Supplementary Online Content

Jull A, Slark J, Parsons J. Prescribed exercise with compression vs compression alone in treating patients with venous leg ulcers: a systematic review and meta-analysis [published online October 3, 2018]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2018.3281

eAppendix. A protocol for a systematic review of exercise as adjuvant treatment for venous leg ulceration

This supplementary material has been provided by the authors to give readers additional information about their work.

Exercise4VLU: A protocol for a systematic review of exercise as adjuvant treatment for venous leg ulceration

PROSPERO Registration Number: 78265

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1.0 Background

1.1 Description of the condition

Venous leg ulceration (VLU) is the most severe presentation of chronic venous insufficiency. About 1% of the adult population will develop VLU during any one year,[1] and prevalence increases with age.[2] Projected increases in the very old suggest the incidence of VLU will increase.

VLU have significant personal impacts on sufferers. Increased pain, impaired sleep, and reduced mobility are all common,[3-7] while social activities are avoided in order to reduce the risk of injury to legs,[8] and work capacity is impaired.[9 10] Patients report is feelings of powerlessness, loss of control, and hopelessness.[3 7 10-12] Participants recruited into VLU trials report much reduced physical performance compared to population norms (submitted paper) for health-related quality of life at baseline.

1.2 Description of the intervention

Four small randomised controlled trials (median number of participants, 40) have reported on the effect exercise-based interventions, including progressive resistance exercise and walking.[13-15] These trials found no significant differences between the groups, but three of the trials found a direction of effect in favour of exercise. Despite the findings, evidence-based guidelines recommend the use of resistance exercise,[16 17] if only to improve calf-muscle pump function.[16].

1.3 Why it is important to do this review

A previous review only included English language studies from three databases to April 2014, included any type of quantitative study, did not the assess studies for risk of bias, and used a narrative approach to synthesizing study results. Furthermore, authors were not approached for information. Thus, recent evidence has not been included and the findings have not been summarised in a meta-analysis.

2.0 Objectives

To summarise the effectiveness of any exercise intervention on ulcer healing in patients VLU when used as an adjuvant to any form of compression in comparison to compression alone.

3.0 Search strategy

3.1 Electronic searches

A keyword search strategy with a subject librarian will be developed in Medline using synonyms for exercise. Variants of this strategy will be adapted to each of the following databases will be searched with a filter for randomised trials:

- Cochrane Controlled Trials Register (latest issue)
- Medline
- Embase
- PsycInfo
- CINAHL
- SCOPUS

No date or language restrictions will be applied. Complete citations (including abstracts) will be imported into an EndNote library for review. This review will be registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), the international prospective register of systematic reviews.

3.2 Other searches

The reference lists in the retrieved references will be reviewed for additional studies of interest.

4.0 Selection criteria

4.1 Types of studies

Only randomised controlled trials or trials described as randomised controlled trials will be included. Pseudo-randomised trials, meaning those that do not employ a truly random method of allocating participants (e.g. date of birth, date or week or month of entry into trial, hospital or patient number) will not be included. Cross-over trials will be excluded as they are not appropriate for evaluating this type of intervention.

4.2 Types of participants

People of any age with current VLU as diagnosed by the trial will be included. Trials that recruit participants other than those with VLU will only be included if they report outcomes separately for participants with VLU.

4.3 Types of intervention

Any exercise intervention designed to improve calf muscle function, ankle rotation, or general fitness, including, but not limited to, progressive resistance exercise, strength training, walking, or other exercise involving the lower legs. The intervention must be used in addition to any form of compression bandaging or hosiery, but does not need to be supervised, and the intervention can be conducted in any setting.

4.4 Types of outcome

The primary outcome measure will be a measure of VLU healing, including percentage of participants with completely healed VLU, time to complete healing, and change in ulcer area. Secondary outcomes will be reported only if a trial reports on a primary outcome measure as above. Secondary outcomes may include adverse events, adherence, pain, costs and quality of life.

5.0 Data collection and analysis

5.1 Selection of studies

Two authors will independently review the citations identified from the electronic and other searches. Titles and abstracts will be screened for congruence with inclusion criteria. Where uncertainty is present, the article will be obtained for further screening. At each step in the selection process, citations will be exported from the source library into a candidate library, a retrieved paper library and a final included study library.

5.2 Data extraction & management

We will develop and use a standardised extraction form to collect data from the included studies based on the tool available from the Cochrane Wounds Group (http://wounds.cochrane.org/resources-review-authors), adapted to incorporate necessary elements from the Template for Intervention Description and Replication (TIDieR). The data will be independently extracted by two reviewers and disagreements resolved by consensus. The data extraction form will include: Country of origin, publication type, care setting, study population, eligibility criteria, study design, trial registration number, unit of randomisation, type of exercise, co-interventions, primary and secondary outcomes, outcome data, overall sample size and methods used to estimate statistical power, duration of treatment period, duration of follow up, number of withdrawals (by group) and reason, and source of funding. We will extract all the necessary data from published reports and protocols, as well as trial registers. If further information is required, we will attempt to contact the original author by email for more information if necessary. Disagreement will be solved by discussion or consultation with a third party.

5.3 Assessment of risk of bias

Both review authors will independently assess the quality of included studies and risk of bias using the guidelines from the Cochrane Wounds Group (http://wounds.cochrane.org/resources-review-authors). The

criteria for assessment will include: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreements will be resolved by discussion, or consultation with a third author. Each criterion will be accessed as: low risk, high risk or unclear risk of bias (either lack of information or uncertainty over the potential for bias). We will present risk of bias using a summary table and by study.

5.4 Measures of treatment effect

Only studies providing similar analyses will be aggregated in meta-analyses; results will be subgrouped by type of exercise. Results were reported separately if studies are not able to be pooled.

5.5 Unit of analysis issues

Normally in individual participant randomisation, the unit of randomisation would be the child. If more than one child has been included in the analysis, the unit of randomisation would normally be the parent. If such approaches have not been adhered to, it will be noted in the description of the studies under randomisation.

5.5 Dealing with missing data

We will use the primary publication and any secondary publications to obtain missing information. We also use trials registers. If additional information cannot be obtained from these sources, we will attempt to obtain further information from the corresponding author. If the data are not available we will record that in the description of the included studies. If any assumptions are made about missing data, such as values imputed by carrying the last value forward, or carrying baseline value forward, or another means of imputation, these will be recorded and discussed.

5.6 Assessment of heterogeneity

Statistical heterogeneity will be assessed using Cochran's Q with the threshold for significant heterogeneity being set at 10% ($P<0.10$). The percentage of variation across the studies that is due to statistical heterogeneity rather than chance will be assessed using the I^2 statistic. The I2 will be interpreted in accord with the methods recommended by the Cochrane Collaboration:[18]

- 0-40% May not be important
- 30-60% May represent moderate heterogenereity
- 50-90% May represent substantial heteroegeneity
- 75-100% Considerable heterogeneity.

If considerable heterogeneity exists, relevant data will be described individually instead of being pooled. Otherwise, the outcomes will be combined in meta-analyses, and reported using either a fixed effects model or a random effects model depending on the degree of heterogeneity.

6.0 Data synthesis

The outcome measures from the included trials will be combined in a meta-analysis to provide a pooled effect estimate if there are sufficient trials. Data extraction will be conducted in Covidence systematic review software. A fixed effects model will not be used unless there are more than three studies in analysis with no or moderate heterogeneity. A random effects model will be used otherwise. Where meta-analysis is possible, the overall effect of the interventions will be summarised using relative risk.

6.1 Sensitivity analysis

The following sensitivity analyses may be performed:

- Excluding the studies at high risk of bias in the sensitivity analysis to access the impact of methodological quality of studies to the results.

7.0 Funding

No external funding will be sought to conduct this review.

8.0 Version control

29092017	Version 1
01022018	Version 2:

	• Removed calf muscle pump measures from secondary outcomes and changed to secondary collection from *will include* to *may include…* • Changed *The data will be extracted by the one reviewer and checked by a second reviewer* to *The data will be independently extracted by two reviewers and disagreements resolved by consensus.* • Changed *Data analysis will be conducted in Covidence systematic review software* to *Data extraction will be conducted in Covidence systematic review software*. • Added *Data analysis will be conducted in RevMan 5.3 software*. • Revised *Where meta-analysis is possible, the overall effect of the interventions will be summarised using relative risk* to *Where meta-analysis is possible, the overall effect of the interventions will be summarised using risk difference.*

9.0 Appendix 1: Search strategies by database

Medline Search strategy

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or (gravit* adj ulcer*) or crural ulcer* or ulcus cruris).tw.
3 or/1-2
4 randomized controlled trial.pt.
5 controlled clinical trial.pt.
6 randomi#ed.ab
7 placebo.ab.
8 clinical trials as topic.sh.
9 randomly.ab.
10 trial.ti.
11 or/4-10
12 exp animals/ not humans.sh.
13 11 not 12
14 3 and 13
15 exp Exercise/
16 exp Exercise Therapy/
17 Physical exertion/
18 exp Sports/
19 exp Exercise movement techniques/
20 exp Locomotion/
21 exp Leisure Activities/
22 Fitness Centers/
23 exp Walking/
24 (Physical adj3 (exertion or endurance or therap* or conditioning or activit* or fitness)).ti,ab,kf
25 (Fitness adj3 (intervention* or protocol* or program* or therap* or activit* or regim* or centre* or center*)).ti,ab,kf
26 Exercis*.ti,ab,kf
27 Activit*.ti,ab,kf
28 (Walk* or run* or treadmill or aerobic or swim* or danc*).ti,ab.kf
29 Kinesiotherap*.ti,ab,kf
30 (endurance or aerobic or cardio) adj3 (fitness or train* or intervention* or protoco* or program* or therap* or activit* or regim*).ti,ab,kf
31 (progres* or resis*) adj (exerc* or train* or regim* or protoco* or intervention* or program* or therap* or activit*).ti,ab,kf
32 or/15-31
33 14 and 32

EMBASE Search Strategy (pre-1980 and post 1980)

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or (gravit* adj ulcer*) or crural ulcer* or ulcus cruris).tw.
3 or/1-2
4 Randomized Controlled Trial/
5 exp Controlled Clinical Trial/
6 randomi#ed.ab
7 placebo.ab
8 exp "Clinical Trial (topic)"/
9 randomly.ab
10 trial.ti
11 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp animal/ not human/
13 11 not 12
14 3 and 13
15 exp Exercise/
16 exp Kinesiotherapy/
17 exp Sport/
18 exp Leisure
19 exp Health Center/
20 exp Walking/
21 (physical adj3 (exertion or endurance or therap* or conditioning or activit* or fitness).ti,ab,kw
22 (fitness adj3 (intervention or protocol* or program* or therap* or activit* or regim* or centre* or center*).ti,ab,kw
23 exercis*.t,ab,kw
24 activit*.ti,ab,kw
25 (walk* or run* or treadmill or aerobic or swim* or danc*).ti,ab,kw
26 kinesiotherap*.ti,ab,kw
27 ((endurance or aerobic or cardio) adj3 (fitness or train* or intervention* or protocol* or program* or therap* or activit* or regim* or exertion)).ti,ab,tw
28 (progres* or resis*) adj (exercise* or train* or protocol* or intervention* or program* or therap* or activit*).ti,ab,kw
29 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 14 and 29

PsycINFO Search Strategy

1 Leg Ulcer.mh
2 (varicose ulcer* or (venous adj3 ulcer*) or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or (gravit* adj ulcer*) or crural ulcer* or ulcus cruris).mp
3 (foot adj3 ulcer).mp
4 1 or 2 or 3
5 exp Clinical Trials/
6 randomly.ab
7 randomi#ed.ab
8 placebo.ab
9 trial.ti
10 5 or 6 or 7 or 8 or 9
11 4 and 10
12 exp Animals/
13 11 not 12

CINAHL (EBSCO) Search Strategy

1 (MH "Leg Ulcer+")
2 TX(varicose ulcer* or (venous adj3 ulcer*) or leg ulcer* or foot ulcer* or (feet N2 ulcer*) or stasis ulcer* or (lower extremit* N2 ulcer*) or (gravit* N2 ulcer*) or crural ulcer* or ulcus cruris)

3 1 or 2
4 (MH “Clinical Trials+”)
5 PT randomized controlled trial
6 PT clinical trial
7 AB randomi?ed
8 AB placebo
9 AB randomly
10 TI Trial
11 4 or 5 or 6 or 7 or 8 or 9 or 10
12 3 and 11
13 (MH Exercise+”)
14 MH “Therapeutic Exercise+”)
15 (MH Exertion+”)
16 (MM “Physical Activity”)
17 (MH “Sports+”)
18 (MH “Leisure Activities+”)
19 (MH “Locomotion+”)
20 (MH “Fitness Centers”)
21 (TX (Physical N3 (exertion or endurance or therap* or conditioning or activit* or fitness))
22 (TX (Fitness N3 (intervention* or protocol* or program* or therap* or activit* or regim* or centre* or center*))
23 TI exercis* or AB exercis*
24 TI activit* or AB activit*
25 TI kinesiotherapy* or AB kinesiotherapy*
26 TI (walk* or run* or treadmill or aerobic* or swim* or danc*) or AB (walk* or run* or treadmill or aerobic* or swim* or danc*)
27 TI (endurance or aerobic or cardio) N3 (fitness or train* or intervention* or protoc* or program* or tehrap* or activit* or regim*) or AB (endurance or aerobic or cardio) N3 (fitness or train* or intervention* or protoc* or program* or tehrap* or activit* or regim*)
28 TI (progress* or resis*) N2 (Exercis* or train* or regim* or protocol* or intervention* or program* or tehrap* or activit*) or AB (progress* or resis*) N2 (Exercis* or train* or regim* or protocol* or intervention* or program* or tehrap* or activit*)
29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 12 and 29

SCOPUS Search Strategy

("leg ulcer*" OR "varicose ulcer*" OR "venous ulcer*" OR "foot ulcer*" OR (feet W/2 ulcer*) OR "stasis ulcer*" OR ("lower extremit*" W/2 ulcer*) OR (gravit* W/2 ulcer*) OR "crural ulcer*" OR "ulcus cruris") AND ("randomi?ed controlled trial*" OR "clinical trial*" OR placebo OR ABS(randomly) OR TITLE(trial*)) AND (exercis* OR kinesiotherap* OR physical W/3 (exertion OR endurance OR therap* OR conditioning OR activit* OR fitness)) OR fitness W/3 (intervention OR protocol* OR program* OR therap* OR activit* OR regim* OR centre* OR center*) OR (walk* OR run* OR treadmill* OR aerobic OR swim* OR danc*) OR ((endurance OR aerobic OR cardio) W/3 (fitness OR train* OR intervention* OR protocol* OR program* OR therap* OR activit* OR regim* OR exertion)) OR ((progress* OR resis*) W/1 (exercis* OR train* OR protocol* OR intervention* OR program* OR therap* OR activit*)) OR (exercis* OR kinesiotherap* OR physical W/3 (exertion OR endurance OR therap* OR conditioning OR activit* OR fitness))

CCTR Search Strategy

1 MeSH descriptor: [Leg Ulcer] explode all trees
2 (“Varicose ulcer*” or “venous ulcer*” or “leg ulcer*” or “foot ulcer*” or (feet next ulcer) or “statis ulcer*” or (“lower extremit*” next ulcer*) or (gravit* next ulcer*) or “crural ulcer” or “Ulcus Cruris”):ti,ab,kw
3 #1 or #2
4 Randomized controlled trial:pt
5 controlled clinical trial:pt
6 radomi?ed:ab
7 placebo:ab

8 MeSH descriptor: [Clinical trials as topic] explode all trees
9 randomly:ab
10 trial:ti
11 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
12 #3 and #11
13 MeSH descriptor [Animals] explode all trees
14 MeSH descriptor [Humans] explode all trees
15 #13 not #14
16 #12 not #15
17 MeSH descriptor [Exercise] explode all trees
18 MeSH descriptor [Exercise Therapy] explode all trees
19 MeSH descriptor [Physical Exertion] explode all trees
20 MeSH descriptor [Sports] explode all trees
21 MeSH descriptor [Exercise movement techniques]
22 MeSH descriptor [Locomotion] explode all trees
23 MeSH descriptor [Leisure activities] explode all trees
24 MeSH descriptor [Fitness Centers] explode all trees
25 MeSH descriptor [Walking] explode all trees
26 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
27 (physical near3 (exertion or endurance or therap* or conditioning or activit* or fitness):ti,ab,kw
28 (fitness near3 (intervention* or protocol* or program* or therap* or activit* or regim* or center* or centre*)):ti,ab,kw
29 exercis*:ti,ab,kw
30 activit*:ti,ab,kw
31 (walk* or run* or treadmill or aerobic or swim* or danc*):ti,ab,kw
334 32 Kinesiotherap*:ti,ab,kw
33 (endurance or aerobic or cardio) near3 (fitness or train* or intervention* or protoc* or program* or therap* or activit* or regim*):ti,ab,kw
34 (progress* or resis*) next (exercis* or train* or regim* or protocol* or intervention* or program* or therap* or activit*):ti,ab,kw
35 #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
36 #16 and #35

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