STUDY PROTOCOL

Systematic review of topical interventions for the management of odour in patients with chronic wounds or malignant fungating wounds: a study protocol [version 1; peer review: awaiting peer review]

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Abstract

Background: Chronic wounds including venous, arterial, diabetic and pressure ulcers affect up to 2.21 per 1000 population. Malignant fungating wounds affect up to 6.6% of oncology patients. These wounds impact patients and health care systems significantly. Microbes colonising chronic wounds can produce volatile molecules with unpleasant odours. Wound odour adversely affects quality of life, yet management strategies are inconsistent. Clinicians express uncertainty regarding the current range of odour management agents, which therefore requires evaluation for effectiveness.

Objective: To determine the effects of topical agents in the management of odour in patients with chronic and malignant fungating wounds.

Methods: Searches of Embase, Medline, CINAHL, Cochrane CENTRAL, PubMed, Web of Science, Scopus, and the clinicaltrials.gov and WudracT trial registries from inception to present will be conducted without language limits. Randomised controlled trials including adults with venous, arterial, mixed arterio-venous, diabetic, decubitus or malignant

Open Peer Review

Reviewer Status  AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.
fungating wounds, investigating topical agents to manage odour are eligible. Reference lists of included studies and identified systematic reviews will be scanned, and unpublished studies will be sought in the BASE database, in conference proceedings and through contacting authors. Two reviewers will independently scan titles/abstracts and full text articles against predetermined eligibility criteria, with discrepancies resolved by discussion between reviewers or through third-party intervention. Two reviewers will independently extract data from included studies. Disagreements will be resolved by discussion between reviewers or through third-party intervention. Bias risk and evidence quality will be assessed with the Cochrane Risk of Bias Tool 2 and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. Meta-analysis will be applied where appropriate. Otherwise, data will be synthesised narratively.

**Discussion:** Wound odour management typically takes a trial-and-error approach. Clinicians are critical of odour management agent effectiveness. This review will evaluate the range of available agents to inform practice and research.

**PROSPERO registration:** CRD42021267668 (14/08/2021)

**Keywords**

Systematic Review, meta-analysis, odour, chronic wound; venous leg ulcer; diabetic foot ulcer; pressure ulcer; mixed aetiology ulcer; malignant fungating wound.
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**Introduction**

Chronic wounds including venous, arterial, diabetic and pressure ulcers affect up to 2.21 per 1000 population and have a significant impact on morbidity.\(^{12}\) Prevalence of malignant fungating wounds (MFWs) is harder to quantify and variations in results are reflected in divergent settings and methods of reporting. However, such wounds account for up to 6.6% of patients in oncology settings\(^3\) with the breast being the most commonly reported site\(^5,8\). Management of chronic wounds can account for up to 4% of total public health care expenditure and the cost is increasing at an approximate rate of 8% -9% per annum in the United Kingdom, accounting for an estimated £8.3 billion (pound sterling) annually\(^6,7\). The impact on the individual can be significant, affecting all areas of their lives\(^8\) including work, socialisation, relationships and contribution to society. Individuals have to cope with protracted healing times, repeated and sometimes daily dressing changes and associated clinical appointments, leakage of exudate, odour, infections and pain.

Odour is now well-recognised as a factor associated with chronic wounds\(^8-10\), although the type, nature, frequency and impact can vary according to wound aetiology, condition of the wound and multiple patient factors. Odour can affect sleep, mood, quality of life and, through its impact on the individual, wound healing\(^14,80,11\). Chronic wounds are colonised by multiple microbial species, some of which are capable of producing volatile molecules with pungent odours\(^12\). Many of the common aerobic bacteria isolated from chronic wounds are members of the family Enterobacteriaceae (Gram negative aerobic bacilli) which are commonly found in human faeces\(^13\). Known volatile agents include n-butryic acid, n-valeric acid, n-caproic acid, n-propanoic acid, cadaverine and putrescine. The latter two are foul-smelling organic compounds produced by the breakdown of amino acids in dead tissue\(^15\).

Malignant fungating wounds are particularly distressing\(^11\). They may be outward or inward growing, and in many cases, depending on the precise aetiology, can grow rapidly and become extensive in size. Life expectancy for those with malignant fungating wounds is approximately six months and so the distress of having a life limiting condition with associated odour and exudate is a significant burden for the individual and indeed for their families to bear\(^13,14\). The most common site of MFW is the breast and therefore by association these wounds affect women, usually over the age of 65 years\(^8-9\).

Heretofore, management of wound odour has been a trial-and-error approach. An international survey among 1,444 clinicians identified a lack of confidence in the effectiveness of current topical agents to manage wound odour and a strong desire to develop interventions to manage this problem\(^10\). In order to develop interventions to manage wound odour, there is a need to evaluate the range of topical agents that are currently available and their level of effectiveness in managing odour in chronic and malignant wounds.

The objective of this review is to answer the question: What are the effects of topical agents in the management of odour in patients with chronic and malignant fungating wounds?

**Methods**

This protocol has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines\(^13,16\). The protocol was registered on PROSPERO on 14th August 2021 (CRD42021267668).

**Eligibility criteria**

**Participants/population.** Our review is limited to adults (18 years and over) with chronic wounds including venous, arterial, mixed arterial-venous, diabetic or pressure ulcers, or those with malignant fungating wounds. The diagnosis of such wounds will be as reported by article authors. We will not place any restrictions on sex, race or ethnicity of participants.

We will exclude those studies whose population includes people with burns, acute wounds, surgical wounds or atypical wounds.

Where a study sample includes more than one wound aetiology, we will include the study if subgroups of the sample meet our inclusion criteria and results are clearly presented by aetiology.

**Intervention(s), exposure(s).** We will include studies where the type or schedule of topical agents to manage odour is the only systematic difference between study arm regimes. Topical agents to manage wound odour include those applied directly to the wound bed or held within or applied to a wound dressing and may fall into the following groups:

- Pharmacological agents: e.g. topical antibiotics
- Non-pharmacological agents: e.g. wound dressings, alternative or complementary therapies

We will exclude aerosol agents or any agent applied into the patients’ environment e.g. burning candles, deodoriser sprays. We will also exclude systemic agents e.g. oral or intravenous antibiotic therapies.

As part of the intervention description, we will provide an overview of the methods and scales used to assess odour throughout the studies.

**Comparator(s)/control.** We will include studies that compare any eligible intervention to any other eligible intervention or to placebo.

**Study design.** We will include randomised controlled trials (RCTs) with any kind of random allocation method, e.g. cluster, individual, stepped-wedge. We will exclude quasi-randomised studies (i.e. where allocation was based on a non-random method such as alternation).
**Context.** Patients with wounds can be treated in any care setting including hospitals, residential care facilities, outpatient departments, general practitioner offices or patient’s own home.

**Outcome(s).**

**Public patient involvement**

This review has been discussed with members of our patient panel from the Alliance for Research and Innovation in Wounds (ARIW). The outcome measures selected for this review reflect both those which are important to our patient panel, and those identified within the literature as being meaningful in determining the benefits or harms of the use of topical agents.

**Primary outcome**

- The proportion of people with any odour intensity reduction/improvement.

**Secondary outcomes**

- Duration of odour reducing effects.
- Change in quality of life, measured using a standardised generic questionnaire (e.g. EuroQol five dimensions questionnaire (EQ-5D), Short Form 36-item (SF-36), Short Form 12-item (SF-12) or Short Form 6-item (SF-6), or wound-specific questionnaires such as the Cardiff Wound Impact Schedule. We will not include ad hoc measures of quality of life that are unlikely to be validated and not common to multiple trials.
- In addition to quality of life assessment using standardised generic questionnaires, we will include other factors of relevance to patients such as:
  - Change in disability or physical functioning as reported by the authors.
  - Change in emotional functioning/mental health impact (including, but not limited to, anxiety, depression, mood, etc) as reported by the authors.
  - Change in sleep duration and quality, as reported by patients.

Adverse events data captured via clear processes will be extracted for this review. Adverse events will include measures of harm, including withdrawal due to serious adverse events or withdrawal because of adverse events. Following the PRISMA Harms Checklist, we will describe how adverse events were addressed, how they were reported, and over what time period the harm was experienced.

If multiple outcomes are reported in a given outcome category, we will collect information on all relevant outcomes. If the same outcome is assessed by two or more outcome measures in the same trial, two review authors will:

- select the primary outcome measure that has been identified by the publication’s authors
- select the measure specified in the sample size calculation when no primary outcome measure has been identified

When an even number of outcome measures is reported, the measure whose effect estimate is ranked n/2, where n is the number of outcome measures, will be selected.

**Searches**

The literature will be searched using a staged approach. We will search Ovid EMBASE, Ovid MEDLINE, EBSCOhost CINAHL, The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Web of Science and Scopus from inception to present with no limits on language. We will search online trial registry databases including clinicaltrials.gov and EudraCT. We will conduct reference and citation searches of included articles to search for further trials and if we identify systematic reviews in the field, we will search their reference lists. The Bielefeld Academic Search Engine (BASE) will be searched for grey literature. Unpublished studies will be sought through conference proceedings, clinical trial registries and author contact where necessary.

Development of the search strategy was an iterative process based on examination of previous literature and a series of sample searches across all chosen databases. Strategies were developed with the PRESS Guideline Evidence-Based Checklist in mind. This was a stepped process, with terms developed to capture three distinct concepts: different types of chronic wound, odour experienced as a result of chronic wounds and treatments used to minimise or eliminate this odour. Terms relating to each of these three constructs were then combined to produce the final strategy, with filters added to limit the search to randomised controlled trials conducted with human populations. The search strategy can be found as extended data.

**Data extraction (selection and coding)**

Following a pilot exercise, two reviewers will independently screen titles and abstracts (randomly allocated). Studies will be reviewed against clearly identified and pre-tested inclusion and exclusion criteria using an online systematic review software package (Rayyan). Discrepancies will be resolved by discussion between reviewers with intervention from a third party to reach consensus if necessary.

We will retrieve the full text of any papers or reports identified as potentially relevant.

Following a pilot exercise, two reviewers will independently screen full-text studies for inclusion against review eligibility criteria. Discrepancies will be resolved by discussion between reviewers with intervention from a third party to reach consensus if necessary.

The screening and selection process will be documented in sufficient detail to complete a PRISMA flow chart and ‘Characteristics of excluded studies’ table. We will also provide citation details and any available information about ongoing studies, and collate and report details of multiple publications.
reporting on one study so that each study (rather than each report) is the unit of interest in the review.

Following a pilot exercise, two review authors will independently extract data from included studies. Discrepancies will be resolved by discussion until consensus is reached or through consultation with a third review author when necessary. Review authors will not extract data from their own studies.

We will develop a data extraction tool \textit{a priori}. Extracted data will include criteria such as mode of delivery, dose, frequency of application, alongside the following items:

- General study information (journal, study contacts, year, country where the study was conducted)
- Methods of the study (aim of study, design, involvement of others including funders, ethical approval)
- Characteristics of participants (gender, age, co-morbidities, current medications, co-morbidities)
- Characteristics of wounds (etiologic, condition of wound bed, size, location, depth, duration)
- Primary and secondary outcomes as stated in outcome measures including methods of assessment, duration of intervention, dosage, frequency of application.

All extracted data will be entered into \textit{Review Manager 2020} (RevMan), version 5.4.1 by one author and will be independently checked for accuracy against the data extraction sheets by a second review author. Where disagreements arise, these will be resolved between the authors with referral to a third if necessary.

\textbf{Risk of bias (quality) assessment}

We will assess methodological risk of bias of included studies with the \textit{Cochrane Risk of Bias Tool 2}\textsuperscript{20} and report on the following elements: random sequence generation; allocation concealment; blinding of participants and personnel and blinding of outcome assessment; completeness of outcome data, selective outcome reporting, study size and other sources of bias. We will consider blinding separately for different outcomes where appropriate. Completeness of outcome data will be considered separately for different lengths of follow-up.

We will consider the outcomes in terms of timing of assessment. We will judge each item as being at high, low or some concerns for risk of bias, as set out in the criteria provided in the Cochrane handbook for Systematic Reviews of Interventions. We will provide a quote from the study report and a justification for our judgement for each item in the risk of bias table.

For cluster RCTs we will also assess and report the risk of bias associated with an additional domain: selective recruitment of cluster participants. In all cases, two review authors will independently assess the risk of bias of included studies. Disagreements will be resolved by discussion between those review authors with intervention of a third party to reach consensus if necessary. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required.

Quality of the evidence will be assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE)\textsuperscript{31}. The GRADE system assesses quality on 4 levels: high, moderate, low and very low, based on factors such as study limitations, unexplained heterogeneity or inconsistency, imprecision, indirectness and publication bias, in order to assess the quality of evidence presented for each outcome.

\textbf{Strategy for data synthesis}

The primary analysis will be per randomised individual and all studies will be assessed to ensure that the unit of randomisation equates to the unit of analysis. For cluster randomised trials, an interclass correlation coefficient will be extracted to adjust for clustering of individuals\textsuperscript{15}.

Descriptive summaries of the extracted data will be tabulated to assist in synthesising commonalities and differences between included studies. Scores, frequency, duration and descriptive details of the topical interventions together with any wound information will be provided as an overview. Description of and frequency of adverse events will be presented in tabular form.

Odour score as the main outcome measure, reported as before/after change or score according to treatment group(s) will be evaluated. Odour score change intervals may be of different length and overviews to identify similar intervals will provide more detailed analyses. The lack of consensus on methods to assess wound odour is well recognised within the literature\textsuperscript{9}. However, numerical scales are the most frequent with the length of the scale varying. Quality of life, other functional, cognitive and sleep outcomes as well as adverse events will be recorded according to time intervals which are expected to be short (maximum one week).

Study authors will be contacted to obtain relevant missing data. Sensitivity analysis will assess the impact on the primary outcome of inclusion of studies with missing data, high attrition, or missing/not reported intention to treat analysis\textsuperscript{15}.

If there are sufficient homogenous studies reporting on each particular treatment (group) with similar outcomes (odour scores), meta-analysis using Revman 5.4.1 will be undertaken and more detailed meta-analyses may be possible. Pooled percentages (proportion of people with any odour intensity reduction/improvement) according to topical treatment category will be calculated and a Bayesian random-effects meta-analysis will be performed when a sufficient number of studies can be included. In case of sufficient studies, pooled median differences (MD) with 95% confidence interval (CI) will be calculated for scale outcomes, relative risk (RR) with 95% CI for dichotomous data will be calculated. Adverse events (total and occurrence) will be calculated according to topical treatment category and pooled mean differences (95% CI) will be calculated. Statistical heterogeneity will be assessed.
using the $I^2$ statistic (0%–40% = might not be important; 40%–60% = moderate heterogeneity; 60%–90% = substantial heterogeneity; 75%–100% considerable heterogeneity). In the event that $I^2 \geq 50$% or $p < 0.1$, study design and characteristics of included studies will be assessed and an attempt will be made to locate the source of heterogeneity through sensitivity analysis or sub-group analysis. If heterogeneity is substantial and does not merit a meta-analysis, a narrative synthesis will describe relationships between findings of included studies.

Analysis of subgroups or subsets
Depending on the quality of the studies included and similarity in outcomes (odour scores) reported, subgroup analysis may be possible to compare different wound aetiologies, treatment groups or time intervals.

Ethics and dissemination
Ethical approval is not required for this review as no experimental or observational research will be carried out, and no identifying personal information will be collected.

The final review will be published in an academic journal and made available through university repositories such as NUI Galway’s ARAN. An abstract will be submitted to a European Wound Management Association (EWMA) international conference and a summary report prepared for the Journal of EWMA. We will report back to our patient panel on the outcomes of the review and make a summary video of the results for publication on the website of our research group: [www.nuigalway.ie/ariw](http://www.nuigalway.ie/ariw). We will also use social media including Twitter and LinkedIn to disseminate the findings.

**Study status**
Not yet initiated.

**Data availability**
Underlying data
No data are associated with this article.

**Extended data**
Open Science Framework: Systematic review of topical interventions for the management of odour in patients with chronic wounds or malignant fungating wounds. [https://doi.org/10.17605/OSF.IO/7YKAH](https://doi.org/10.17605/OSF.IO/7YKAH).

This project contains the following extended data:
- Wound Odour SR_Embase search_26 Apr 21.docx (search strategy for Embase)

**Reporting guidelines**
Open Science Framework: PRISMA-P checklist for ‘Systematic review of topical interventions for the management of odour in patients with chronic wounds or malignant fungating wounds: a study protocol.’ [https://doi.org/10.17605/OSF.IO/7YKAH](https://doi.org/10.17605/OSF.IO/7YKAH).

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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