed from Tapia-Haro 2000, as this was most similar with respect to the intervention and sample size.
(7) Week 7. VAS from pre-Cold stimulation test.
(8) Week 12. Means and SD scores multiplied by 2. 5-point scale was used.
(9) Week 12. Means and SD multiplied by 2. 5-point scale was used. We report arm cranking ergometer vs control.
(10) Day 19. Mean and SD divided by 10 to convert from mm to cm. Huskisson VAS (0 to 10 cm) uesd.
(11) RCT crossover. Mean difference between intervention and control groups was -0.4 (p=0.89).
(12) Week 12. Mean and SD divided by 10. VAS 0 to 100 used.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel...
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 5. Forest plot of comparison—Pain (0 to 10 scale) in Non-Pharmacologic Intervention vs Control Groups for Primary or Secondary Raynaud's Phenomenon or Both Primary and Secondary.

Lasers and Electrotherapy

The overall mean difference in the mean frequency of RP attacks per week between laser or electrotherapy and placebo groups in primary RP ranged from -0.36 (-0.76, -0.04) to 0 (-0.57, 0.57),[20,22,33] and -1.83 (-2.64, -1.01) to -1.65 (-2.32 to -0.98) in studies that combined primary and secondary RP[27,34] (Figure 3). Hirschl et al. (2002)[22] and Hirschl et al. (2004)[20] conducted RCT crossover studies on primary RP (n= 30 and 64 respectively) comparing low level laser therapy with placebo laser irradiation. Both studies used 200 mW lasers with either 685 nm[20] or 625 nm[22] wavelengths, and the placebos had wavelengths of either 640-685 nm[20] or 670 nm[22] for 3 to 5 sessions per week. In the 3rd week, the frequency of attacks per week was significantly lower (p=0.001) in the laser intervention compared to the control in Hirschl et al. (2004)[20] However, the differences between the two groups in 2002 were not statistically significant (p = 0.520) when comparing the relative frequency of attacks per week. Al Awami et al.[27] also compared laser therapy (40 mW, 670 nm) with a sham laser in primary and secondary RP combined and demonstrated statistically significantly lower frequencies in the intervention group at 6 weeks (p=0.007), 21 versus 35 attacks per week (Figure 3).

Similar to laser therapy, Tapia-Haro et al.[34] compared galvanic current electrotherapy (f 220–240V and 50/60+10% Hz) and conservative therapy (e.g., anti-inflammatory, vasodilatory and analgesic drugs and lifestyle recommendations) to conservative therapy alone, in primary and secondary RP (the results were combined). The electrotherapy resulted in statistically significantly fewer attacks per week compared to the control at week 7, 11.53(8.55) versus 27.17(8.16).

Kuryliszyn-Moskal et al.[33] further compared 2 groups receiving either laser bio-stimulation with a magnetic field (frequency 40 Hz, induction 1–5 mT, 10–20 min per session) or only laser bio-stimulation. In both groups, the participants received 3 weeks of pentoxifylline and 3 weeks of physiotherapy. After 3 weeks of laser or laser and magnetic field, both groups had roughly 12 attacks per week. Magnetic field therapy added no therapeutic benefit. In addition, this study did not find a significant difference in the duration of the attacks (Figure 4).

Three of the studies above consistently reported statistically significant lower VAS scores in the intervention group compared to the control from weeks 6 to 12.[20,27,34] Tapia-Haro et al.[34] reported a smaller mean difference between the intervention and control groups before and after a cold stimulation test, -2.74(0.8) versus -0.05(0.4) at 7 weeks. The overall mean difference in pain for primary RP and both primary and secondary RP respectively ranged from -0.47 (-0.88, -0.07) to 0 (-0.62, 0.62) and -1.28 (-1.91, -0.64) to -1.15 (-1.89, -0.42). Kuryliszyn-Moskal et al.[33] did not report a difference between their 2 groups (Figure 5).

Exercise Therapy

Mitropoulos et al. 2020[35] and 2018[25] both assessed the efficacy of exercise in treating RP; however, it is unclear whether these studies combined data for secondary and primary RP. The interventions included either a 12 week high-intensity interval training (e.g., arm crank warm-up, high intensity exercise, and light aerobic exercises)[35] or arm crank ergometer[25] (Figure 5). The control groups did not perform these organized exercises. Both studies reported pain outcomes (5-point scale) and minor outcomes, including life satisfaction scores out of 10. In both studies, the pain was statistically significantly lower after the exercise intervention compared to the control ($p<0.05$). The life satisfaction after exercise therapy was significantly higher than the control groups in 2020 and 2018, 9.25(0.9) versus 7.33(1.8) and 8.1(1.7) versus 4.9(1.5), respectively.

Other Therapies

Schmidt et al.[26] compared natural carbon dioxide gas therapy for 18 days to a control group receiving placebo gas for 9 days and COS for 9 days in patients with both primary and secondary RP. At day 19, there were no statistically significant differences in the frequency or severity of attacks between the 2 groups (Figure 4 and 5). The risk of bias for this study was low.

Ko et al.[36] described the use of ceramic impregnated "thermoflow" gloves, which include 95% polypropylene and polyethylene; 5% ceramic. These gloves supposedly absorb external ambient infrared radiation and reflect it into the underlying tissues. The control group received placebo gloves. At 12 weeks, the frequency of attacks significantly reduced from baseline (50.8[4.3] attacks per week; p=0.001) in the intervention group with no statistically significant difference in the control group (57.9[4.1]; p=0.2; Figure 3). This study also assessed the participant's subjective response to treatment using a Likert scale (1: markedly worse to 7: markedly improved). The intervention group

had a statistically significant higher score compared to the placebo (5.66 vs 4.13; p=0.001). This study has a low risk of bias overall, however, it is unclear how the participants and subjects were blinded.

Ischemic preconditioning for the treatment of primary and secondary RP was assessed by Neferu et al.[21] in a crossover trial. Compared to the control (sham preconditioning), ischemic preconditioning did not differ significantly in the frequency of attack (increased by 0.5[10]; p = 0.84), duration of attacks (decreased by 55.6[516.4] minutes; p = 0.66), and pain (decreased by 0.4[12.9] on VAS; p = 0.88). This study included both primary and secondary RP and combined the results.

The included studies inconsistently reported adverse side effects; 6 studies had mentioned side effects. Out of these studies, only Ko et al.[36] reported skin irritation in 3 participants, and the Raynaud's Treatment Investigators[24] reported a headache in 1 participant receiving biofeedback. There were no serious adverse events nor any withdrawals due to serious adverse events reported.

DISCUSSION

The main categories of NPIs identified included acupuncture and other needling techniques, skin temperature biofeedback, lasers and electrotherapy, exercise therapy, gas therapy, therapeutic gloves, and ischemic preconditioning. Generally, most of the studies demonstrated a trend towards therapeutic benefit for treating primary or secondary RP when assessing frequency, duration, and severity of attacks. However, there was substantial heterogeneity amongst the studies, including the timeframe of interventions and data collection, control groups, diagnostic methods for RP, population demographics, and characteristics of comparable interventions (e.g., differences in wavelengths for laser therapy). Overall, the studies had a low to moderate risk of bias with a few studies, including Sporbeck et al.,[23] the Raynaud's Treatment Investigators,[24] and Gladue et al.,[29] mainly due to concerns with blinding of participants or subjects.

Overall, laser therapy and electrotherapy had the largest pool of studies with consistent evidence compared to other NPIs. The risk of bias for these studies was low overall, with only Tapia-Haro et al.,[34] have a moderate-to-high risk of bias due to concerns with the blinding in the study. Al Awami et al.[27] had the lowest risk of bias; however, they did not differentiate the results between patients with primary or secondary RP. More than half (60%) of the studies reported significant reductions in frequency per week compared to the control, 40% of which included both primary and secondary RP. Most (75%) of the studies demonstrated a significant decrease in the severity/painfulness of attacks in both primary and secondary RP.

In the trials assessing the use of acupuncture, acupressure or warm needling therapies, there were generally no statistically significant reductions in the frequency or duration of attacks when compared to the control overall. Appiah et al.[11] showed a significant difference in the frequency of attacks in primary RP, but the control group received no treatment. Thus, there is a high possibility that the study participants and subjects were not blinded. Similarly, there is a moderate risk of bias for these studies as 2 studies have low risk, and 2 studies have high risk. The populations in these studies are also inconsistent, as only 2 studies included primary RP, one included secondary RP, and one study combined both types. Acupuncture is a time consuming and costly therapy; the current evidence does not justify its use over other interventions.[28]

With regards to temperature biofeedback, the data are inconsistent, and many studies were of low quality. All but 1 study included only primary RP, although it is unclear whether Sporbeck et al.[23] included both secondary and primary RP. Two studies reported a higher number of attacks in the biofeedback group compared to the control whereas, other studies reported a statistically insignificant decrease in the frequency of attacks. However, the duration of attacks was reported to be significantly lower by Büttner et al.[32] Temperature biofeedback seemed to have a statistically insignificant effect on the level of RP pain and physician's global assessment.

More recently, exercise therapy has been explored, showing strong statistical evidence. Two studies noted a marked decrease in pain and improvements in life satisfaction.[25,35] However, there is a moderate-to-high risk of bias for these studies as it is difficult to control for the level of baseline and ongoing physical activity amongst the subjects outside of the structured exercise programs. It is also likely difficult to blind the participants and subjects when the control group does not receive any form of structured exercise. It is also unclear from the inclusion criteria of both studies whether the participants had primary or secondary RP or both. In a similar sense, although Ko et al.[36] showed strong

statistical evidence supporting the therapeutic benefits of "thermoflow" gloves, further studies are required to replicate their findings. It is also unclear whether this study included both primary and secondary RP, as the "Pal criteria" was used for diagnosis. Thus, it is worthwhile to further explore the use of therapeutic gloves and exercise therapy moving forward, as these modalities are affordable and clinically realistic.

A previous review conducted by Malenfant et al.[37] in 2009 also reviewed complementary and alternative medicine in the treatment of RP. This review also found that high-quality evidence is limited, with biofeedback having the least consistent and supportive evidence. This study noted the efficacy of laser therapy, supported by our findings along with the addition of 2 new RCTs since 2009.

Nevertheless, due to the inconsistent and low-quality evidence on NPIs for RP, it is difficult to make clinically relevant decisions for patient care. Notably, some studies did not differentiate between primary and secondary RP when presenting the efficacy of NPIs.[21,23,26,27,29,34] This limits the generalizability of the results in a clinical setting as the management and prognoses of secondary and primary RP are different. Most of the studies did not discuss adverse events. Thus, further information is required to better understand the safety of NPIs, especially those that are more invasive such as acupunctures and lasers.

The predominance of RP in colder climates is reflected in the studies in this review; the majority took place in countries located in the Northern hemisphere. In addition, the participants of the studies were primarily sourced from clinics, making the results more generalizable to clinical settings with patients with comorbidities. For instance, the trial by the Raynaud's Treatment Study Investigators[24] was advertised to five clinics in different geographical areas and climates.

A limitation of this current review includes the exclusion of 5 articles[12,16-19] for which we had emailed the authors for clarification or could not translate (Junger et al.[16]). The NPIs being assessed in these studies included bathing with Chinese medicine, infrared sauna and relaxation therapy, and temperature biofeedback. For the purposes of this review and the forest plots, we used the SDs for major outcomes from similar studies assessing similar interventions with the SD was not provided or when only the change from baseline difference was provided. Thus, the data in the forest plots may not accurately reflect the studies. Some of the studies also included both secondary and primary RP and combined the results when presenting the data. This is a major limitation clinically, as the pathogenesis and treatment of primary and secondary RP differ. It is important to note that this review did not include studies assessing the therapeutic use of natural dietary adjuvants, supplements, extracts, smoking cessation or complementary medicine in treating RP.

CONCLUSION

In summary, the literature on the therapeutic efficacy and safety of the NPIs for the treatment of RP is limited and inconsistent. Although the studies included in this review trended towards decreased frequency, duration, and severity of RP attacks with the NPIs, many of these improvements were not statistically significant. We found that the laser and electrotherapy had the largest pool of studies and consistent evidence. Further high-quality and multi-center RCTs are required to make definitive clinical decisions when treating patients with RP with NPIs.

Conflict of Interest: None

Funding: University of Ottawa Journal of Medicine Research Assistantship

REFERENCES

1. Herrick AL. Pathogenesis of Raynaud's phenomenon. Rheumatology (Oxford). May 2005;44(5):587-96. doi:10.1093/rheumatology/keh552
2. Wigley FM. Clinical practice. Raynaud's Phenomenon. N Engl J Med. Sep 26 2002;347(13):1001-8. doi:10.1056/NEJMcp013013
3. García-Carrasco M, Jiménez-Hernández M, Escárcega RO, et al. Treatment of Raynaud's phenomenon. Autoimmun Rev. Oct 2008;8(1):62-8. doi:10.1016/j.autrev.2008.07.002
4. Maundrell A, Proudman SM. Epidemiology of Raynaud's Phenomenon. Springer New York; 2014:21-35.
5. Silman A, Holligan S, Brennan P, Maddison P. Prevalence of symptoms of Raynaud's phenomenon in general practice. British Medical Journal. 1990;301(6752):590-592. doi:10.1136/bmj.301.6752.590
6. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski J-L. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Annals of the rheumatic diseases. 2013;72(10):1696-1699. doi:10.1136/annrheumdis-2012-202836
7. Rirash F, Tingey PC, Harding SE, et al. Calcium channel blockers for primary and secondary Raynaud's phenomenon. Cochrane library. 2017;2017(12):CD000467-CD000467. doi:10.1002/14651858.CD000467.pub2
8. Herrick AL, van den Hoogen F, Gabrielli A, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Arthritis and rheumatism. 2011;63(3):775-782. doi:10.1002/art.30195

9. Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of Raynaud's phenomenon. BMJ. 2012;344(7843):66-42. doi:10.1136/bmj.e289
10. Fraenkel L. Raynaud's phenomenon: Epidemiology and risk factors. Current rheumatology reports. 2002;4(2):123-128. doi:10.1007/s11926-002-0007-z
11. Appiah R, Hiller S, Caspary L, Alexande K, Creutzig A. Treatment of primary Raynaud's syndrome with traditional Chinese acupuncture. Journal of internal medicine. 1997;241(2):119-124. doi:10.1046/j.1365-2796.1997.91105000.x
12. Freedman RR, Ianni P, Wenig P. Behavioral treatment of Raynaud's phenomenon in scleroderma. Journal of behavioral medicine. 1984;7(4):343-353. doi:10.1007/BF00845268
13. Daniels J, Pauling JD, Eccelston C. Behaviour change interventions for the management of Raynaud's phenomenon: a systematic review protocol. BMJ open. 2017;7(8):e017039-e017039. doi:10.1136/bmjopen-2017-017039
14. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane; 2021. www.training.cochrane.org/handbook.
15. Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-non-cochrane-reviews
16. Junger M, Rosch G, Mohrle M, et al. Efficiency of acupuncture in acral circulatory disturbances. Wirkung der Akupunktur bei akralen Durchblutungsstorungen. Phlebol. 1996;25(4):139-143.
17. Guo M-h, Tu W-Z, Chen D-d, Sun J-y, Sui M. Therapeutic effects on systemic scleroderma of integrated therapy of Traditional Chinese Medicine with penicillamine. Journal of Clinical Dermatology. 2008;37(7):464-466.
18. Dąbek A, Domaniecki J, Czyżewski P, Bujar-Misztal M. Evaluation of selected therapeutic methods in patients with primary raynaud's syndrome. Borgis- New Medicine. 2013:3-8.
19. Zhou J, Yang D, Zhou S-h, Wang J-p, Liu Y-s, Wang S-l. Clinical Efficacy and Safety of Bathing with Chinese Medicine Taohong Siwu Decoction (桃□四物□) for Treatment of Diffuse Cutaneous Systemic Sclerosis: A Randomized Placebo-Controlled Trial. Chinese journal of integrative medicine. 2017;24(3):185-192. doi:10.1007/s11655-017-2954-2
20. Hirschl M, Katzenschlager R, Francesconi C, Kundi M. Low level laser therapy in primary Raynaud's phenomenon--results of a placebo controlled, double blind intervention study. Journal of rheumatology. 2004;31(12):2408-2412.
21. Neferu R, Vanderhoek L, Hewitt S, Nevskaya T, Pope JE. A randomized, single-blinded cross-over trial of ischemic preconditioning in Raynaud's phenomenon. Journal of scleroderma and related disorders. 2017;2(3):213-220. doi:10.5301/jsrd.5000253
22. Hirschl M, Katzenschlager R, Ammer K, Melnizky P, Rathkolb O, Kundi M. Double-blind, randomised, placebo controlled low level laser therapy study in patients with primary Raynaud's phenomenon. Vasa. May 2002;31(2):91-4. doi:10.1024/0301-1526.31.2.91
23. Sporbeck B, Mathiske-Schmidt K, Jahr S, et al. Effect of biofeedback and deep oscillation on Raynaud's phenomenon secondary to systemic sclerosis: results of a controlled prospective randomized clinical trial. Rheumatology international. 2011;32(5):1469-1473. doi:10.1007/s00296-011-1882-2
24. Comparison of Sustained-Release Nifedipine and Temperature Biofeedback for Treatment of Primary Raynaud Phenomenon: Results From a Randomized Clinical Trial With 1-Year Follow-up. Archives of internal medicine (1960). 2000;160(8):1101-1108. doi:10.1001/archinte.160.8.1101
25. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. The effects of upper and lower limb exercise on the microvascular reactivity in limited cutaneous systemic sclerosis patients. Arthritis research & therapy. 2018;20(1):112-112. doi:10.1186/s13075-018-1605-0
26. Schmidt J, Monnet P, Normand B, Fabry R. Microcirculatory and clinical effects of serial percutaneous application of carbon dioxide in primary and secondary Raynaud's phenomenon. Vasa. May 2005;34(2):93-100. doi:10.1024/0301-1526.34.2.93
27. al-Awami M, Schillinger M, Maca T, Pollanz S, Minar E. Low level laser therapy for treatment of primary and secondary Raynaud's phenomenon. Vasa. Feb 2004;33(1):25-9. doi:10.1024/0301-1526.33.1.25
28. Hahn M, Steins A, Möhrle M, Blum A, Jünger M. Is there a vasospasmolytic effect of acupuncture in patients with secondary Raynaud phenomenon? Journal der Deutschen Dermatologischen Gesellschaft. 2004;2(9):758-762. doi:10.1046/j.1439-0353.2004.04729.x
29. Gladue H, Berrocal V, Harris R, et al. A randomized controlled trial of acupressure for the treatment of Raynaud's phenomenon: the difficulty of conducting a trial in Raynaud's phenomenon. Journal of scleroderma and related disorders. 2016;1(2):226-233. doi:10.5301/jsrd.5000206
30. WANG S, Cai Yy, LU J-r. Warm Needling Therapy for Raynaud's Syndrome in30Cases. Shanghai Journal of Traditional Chinese Medicine. 2003;37(3):38-39.
31. Guglielmi RS, Roberts AH, Patterson R. Skin temperature biofeedback for Raynaud's disease: a double-blind study. Biofeedback and self-regulation. 1982;7(1):99-120. doi:10.1007/BF00999058
32. Büttner M, Henschel G, Spengel FA. [Effectiveness of temperature biofeedback in therapy of Raynaud's disease]. Vasa Suppl. 1991;32:411-5. Wirksamkeit von Temperatur-Biofeedback in der Therapie des Morbus Raynaud.
33. Kuryliszyn-Moskal A, Kita J, Dakowicz A, Klimiuk P, Kowal-Bielecka O. Assessment of the efficacy of laser biostimulation and low-frequency pulsed magnetic field in the treatment of microvascular abnormalities in patients with Raynaud's phenomenon. Reumatologia. 2012;50(5):410-415.
34. Tapia-Haro RM, García-Ríos MC, Toledano-Moreno S, Casas-Barragán A, Castro-Sánchez AM, Aguilar-Ferrándiz ME. The complementary effects of galvanic current electrical stimulation associated with conservative treatment to increase vasodilation in patients with Raynaud's phenomenon: a randomized trial. Clinical rehabilitation. 2020;34(5):595-606. doi:10.1177/0269215520907652
35. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. Exploring the feasibility of an exercise programme including aerobic and resistance training in people with limited cutaneous systemic sclerosis. Clinical rheumatology. 2020;39(6):1889-1898. doi:10.1007/s10067-019-04921-7
36. Ko GD, Berbrayer D. Effect of ceramic-impregnated "thermoflow" gloves on patients with Raynaud's syndrome: randomized, placebo-controlled study. Alternative medicine review. 2002;7(4):328-335.
37. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. Rheumatology (Oxford, England). 2009;48(7):791-795. doi:10.1093/rheumatology/kep039
38. Visual Rx . Version 4. Dr. Christopher Cates EBM. http://www.nntonline.net
39. SchÃƒÂ¼nemann H, Oxman A, Vist G, Higgins J, Deeks J, et al. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011. The Cochrane Collaboration; 2011.
40. Higgins JPT, Deeks JJ, Altman DG on behalf of the Cochrane Statistical Methods Group (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 . Available from handbook.cochrane.org.
41. Deeks JJ, Higgins JPT, Altman DG, editors. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 . Available from handbook.cochrane.org.

42. Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. The Lancet (British edition). 1997;350(9074):326-329. doi:10.1016/S0140-6736(97)02419-7
43. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343(7818):c4737-307. doi:10.1136/bmj.d4002
44. Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011.
45. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Cochrane book series. Wiley-Blackwell; 2008.

Table 1. Study Characteristics of the Studies Assessing Non-Pharmacologic Interventions to Treat Raynaud's Phenomenon.

First author, Year	Study country	Design	Intervention	Comparator	Inclusion criteria	Exclusion criteria	Length of follow up	Primary outcome
Hahn, 2004	Germany	RCT	Acupuncture	Sham acupuncture	Diagnosis of secondary RP using the American Rheumatism Association Criteria		16 weeks	Frequency Duration Severity
Gladue*, 2016	US	RCT	Vasodilation acupressure (group A) and Relaxation acupressure (group B)	Education	> 18 years Diagnosis of primary or secondary RP Reported at least three attacks per week Had been on stable vasodilator medications for the previous 2 weeks Willing to comply with study visits and treatment plans	Patients with a history of stroke, myocardial infarction or life-threatening arrhythmia within the previous six months, uncontrolled hypertension (SBP > 140 mm Hg, DBP > 90 mmHg), significant digital ulcers or difficulty with hand dexterity limiting their ability to perform acupressure	8 weeks	Frequency Duration Severity
Appiah, 1997	Germany	RCT	Acupuncture	No treatment	18-60 years Diagnosis of primary RP No use of vasoactive drugs during the study and 6 weeks before	History of myocardial infarction or angina pectoris Pregnant	1 week 12 weeks 23 weeks	Frequency Duration Severity
Wang, 2003	China	RCT	Warm needling treatment	Betaloc tablets	Diagnosis of primary RP		15 days	Raynaud's condition score
Sporbeck, 2011	Germany	RCT	Skin temperature Biofeedback	Untreated vasculopathy	Diagnosed by American College of Rheumatology criteria for Systemic sclerosis and suffering from RP		4 weeks 12 weeks	Scleroderma-Visual Analog Scale (VAS) for Raynaud's phenomenon

Raynaud's Treatment Study Investigators**, 2000	US	RCT	Skin Temperature biofeedback	Electromyography	Diagnosis of primary RP History of 2 or more attacks per day during the previous cold season	Secondary RP	2 months	Frequency Physician's global assessment
Guglielmi, 1982	US	RCT	Skin temperature biofeedback	Electromyography	Diagnosis of RP Bilateral discoloration of the fingers precipitated by cold or emotional stimuli Absence of nutritional changes	Complicating organic disorders Evidence neurovascular syndromes Excessive swelling in extremities Skin changes typical of scleroderma or lupus erythematosus Pain in the joints or deformity of the fingers Hypertension Evidence of occupationally induced symptoms Taking medications known to cause vasospastic symptoms Taking medications for Raynaud's disease History of sympathectomy	Monthly (1 to 5 months)	Frequency Duration Severity
Buttner, 1991		RCT	Skin temperature biofeedback	Gymnastic hand exercises	Diagnosis of primary RP		5 weeks 3-week follow-up-post-treamt-ment	Frequency Duration
Hirschl, 2002	Austria	RCT cross-over	Low level laser therapy	Placebo laser	Diagnosis of primary RP		2 weeks	Frequency Severity
Hirschl, 2004	Austria	RCT cross-over	Low level laser therapy	Placebo laser	Diagnosis of primary RP Not currently taking vasoactive medication	Secondary RP	3 weeks 12 weeks	Frequency Severity

Kuryliszyn-Moskal, 2012	Poland	RCT	Laser bio stimulation with low frequency pulsed magnetic field	Laser bio stimulation	Diagnosis of primary RP		3 weeks	Frequency Duration Severity
Al-Awami, 2004	Austria	RCT	Low level laser irradiation	Placebo laser	Diagnosis of primary RP for 2 years or more and on average At least 4 episodes of RP per week	Under 18 years Over 65 years Women of childbearing age who were not using adequate contraception Patients with a history of severe cardiorespiratory or metabolic disorders	6 weeks 3 months	Frequency Duration Severity
Tapia-Haro***, 2020	Spain	RCT	Conservative treatment and galvanic current electrotherapy	Conservative treatment	>18 years Diagnosis of primary or secondary RP	Skin alterations (scars, gangrene or ulcers in the area to be treated) Upper limb entrapment syndrome Pregnancy or breastfeeding Tumoral process	7 weeks 15 weeks	Frequency Severity
Mitropoulos, 2020	UK	RCT	Exercise group (twice/week)	No physical activity	>18 years Diagnosed by American College of Rheumatology criteria for limited systemic sclerosis and suffering from RP Disease duration between 1 and 10 years Patients should be able to perform exercise	Advanced pulmonary arterial hypertension or interstitial lung disease Diagnosed with another inflammatory condition Patients presenting myositis, proximal muscle weakness Patients with New York Heart Association class 3 or 4 Current smokers or people who stopped smoking within 4 weeks of health screening Pregnant	12 weeks	Severity Quality of life

Mitropoulos, 2018	UK	RCT	Arm cranking ergometer (twice/ week)	No physical activity	Same as above	Same as above	12 weeks	Severity Quality of life
Schmidt****, 2005	France	RCT	Natural CO2 gas therapy	Placebo and natural CO2 gas therapy	Diagnosis of mild primary or secondary RP with synoptic phase as defined by the criteria of Allen and Brown	All other causes of RP (drug induced, toxic, traumatic, endocrine, vasculitis, and arterial disease other than atheroma)	12 weeks	Frequency
Ko, 2002	Canada	RCT	Ceramic-impregnated thermoflow gloves	Placebo gloves	>18 years Diagnosis of RP using the Pal criteria	Severe pulmonary disease Myocardial infarction Terminal cancer Pregnant	12 weeks	Severity Patient's response to treatment
Neferu, 2017	Canada	RCT cross-over	Ischemic preconditioning	Placebo	>18 years Diagnosis of RP 7 attacks per week sBP>80 mmHg Ability to provide consent and complete RP diary	New therapy in the 2 weeks prior sBP > 180 Previous non-compliance with treatments	8 weeks	Frequency Severity Patient's global assessment

*High dropout rate approaching 30 hypothesized to be due to the difficulty with keeping up the daily acupressure treatment or inefficacy

**85% of biofeedback and 83% of medication participants completed attack cards (for primary outcome); By 2 month follow up, 68% biofeedback and 82% medication completed attack cards

***Conservative treatment includes anti-inflammatory, vasodilatory and analgesic drugs, lifestyle recommendations (maintaining high core body temperature, avoidance of cold exposure, use of gloves and cessation of smoking, etc.)

****Control: 18 days of intervention; 9 days of placebo treatment followed by 9 days of CO2 gas therapy

Table 2. Population Demographics in the Studies Assessing Non-Pharmacologic Interventions to Treat Raynaud's Phenomenon.

Study	Sample size (n)		Primary Raynaud's		Secondary Raynaud's		Disease duration (years; SD)		Age (years; SD)		Sex (female)		Comments
	INT	COM	INT	COM	INT	COM	INT	COM	INT	COM	INT	COM	
Hahn, 2004	11	8			11	8			47± 12	41± 11	10	6	All secondary RP
Gladue, 2016	16	7	10	5	6	2			52.3 ± 16.1	44.3± 15.5	12	6	This study did not differentiate between primary or secondary RP when presenting the results.
Appiah, 1997	17	16	17	16			16.1± 14.6	11.4± 11.1	45.5± 11.5	41.5± 10.7	12	11	All primary RP
Wang 2003	30	30	30	30					26-58	24-57	21	23	All primary RP
Sporbeck, 2011	8	10					6	1.5	50± 15.1	58.9± 5.3	15	9	Unclear whether secondary and primary RP were combined
Raynaud's Treatment Study Investigators, 2000	81	74					12.3± 10.4	14.0± 11.1	44.1± 12.5	45.5± 11.7	109		70% of the total participants were women; all primary RP
Guglielmi, 1982	12	12	12	12			9.5± 7.42	11± 9.61	33.25± 9.62	33.83± 8.72			Duration is specified as "years since onset"; sex not specified; all primary RP
Buttner, 1991	10	10	10	10					35-59 (all subjects)		17 females, 3 males**		All primary RP
Hirschl, 2002	18						24± 16		53± 17		15		Crossover study, therefore, intervention and comparator had same population; all primary RP
Hirschl, 2004	48						20± 10		46± 14		38	38	Crossover study, therefore, intervention and comparator had same population. All primary RP

Kuryliszyn-Moskal, 2012	24	24					10.1 (1 to 30)*	11.0 (1 to 40)*	45.2 (19 - 66)*	37.4 (19-77)*			Sex not specified; all primary RP
Al-Awami, 2004	24	23	9	9	15	14	6 (3 to 13)*	13 (4 to 25)*	45 (36 - 53)*	46 (37 - 56)*	16	21	Both primary and secondary RP
Tapia-Haro, 2020	17	17	6	7	11	10	12.8± 10.5	12.8± 9.8	43.2± 18.1	43.5± 17.7	12	11	Duration is specified as "years since onset"; both primary and secondary RP
Mitropoulos, 2020	16	16					8± 2	8± 2	69.6± 11.4	63.6± 12.2	29**		Unclear whether secondary and primary RP were combined
Mitropoulos, 2018	10	11					7.8± 2.3	6.3± 2.0	69.1± 9.7	62.2± 14.3	31**		Unclear whether secondary and primary RP were combined
Schmidt, 2005	43	44	37	39	6	5	13.3± 10.9	14.4± 10.6	48.6± 14.4	48.8± 13.9	39	35	Both primary and secondary RP
Ko, 2002	30	30							54.1± 12.1	51.8± 12.3	20	26	Diagnosis of RP made using the “Pal criteria”
Neferu, 2017	18		1		17		13.9± 7.6		60.8± 9.4		16		Crossover study, therefore, intervention and comparator had same population; 5.6% were primary RP; included both secondary and primary RP

*Range
**# of participants in total sample size combined; not specified based on intervention versus comparison
INT: intervention; COM: comparison

SUPPLEMENTARY INFORMATION

Non-Pharmacological Interventions for the Treatment of Raynaud's Phenomenon: A Systematic Review

DOI for the original publication: https://doi.org/10.18192/uojm.v13i1.6175

Supplementary 1. Search Strategy used for Searching the Databases for Articles to be Screened

Embase Classic+Embase <1947 to 2021 June 08>
Ovid MEDLINE(R) ALL <1946 to June 08, 2021>
EBM Reviews - Cochrane Central Register of Controlled Trials <May 2021>

1. Raynaud Disease/ 13938
2. Vasospasm.ti,ab. 29094
3. raynaud$.tw. 20745
4. or/1-3 54027
5. Raynaud phenomenon/ 22400
6. vasospasm/ 10888
7. raynaud$.tw. 20745
8. or/5-7 39263
9. Randomized controlled trial/ 1195698
10. Controlled clinical study/ 463861
11. random$.ti,ab. 3961563
12. randomization/ 196576
13. intermethod comparison/ 272183
14. placebo.ti,ab. 874737
15. (compare or compared or comparison).ti. 1125316
16. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 4165075
17. (open adj label).ti,ab. 196913
18. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 708607
19. double blind procedure/ 187161
20. parallel group$1.ti,ab. 83969
21. (crossover or cross over).ti,ab. 294838
22. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 771565
23. (assigned or allocated).ti,ab. 992819
24. (controlled adj7 (study or design or trial)).ti,ab. 1077946
25. (volunteer or volunteers).ti,ab. 525254
26. human experiment/ 547398
27. trial.ti. 932808
28. or/9-27 10300096
29. (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 17795
30. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) 631245

31. (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 36052
32. (Systematic review not (trial or study)).ti. 330017
33. (nonrandom$ not random$).ti,ab. 33813
34. Random field$.ti,ab. 5461
35. (random cluster adj3 sampl$).ti,ab. 2526
36. (review.ab. and review.pt.) not trial.ti. 1839156
37. we searched.ab. and (review.ti. or review.pt.) 71186
38. update review.ab. 277
39. (databases adj4 searched).ab. 80917
40. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1110527
41. Animal experiment/ not (human experiment/ or human/) 2335916
42. or/29-41 5170036
43. 28 not 42 9425482
44. 8 and 43 5675
45. Raynaud Disease/ 13938
46. Vasospasm.ti,ab. 29094
47. raynaud$.tw. 20745
48. or/45-47 54027
49. randomized controlled trial.pt. 1054307
50. controlled clinical trial.pt. 186338
51. randomized.ab. 1884668
52. placebo.ab. 839620
53. clinical trials as topic.sh. 229494
54. randomly.ab. 1111443
55. trial.ti. 932808
56. or/49-55 4090332
57. exp animals/ not humans.sh. 34135393
58. 56 not 57 2637796
59. 48 and 58 2745
60. 8 use cctr 1753
61. 44 use emczd 3864
62. 59 use medall 1275
63. 60 or 61 or 62 6892

Supplementary 2. Methods Pertaining to a Meta-Analysis in our Protocol

Data Synthesis

We will undertake meta-analyses only where this is clinically meaningful do so. We will use fixed-effect models for combining data from studies where we are confident that the studies are estimating the same treatment effect: i.e., where trials are examining the same interventions and trials' populations and methods are sufficiently similar. Where studies may be estimating different treatment effects (i.e., due to different mechanisms of action of interventions), we will use random effects models for the meta-analysis. The primary analysis for our reviews for self-reported outcomes (e.g., pain and participant global assessment) will be restricted to trials with low risk of detection and selection bias.

If a meta-analysis cannot be conducted due to heterogeneity amongst the included articles, the values (e.g., means and standard deviations) of major outcomes will be presented in forest plots without a total. The major outcomes and findings of each category of NPI will be discussed and the range of mean differences will be reported when necessary for major outcomes. The articles will be reviewed narratively discussing the NPI, the patient population, and whether the major outcomes are statistically significant.

Data Analysis and Meta-Analysis

Dichotomous Data
Dichotomous outcomes will be presented as summary risk ratios with 95% confidence intervals. In the case of rare events (<10%), the Peto odds ratio will be reported. We will calculate the number needed to treat to benefit (NNTB) from the control group event rate and the risk ratio using the Visual Rx[38] NNT calculator.

Continuous Data
Continuous outcomes measured in the same way between trials will be pooled as mean difference (MD) with the corresponding 95% confidence intervals.

When different scales are used to measure the same outcome, standardised mean differences (SMD) will be calculated, with the corresponding 95% CI. SMDs will be back-translated to a typical scale (e.g., 0 to 10 cm visual analogue scale for severity) by multiplying the SMD by a typical among-person standard deviation (e.g., the standard deviation of the control group at baseline from the most representative trial) (as per Chapter 12 of the Cochrane Handbook).[39]

Unit of Analysis Issues

The unit of analysis for each outcome will be the participant. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Cross-over trials will be assessed to determine if it is likely that there is a problem with a carry-over effect, taking into consideration the type of intervention and the length of the washout period. If this is deemed a concern, then only first-phase data from cross-over trials will be included. When data from both periods of the cross-over trial are available, we will follow the methods described in Ch.16.4 of the Handbook[40] and consult with a statistician to ensure the analysis is performed correctly.

Assessment of Heterogeneity

Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes, and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be conducted by

observing this data from the data extraction tables. Statistical heterogeneity will be assessed by visual inspection of the forest plot to assess for obvious differences in result between the studies and using the I-squared and chi-squared test.

As recommended in the Cochrane Handbook[41], the interpretation of an I-squared and chi-squared value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. As noted in the Handbook, we will keep in mind that the importance of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity.

The chi-squared test will be interpreted where a P value ≤ 0.10 will indicate evidence of statistical heterogeneity.

If we identify substantial heterogeneity, we will report it and investigate possible causes by following the recommendations in section 9.6 of the Handbook.

Assessment of Reporting Biases

For meta-analyses with 10 or more studies, we will assess for reporting bias (publication bias) by inspecting for asymmetry in funnel plots as is recommended.[42,43] Where publication bias is detected, we will follow the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*[44] to explore possible reasons.

Subgroup Analysis and Investigation of Heterogeneity

We plan to carry out the following subgroup analyses for each review when there is sufficient data:
1. by RP type (primary or secondary).
2. by intervention type.

Subgroup analyses will be limited to the major outcomes.

We will use the formal test for subgroup interactions in RevMan[15] and will use caution in the interpretation of subgroup analyses as advised in section 9.6 of the Handbook.[45] The magnitude of the effects will be compared between the subgroups by means of assessing the overlap of the confidence intervals of the summary estimated. Non-overlap of the confidence intervals indicates statistical significance.

Sensitivity analysis

We will perform sensitivity analyses to explore the robustness of the results of the major outcomes, stratified on the following factors when there is sufficient data:
1. trial quality - trials at low risk of bias for allocation concealment and blinding of outcome assessor
2. trial duration
3. diagnostic inclusion criteria used in the trial
4. time of the year trial was performed
5. estimations or imputations of standard deviations or correlation coefficients from cross-over studies

Results from these exploratory analyses will be interpreted with caution