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Behaviour-change interventions for the management of Raynaud's Phenomenon: a systematic literature review

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PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. Info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
8Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

Behaviour-change interventions for the management of Raynaud's Phenomenon: a systematic literature review

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Key words: Raynaud's Phenomenon, behaviour-change, systematic review

ABSTRACT

Objectives: Raynaud's phenomenon (RP) is a significant cause of morbidity. Vasodilator medications can cause unwanted adverse effects, with behavioural and lifestyle changes forming the mainstay of symptom self-management. Long-term behavioural change is difficult to implement successfully. This systematic literature review evaluates the efficacy and safety of behaviour-change interventions for RP.

Interventions: Searches of EMBASE, PubMED, Cochrane and Psychinfo identified randomised controlled trials (RCTs) of behaviour-change interventions for adults with RP. The term 'behaviour-change interventions' was defined *a priori.*

Primary and secondary outcomes: Primary outcomes of interest included severity/impact, frequency and duration of RP episodes, pain, disability, adverse events and study withdrawal. Secondary outcomes of interest included physician and participant global assessment of impact, change in digital ulceration, treatment preference, and general improvement.

Results: Study selection, data extraction and risk-of-bias was assessed independently by two reviewers, and reached consensus with the third when necessary. Of 638 articles retrieved, eight studies fulfilled criteria for inclusion. Biofeedback was the active behaviour-change treatment arm for seven studies, with one study reporting a behavioural intervention. Studies were published 1978–2002; six were USA based studies, one was German and one Swedish. There was a generally high risk-of-bias across studies, with the exception of one large RCT. The total sample included 495 participants (study median=29), with a median age of 39.5y and preponderance towards females (73%). Five studies individually reported positive gains in primary outcomes of interest, however due to high risk of bias and missing data, meta-analysis was not possible.

Conclusions: There is no evidence to support or refute claims of the efficacy or safety of behaviour-change interventions for the management of RP. There remains a strong case for developing and testing behaviour-change interventions that focus on self-management of RP, however theoretical development and advancement in trial quality is imperative to underpin future work.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first comprehensive and contemporary systematic literature review of behaviour-change interventions in RP, making a novel contribution to the field of knowledge regarding pharmacological alternatives in the field of RP.
- The published protocol was strictly adhered to, reducing likelihood of bias and offering a robust systematic review methodology, however due to limitations in study design and incompleteness of data, a meta-analysis to assess comparative efficacy was not viable.
- A narrative analysis and synthesis of study findings offer a novel contribution to our understanding of the best evidence available, particularly pertaining to the quality of existent trials.
- Recommendations are presented for future RP behaviour-change interventions, derived from reported and observed methodological flaws and treatment limitations of included studies. This offers a more scientifically rigorous and clinically meaningful basis from which to develop more robust interventions for this population.

INTRODUCTION

Peripheral vasoconstriction of thermoregulatory pre-capillary arterioles and arteriovenous anastomoses is a normal physiological thermoregulatory response to cold exposure.[1] Raynaud's Phenomenon (RP) describes excessive peripheral vasoconstriction to cold exposure and/or emotional stress. Attacks of RP are associated with characteristic digital colour changes (reflecting blood oxygenation and tissue perfusion).[2-3] Tissue ischaemia (and subsequent reperfusion) during attacks of RP results in pain and paraesthesia causing distress, loss of hand function and reduced quality of life.[2-3] RP is common, affecting approximately 5% of people. The majority of sufferers have a functional vasospastic disorder that, whilst intrusive, is otherwise benign in nature (termed primary RP). Digital perfusion is generally normal in between attacks. The term secondary RP is applied to disorders in which RP symptoms occur as a result of disturbed digital tissue perfusion related to separate underlying pathology. Important causes of secondary RP are autoimmune rheumatic diseases such as systemic sclerosis (SSc), in which a progressive obliterative microangiopathy can result in persistent 4digital ischaemia and tissue damage.[4] Despite being rare, with an estimated prevalence of 250/million, SSc is often used as the focus of RP research.[5]

Cold exposure appears to be the major factor precipitating RP symptoms in SSc, although emotional stress provokes symptoms in approximately 30% of episodes.[6] Emotional stress appears to represent a more prominent aggravating factor in primary RP.[7] Thematically relevant emotional stressors appear to be important. For example, imagining the threat of cold exposure (losing gloves and car keys during a snowstorm) results in reduced finger temperature in people with primary RP but not healthy controls.[8] These observations could have important implications for the behavioural management of RP within different patient populations. Self-management measures are typically included in recommendations on the management of RP but do not typically extend beyond general advice on avoiding cold exposure, conserving heat loss, smoking cessation, increasing exercise, and reducing stress levels.[9-10] Adherence with interventions of this nature is typically poor, with estimates of 30-50% of patients demonstrating poor compliance, regardless of condition, expected outcome, or setting.[11] Despite the perceived importance of non-pharmacological interventions for RP, the comparative efficacy, adoption and compliance with lifestyle interventions has not been fully evaluated. A number of behaviour-change interventions have been tested for RP but the comparative efficacy of a range of interventions within different disease populations (primary and secondary RP) has not previously formed the focus of a systematic review. We report the findings of a systematic literature review evaluating the efficacy of behaviour-change interventions for the management of primary and secondary RP. We consider how the findings inform recommendations on behaviour-change interventions for RP and future research efforts in this field.

Objectives

The specific objectives of this systematic review were to (1) assess the comparative safety and efficacy of a range of behavioural interventions for the management of symptoms associated with primary and secondary RP, and (2) identify what we can learn from the studies reviewed to inform study protocols for future behaviour-change interventions for RP.

METHODS

The protocol and supplementary material used to develop and conduct this systematic review has been published with open access [12] and registered in the International Prospective Register of Systematic Reviews (registration number CRD42017049643). The protocol and supplementary material is available from http://bmjopen.bmj.com/content/7/8/e017039.

Search strategy

The search strategy was designed to identify treatment studies examining the efficacy of behaviour-change interventions in the treatment of adults with RP (primary or secondary). MEDLINE, EMBASE, PsycInfo and the

Cochrane library were searched on 22nd August 2017 using terms developed by the research team and in collaboration with an information specialist (JH). The term 'behaviour-change interventions' were defined *a priori* as interventions which target symptomatic relief of RP through directed or advised change in patient determined behaviour.[12] To include all possible permutations of the interventions designed to change behaviour, the search terms were purposively broad and inclusive (behavio(u)ral therapy, cognitive therapy, education, psychoeducation, biofeedback, clinical psychology, psychotherapy, self-management, cognitive behavio(u)r therapy, and behavioural medicine).

To ensure a comprehensive capture of relevant high quality and relevant studies, reference lists of articles included at the full-text review stage were hand-searched November 24th 2017. Authors of papers in the final stage of the review were also contacted for further grey literature. Published studies in any language were included, with no date restrictions.

Inclusion criteria

Randomised Controlled Trials (RCTs) testing behaviour-change interventions for the treatment or management of adults with RP (primary or secondary) were included in the systematic review. Due to the lack of consensus in the use of RP diagnostic criteria, all clinical definitions were included. Other clinical trial designs (e.g. non-randomised controlled trials and those without a control comparator) were excluded; however non-blinded studies were included due to the difficulties of blinding in trials of this nature.

Selection of Studies

Studies generated by the initial search were screened by two authors for eligibility (JD, JP). All full texts were reviewed and independently rated for inclusion by two review authors using a pre-specified, published data extraction form.[12] Bibliographies of included studies and grey literature search were conducted by the first author and were subject to review of eligibility. Discrepancies at each stage were resolved through consultation with the third author reviewer (CE).

Data extraction

Data were independently extracted from included studies by two review authors, using the pre-specified data extraction form. Study authors were contacted in cases of missing or incomplete data. In addition to outcome data, data pertaining to the quality of psychotherapeutic interventions was extracted. Specifically: reference to a theoretical model; level of therapist training; whether the integrity of the intervention was checked. These criteria were drawn from an authoritative review of empirically supported psychotherapies.[13]

Due to the absence of agreement regarding domains of measurement or measurement technology in RP [14] the primary outcomes measures chosen for our analyses mirror those adopted in a recent generic systematic review protocol for RP,[15] including: (1) *severity/impact of RP episodes* assessed using visual analogue scales (VAS); Likert scales, or the Raynaud's Condition Score (RCS) [16] (either at a single time point using a standardised recall period) or as an average daily score (obtained from the RCS diary or equivalent from RP symptom diary); (2) *frequency of RP attacks* (adopted from the RCS diary or equivalent symptom diary approach) reported as average daily or weekly frequency of RP attacks; (3) *duration of RP attacks* (adopted from the RCS diary or equivalent symptom diary approach) reported as the average daily duration of RP attacks over 1-2 weeks; (4) *pain* assessed using a VAS or Likert scale (reporting intensity of pain during RP attacks); and (5) patient assessment of disability due to RP/interference on daily activities e.g. the Scleroderma Health Assessment Questionnaire (HAQ) [17] Raynaud's phenomenon VAS or equivalent. (6) *Adverse events* (hospitalization/death) and (7) *withdrawals from study* were also included within primary outcomes.

Secondary outcomes included (1) *physician global assessment of severity/impact of RP*; (2) *patient global assessment of function/disability secondary to RP* (e.g. the HAQ score); (3) *change in digital ulceration (positive/negative)*; (4) *treatment preference*, and (5) *general improvement* (self-reported overall

improvement). Most RP clinical trials involve assessments over 1 or more weeks. Sensitivity analyses were planned for trials with marked differences in durations of treatment/assessment.

Risk of Bias

Risk of bias was independently assessed on an outcome and study level by two authors using the Cochrane risk of bias assessment tool (see supplementary material).[18] Unresolved discrepancies were reviewed by the third author. Risk of bias was assessed according to the following dimensions: random sequence generation (adequate description and method of participant allocation in accordance with standard randomisation); allocation concealment (adequate concealment of group assignment to prevent selection bias); blinding of participants and personnel (adequacy of measures taken to prevent performance bias and conceal group assignment); blinding outcome assessors (adequacy of measures taken to prevent detection bias and conceal group assignment to outcome assessors); incomplete data (adequacy of the management of missing data and potential implications for bias); selective outcome reporting (reporting bias relating to the consistency between pre-specified and reported outcomes); other sources of bias (other concerns not covered elsewhere but may lead to a risk of bias). Eligible studies were rated as high, low, or unclear (risk of bias), on each of these dimensions, culminating in an overall risk of bias (high/low/unclear) in accordance with the Cochrane handbook for systematic reviews of interventions.[18] Investigator agreement was evaluated using Kappa statistics.

Quality of evidence

Quality of evidence and confidence in estimates of effect were assessed using GRADE: (in)consistency of effect, imprecision, indirectness and publication bias.[19] A GRADE summary of findings table was planned on this basis.

Data synthesis and analysis

A comprehensive meta-analysis and secondary sub-group analysis were planned however due to the low numbers of studies included for analysis, insufficient data available from several studies and the heterogeneity of the available data and outcomes, an attempt at formal meta-analysis was not considered clinically or statistically meaningful. Funnel and forest plots were not generated for the aforementioned reasons.

In the absence of meta-analyses, a narrative (descriptive) analysis of primary and secondary outcomes was planned to include: description of individual study outcomes in terms of frequency/severity/duration of episodes, patient global assessment of disability and changes on RCS scores where available; analysis of reported design or intervention features in behaviour-change interventions; analysis of reported considerations as regards of future behaviour-change interventions. [12]

RESULTS

Selection and inclusion of studies

The initial search generated 638 studies, resulting in 304 abstracts/titles following removal of duplicates. Independent review at this stage removed a further 282 for irrelevance, with 22 studies retrieved for full-text retrieval. Full-text review resulted in removal of a further 14 studies (see figure 1), leaving a final set of 8 studies reported across 9 papers. This included a single original study associated with a follow-up paper retrieved from the authors for inclusion; the late addition was attributed to the original paper having been written in Swedish and unavailable electronically/online therefore not identified within the original search. No additional studies were added as a result of grey or reference list searches. Consultation and resolution with the third reviewer (CE) was required on review of three separate papers. The PRISMA flowchart is given in figure 1.

[Figure 1 about here]

Figure 1: PRISMA flowchart

Study characteristics

Six of eight studies included participants diagnosed with primary RP, the remaining two used secondary RP samples (secondary to Systemic Sclerosis, SSc).[20-21] Studies did not mix participants with primary and secondary RP. All studies randomised participants to an active control. Three studies described one comparator treatment.[22-24] Three described reported two comparator arms [20, 25, 26] and one study reported three comparator arms.[27] All studies indicated a non-active comparator: two studies used a placebo [24, 27] four studies used interventions to isolate the effects of the active treatment (gymnastic hand movement N=1; frontalis EMG for physiological feedback N=4; autogenic training N=3). Two other active treatments formed part of the treatment trials and included deep oscillation (N=1) and nifedipine medication (N=1) (see interventions section for detail). Only two studies used a no treatment condition as a control comparator.[21, 26] Sample sizes ranged from 12-313, with a median of 29 (IQR 12). A total of 495 participants were included across studies; 156 in active treatment and 339 in comparator arms.

Females accounted for 73% of the overall sample. Five studies reported age ranges from 17-65 years. Mean age was reported in four studies, ranging from 28-54.4, with a calculated median of 39.5 (IQR 18.7). Ethnicity was not consistently reported and could not be meaningfully estimated. The publication dates of the nine papers (eight studies) ranged from 1978-2002, with five of eight studies completed prior to 1984 and none of the included studies published after 2002. The majority of the studies were USA-based and written in the English language (N=6), with one German language and one Swedish language study.

Study outcomes

All studies targeting primary RP used diary-based approaches to assessing RP (predecessors of the RCS diary), including measures of severity/impact frequency, duration and severity of episodes, with some studies expanding further (see table 1). Other outcome measures included physiological measures, physician rated measures, stress and general health measures. One study used the RP Visual Analogue Scale (VAS) subscale of the Scleroderma Health Assessment Questionnaire (SHAQ) which was developed specifically for the secondary RP population. [17] Primary outcomes of interest are highlighted in bold.

Table 1: Included study characteristics

Study	**Setting**	**Diagnostic criteria applied**	**No. Pts**	**Treatment arms**	**Treatment Period (weeks)**	**No. sessions & duration (mins)**	**Total dose (mins)**	**Outcomes investigated** *Self-report*	*Objective*	**Any effect (BC)**	**Domain of positive effect**	**Overall Risk of Bias**
Buttner (1991)	Germany	-	20	BFB Gymnastic hand movement	5	15 (25)	375	**Frequency** **Duration** **Severity** Antecedents	Skin temp.	+	Frequency Duration Skin temp.	High
Freedman et al. (1983)	US	-	32	Biofeedback Autogenic EMG	5	10 (42)	420	**Frequency** Description Antecedents	Skin temp. Skin conductance Ambulatory belt temperature Heart rate Respiration rate	+	Frequency	High
Freedman et al. (1984) *	US	1980 ARA	24	Biofeedback Autogenic EMG	5	10 (42)	420	**Frequency** Description Antecedents	Skin temp Skin conductance Ambulatory belt temperature Heart rate Respiration rate	<>		High
Gugliemli et al. (1982)	US	Clinical assessment	39 (36)	Biofeedback EMG No treatment	5	20 (60)	1200	**Frequency** **Duration** **Severity** **Pain Improvement** Hand Involvement Antecedents Range of symptoms		<>		High
Melin & Fagerstrom (1981, 1996)	Sweden	Clinical assessment	12	Behavioural Placebo	<1	10 (8)	80	**Frequency**	Skin temp	**+**	Frequency Skin temp	High
RTS group (2000)	US	Clinical assessment Capillaroscopy	313	Biofeedback Nifedipine Placebo	5-10	10 (60)	600	**Frequency** **Severity** **Impact**	Blood pressure	<>		Low

				EMG control				**Improvement Adv. outcome** General health/ Quality of life				
Sporbeck et al. (2002) *	US	1980 ARA	28	Oscillation Biofeedback Wait list	12	12 (n/s)	-	Scleroderma VAS		+	VAS Scleroderma scale	High
Surwit et al. (1978)	US	-	32 (30)	Biofeedback Autogenic	4	6 (n/s)	-	**Frequency Severity Intensity**	Skin temp Heart rate	+	Frequency Intensity Skin temp	High

Key:
Outcomes emboldened represent primary outcome of interest.
** Secondary RP only, all other studies primary RP*
+positive effect
<> no effect

Interventions

Seven studies tested 'biofeedback' and one tested 'behavioural treatment' as the active behaviour-change interventions for RP. Biofeedback interventions were similar in procedure (notwithstanding differences in duration/frequency) however three studies did not provide detailed descriptions of the reported interventions. The behavioural intervention [24, 28] was sufficiently detailed, reporting a classical conditioning intervention involving the "*weakening of the unconditioned link between cold and peripheral vasospasms*" (p111, [24]). One study delivered 'cognitive stress management' to 50% of each of the four groups in the participant sample (total n=32).

Six of eight studies used cold stress tests prior to and/or following intervention for purposes of maximising demonstration of treatment effect. Temperatures were manipulated within a range of 4-20 degrees Celsius, for periods of between 7 and 17 minutes (not all studies specified exact duration).

Other active comparators included deep oscillation, targeting restoration of blood supply via an intermittent electrostatic field [21] and first-line RP calcium channel blocker nifedipine [27] to target pharmacological vasodilation in RP. Of note, no RCTs within this study (or outwith) have assessed the self-management approaches that form recommended first line intervention outlined in NICE guidance for the management of RP [10] (e.g. stress reduction, increased exercise, measures to retain warmth).

Treatment interventions varied in length and duration of session; number of sessions ranged from 10-20 sessions (median=12), from 8-60 minutes duration per session (median=40min). Two trials did not specify treatment session duration. Sessions took place over 2-10 weeks (plus follow-up) on a bi-weekly, thrice weekly (or unclear) basis. Six studies provided sufficient detail to calculate dose of intervention: biofeedback intervention (N=5) treatment dose ranged from 375-1200min (median=420min), dose for the behavioural intervention (N=1) was 80 minutes.

Quality of psychotherapeutic intervention

Four studies made explicit reference to an *underpinning theoretical model* of the active treatment approach, providing rationale for the application of biofeedback (N=3) [23, 25, 27] and Behavioural theory (N=1) [24, 28] in RP. The remaining four studies reported the application of biofeedback, but in the absence of theoretical explanation as to the relevance of application in RP. Studies referred to earlier work on the use of biofeedback, looking to replicate or improve previous studies. The underpinning theory relating to 'cognitive stress management' was referred to in the main report of a biofeedback for RP study,[25] with indications that a protocol had been adhered to and made available on request, however authors note that the analysis of the data is limited by small cell size.

One study reported the level of therapist training [26] describing those facilitating the intervention as 'assistants', however no studies reported level of therapist training or any additional information pertaining to qualifications of therapists delivering the interventions. Finally, despite all studies bearing an RCT design, no studies reported checking treatment integrity/fidelity of interventions.

Risk of bias

Risk of bias assessments for each of the studies is shown in table 2. Inter-rater reliability between JD and JP was 73% (k=.59), indicating fair agreement.[29] The main discrepancy between raters was inconsistent interpretation of selective reporting and lack of agreement in four of seven domains in one paper.[26] This was attributed to the variability in quality and completeness of reporting. The final risk of bias assessment includes the adjudicated ratings.

As highlighted in the risk of bias assessment table (table 2), a lack of clarity in reporting random sequence generation, allocation concealment and blinding of participants were common limitations of the studies assessed. The lowest overall risk of bias was in the RTS group (RTS). This was the largest study and benefited

from higher quality reporting typical of larger well controlled RCTs. Two of eight studies included were published as short reports. All authors were contacted for information to support a comprehensive assessment of risk of bias, however data were no longer available due to the studies having been completed up to 36 years previously, or authors unresponsiveness.

Table 2: Risk of Bias assessment

	Random Sequence Generation	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcome reporting	Selective outcome reporting	Other bias
Buttner et al. (1991)	?	?	?	-	+	-	-
Freedman et al. (1983)	?	?	-	?	-	+	-
Freedman et al. (1984)	?	?	-	-	?	-	-
Gugliemli et al. (1982)	-	-	+	+	+	-	+
Melin & Fagestrom (1981/96)	?	?	?	-	-	-	+
RTS Group (2000)	+	+	-	+	+	-	?
Sporbeck et al. (2002)	?	?	?	?	?	+	-
Surwit et al. (1978)	?	?	?	?	-	-	-

Key
? =unsure
+ =high risk
- = low risk of bias

GRADE

The quality of the evidence for all seven primary outcomes was judged to be very low. No data could be extracted for analysis meaning that by definition our confidence in judging the efficacy and safety of behaviour-change interventions is low and any estimate would be highly likely to change with the addition of new evidence. As such we judged that an empty summary of findings table would be unhelpful

Data synthesis and descriptive (narrative) analysis of findings

Primary and secondary outcomes

Of the seven primary outcomes there were insufficient data reported on any of the outcomes to assess comparative safety and efficacy. For the primary outcome of RP episode *frequency* three studies reported means and standard deviations,[20, 22, 24] however two of three studies used primary RP samples (therefore only two studies could be meaningfully compared) and time points were unclear on one study.[20] This restricted any further robust comparative measurement of efficacy as regards *frequency*. Means and/or standard deviations could not be reliably calculated based on available or acquired data for the remaining studies.

One study reported means and standard deviation of *duration of RP episodes*,[22] however only one other study examined duration but did not provided relevant data. Attempts to recover data directly from authors were unsuccessful.

Of the five remaining primary outcomes (*severity/impact, pain intensity, patient assessment of disability/interference on daily activities, adverse events, withdrawals*) data were largely missing with the exception of narrative information relating to adverse events in one study [27] and full sample retention indicated in all but two studies which reported an attrition rate of ≤10%.[23, 26] The extensive missing and/or incomplete data formed the rationale for the lack of viability of a meta-analysis. Table 3 reports all reported means and standard deviations pertaining to study primary outcomes, highlighting the paucity of reported data.

In relation to pre-determined secondary outcomes of interest (*physician global assessment of severity/impact of RP; patient global assessment of function/disability secondary to RP; change in digital ulceration; treatment preference and general improvement; self-reported overall improvement*) data available on patient perceived improvement and quality of life on one study [27] indicated that all treatments had little effect on quality of life, however both patients and clinicians rated a high degree of improvement in the pharmacological intervention (nifedipine) in comparison to biofeedback and control conditions. The Gugliemli [26] paper reported findings relating to perceived improvement, however unplanned post-hoc analysis based on learning criteria associated with the biofeedback technique obscured meaningful interpretation of results. In relation to these and other aforementioned secondary outcomes, there was again insufficient data to warrant a meta-analysis. Data pertaining to anxiety/stress were generally measured using unvalidated methods such as heart/respiration rates or other unstandardized measures. Mood was not investigated.

Table 3: Means and standard deviations of study primary outcomes

Immediately Post Treatment					
	N (Post)	Number of attacks (monthly)		Duration of attacks	
		Rx	Control	Rx	Control
Buttner et al. (1991)	20	3.4 (2.1) (weekly)	3.1 (2.1) (weekly)	15 (3)	21 (13)
Freedman et al.(1983)	32				
Freedman et al.* (1984)	24	60.1 (54.9)	37.4 (47.7)		
Gugliemli et al. (1982)	36	45 (calculated	50.8 (calculated		

		mean)	mean)		
Melin & Fagerstrom (1981) *1996*	6 *11*	4.3 *1..5*	2.8 *1.2*		
RTS Group (2000)	313				
Sporbeck et al.* (2002)	28				
Surwit et al. (1978)	30				

In summary of study reported outcomes, five of the eight studies reported positive outcomes in at least one domain. This consisted of relative reductions in frequency (N=3);[7, 22, 24] finger-tip temperature (N=3) [22-24] VAS Pain score (N=1);[21] duration of episodes (N=1);[22] intensity of episodes (N=1),[23] with three studies demonstrating significant change in more than one area. Three of eight studies reported no difference in any domains.[20, 26, 27] Six of eight studies reported no viable data in any domains pertaining to primary and secondary outcomes [20, 21, 23, 25 -27] two of these provided data that required further calculations to produce or estimate mean values however the data/calculated means were deemed insufficiently reliable to use in analysis. [20, 26]

Trial design or intervention features and future considerations

There were four features of trial design and reporting which hampered any analysis of efficacy and safety of this technology. First, inadequate measurement, storage and/or reporting of data meant no meta-analysis was possible. Second, the historical lack of consensus over nosology, measurement, and classification led inevitably to a lack of clarity over exactly who was entering trials. Third, small trials even when properly reported threaten precision of the effect estimates and would have introduced unreliability. And finally, there were multiple considerations throughout the individual studies about the content, dose, conduct, and delivery of the therapies, ranging from two studies that discussed the potential implications of change in weather over the course of treatment,[22, 26] difficulties in the acquisition and application of training skills [26-27], and the validity and generalizability of biofeedback assessed via finger-tip skin temperature.[20, 23-24] These considerations may be historical given dates of publication range from 1978 to 2002, before the development of a consensus in the use of the Raynaud's Condition Scale (RCS), disease classification criteria, and clinical trial reporting standards. A summary of the recommended critical features of any new trials in this field is presented (table 4).

Table 4: Future trial considerations

Trial design reported flaws	Future considerations
Underpinning theory and conceptual framework	• The treatment model or underpinning mechanisms of the intervention should be clearly stated to provide a clear rationale and transparency relating the scientific credibility of the intervention. The intervention mapping framework (Bartholomew 2011) provides a good example of a mapping tool used in the development of behaviour change interventions and would be highly relevant to treatment development in RP
Classification and inclusion criteria	• Standardised use of ARA diagnostic criteria for inclusion criteria will allow clearer comparison of outcomes and reduce risk of bias • Systematic use of a diagnostic criteria will introduce a higher degree of objectivity in assessment • Due to the widely acknowledged disparity in the known underlying pathogenesis between primary and secondary RP, these groups should be considered distinct and separate
Measurement	• The RCS diary (or any future validated tools for assessing RP) should be employed as a standardised tool of choice in RP trials to allow for meaningful comparisons across treatment conditions and studies and gather relevant outcome data in one measure • Consideration should be given to technologically enhanced methods to

	increase reliability such as ecological momentary interventions, to allow provision of regular prompts for RCS completion, rather than over-reliance on self- report measures which may be confounded by recall bias. • Verification of RP episodes through the use of colour charts (see RTS study) and capilliaroscopy would provide reliable data for use with self-report measures. • Physiological measures (e.g. Laser-derived imaging modalities or thermal imaging to assess digital vascular function) should be continued to be used to triangulate with subjective measures, however this should be interpreted conservatively. • Patient reported outcome instruments and objective imaging modalities could be applied as co-primary endpoints in future clinical trials. • Measures relating to psychological wellbeing (e.g. quality of life, anxiety/stress and pain) should be used due to the known pivotal role of these factors in self-management and outcome.
Treatment arms and sample	• Appropriately powered samples with full reporting of findings will generate more reliable
Protocol/procedure reporting	• The Template for Intervention Description and Replication (TIDieR[40) should be adopted for the reporting of behaviour change interventions in RP. This would provide consistency and transparency in reporting, making relevant information available for scrutiny. TiDieR requires information relating to the experience and training required for the intervention, providing further clarity on the necessary skills to deliver the intervention. • Integrity to a protocol driven intervention procedure with appropriate quality control measures such as (a) fidelity checks (b) clarity of reporting for risk of bias and purposes of replication. This is likely to increase compliance and improve the quality and outcomes of treatment interventions.
Appropriately controlled conditions	• A no-treatment/wait list control or equivalent should be adopted in future trials as a minimum comparator. • Consideration of temperate climate should form part of the methodological trial plan, controlled for where possible, measured and reported on.

DISCUSSION

Our primary objective was to assess the comparative safety and efficacy of a range of behaviour-change interventions for the management of symptoms associated with primary and secondary RP. Due to limitations in study design, reporting, and the absence of meaningful data we are unable to offer any effect estimates. Essentially, there is no evidence to support or refute claims made for the efficacy and safety of behaviour-change interventions for the management of RP.

Given the burden of RP,[2, 10, 30-31] the relatively mature development of psychological interventions in cognate fields (e.g. chronic pain, [32-33]) and potential for self-management interventions given the importance of cold exposure and stress as exacerbating factors for RP, it is surprising that there is no modern tradition of therapy development and that little work has been undertaken in this field in the last 20 years. We have speculated elsewhere that this is due to the deleterious effect of the RTS study.[31] The RTS was a high profile negative study conducted and reported in Archives of Internal Medicine, which from a modern perspective used a treatment modality waning medical support owing to absent or unimpressive outcomes. Advancement in the application of biofeedback appears to have ceased at the point at which a high quality study deemed it ineffective.

The question as to the efficacy and safety of behaviour-change interventions remains unanswered, and the case for further investigation persists if we are to continue championing the utilisation of self-management approaches in the management of RP, as per NICE guidance. [10] We have drawn lessons from the existing data in relation to study design, conduct, and reporting. Comparison has been most notably limited by heterogeneity in study design and measurement. There is a need for further development in a programme of research in behavioural influences in the onset and management of RP episodes (e.g. stress/anxiety, behavioural change including retaining more warmth, increasing exercise) which are central to the primary and secondary prevention of RP episodes. With up to a third of RP episodes are stress/anxiety related [25] and the remainder associated with cold exposure, episodes are potentially preventable. Due to the pivotal role of psychological and physical stress as a trigger in RP, psychophysiology in RP appears to be important: The essential role of the Limbic Hypothalmic Pituatary Adrenal Axis and neuroendocrine system in stress and physiological disregulation has been explored elsewhere in medical conditions complicated by anxiety [34-36] however, not within RP.

The cognitive-emotional perspective of RP is unchartered territory, despite the known reciprocal negative impact of stress and anxiety on the body and the role of anxiety/stress in RP. Studies report significant associations between anxiety and increases in both severity and pain in RP [37] and despite clear evidence for the effective treatment of anxiety and pain in other long-term conditions,[38-39] there are no recommended non-pharmacological interventions for RP [10, 40-41] and no known evidence to support efficacy of behavioural and lifestyle changes recommended by NICE.[10, 41] There has been no research in RP examining illness beliefs, psychological distress, knowledge deficits, [44] or other non-medical factors commonly associated with outcome. Related conditions such as Rheumatoid Arthritis have reported improved outcomes through illness belief targeted behaviour-change interventions [42] with emerging evidence for the efficacy of behavioural and lifestyle behaviour-change interventions in other health conditions [43] but not in RP, despite recommendations.[10] These factors could serve as a target for intervention in RP. The complex interplay between cognitive, social and behavioural factors that underpin a stress response warrant further investigation in RP.

The findings of this systematic review are limited to the inclusion of RCTs only. The application of these stringent criteria is likely to have produced fewer results than a broader inclusion of uncontrolled studies. However, RP clinical trials are particularly prone to placebo effects [14] and interpretation of open-label studies of RP is challenging. We do not believe that the inclusion of non-randomized studies would have reduced any uncertainty over efficacy and safety. We note also note the moderate agreement on risk of bias between raters (k=.59, 73% agreement). The lack of agreement centred on one specific paper [26] and poor agreement on the 'selective reporting' domain, which was adjudicated by a third author (CE). We suggest that the broad hetereogenity of the data and study design obscured reporting and in places, the assessment of reporting. Our recommendations for future trials should go some way to address this.

CONCLUSION

There is no evidence to support or refute claims for the efficacy and safety of behaviour-change interventions for the management of Raynaud's Phenomenon. Little work has focussed on behaviour-change in RP management in recent years despite the importance attached to self-management in clinical practice guidelines .[9, 10] There remains a strong case for developing and testing behavioural based interventions that focus the self-management of RP by addressing a) behavioural avoidance of environmental exposure to triggers of RP attacks, b) promoting a cognitive-emotional understanding of RP c) learning from the vast body of evidence underpinning behaviour-change in complex, poorly understood medical conditions that are amenable to intervention.

ETHICS AND DISSEMINATION

This systematic review did not require ethical approval because it summarises published studies with non-identifiable data. This systematic review complies with the 'Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines [45] and is reported according to the PRISMA statement (see supplementary materials).

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Contribution of authors

All authors, JD, JP and CE were involved in developing the focus of the systematic review, arriving at the final conception of the proposed systematic review through an iterative process. JD produced the first draft of the paper and supplementary information, coordinated and assimilated comments from JP and CE, approved the final version for publication and is the guarantor of the manuscript. JP also critically revised successive drafts of the manuscript, provided expert advice and intellectual input regarding the subject area (Raynaud's Phenomenon) and approved the final version for publication. CE critically revised successive drafts of the manuscript, provided expert advice on systematic review methodology and approved the final version for publication.

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Competing Interests

None to declare.

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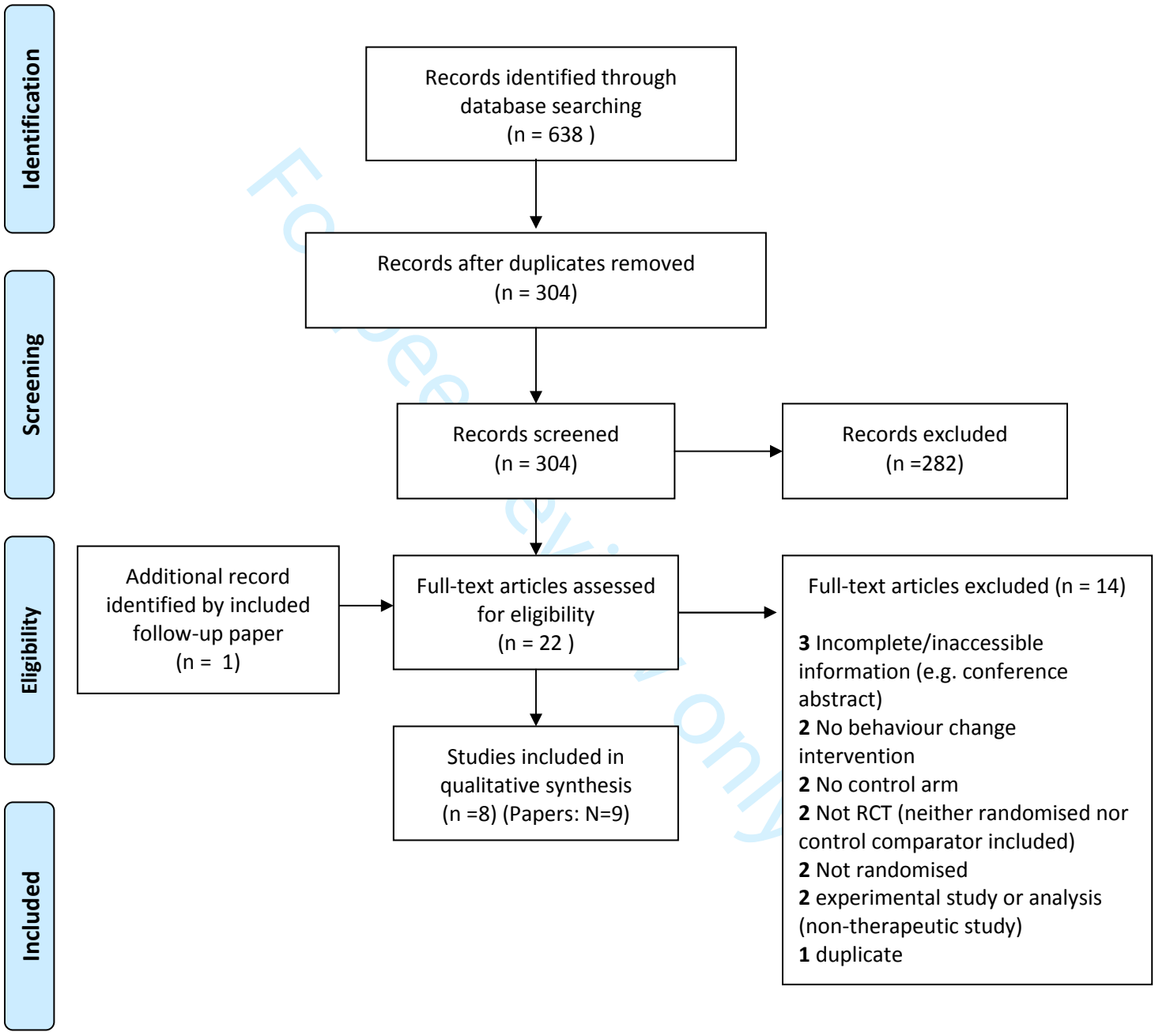
PRISMA Flow Diagram: Behaviour change interventions for the management of Raynaud's Phenomenon



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097