



## Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

<b>Topic exploration report number:</b>	TER320
<b>Topic:</b>	Topical oxygen therapy for the treatment of non-healing wounds
<b>Summary of findings:</b>	<p>Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of topical oxygen wound therapy in comparison to standard care. This Topic Exploration Report updates an earlier version published in January 2020.</p> <p>We identified a technology assessment, four systematic reviews and two primary studies on the effectiveness of topical oxygen therapy (TOT) as a treatment for diabetic foot ulcers or other chronic non-healing wounds (such as ulcers, granulation tissue, pressure wounds). The evidence suggests that TOT can have positive effects on wound healing and wound closure. Fuller assessment would be needed to establish the cost effectiveness of TOT, the types of wounds where it is most likely to offer benefit, and the its place in the care pathway relative to other types of wound care.</p>

## Introduction and aims

Delivery of oxygen may promote healing in certain types of wounds. NATROX Oxygen Wound Therapy is a type of topical oxygen therapy (TOT); it is a CE-marked class IIb medical device that delivers a continuous topical flow of pure, humidified oxygen (98%) over wound tissue. The device claims to promote healing of chronic wounds by reversing the hypoxic surroundings of the wound tissue.

Health Technology Wales researchers searched for evidence on continuous topical oxygen therapy for the treatment of chronic, non-healing wounds. This Topic Exploration Report is an update: our original report covered evidence up to October 2019. Here, we summarise evidence published from October 2019 to date in addition to previously identified studies that are still considered relevant.

## Evidence overview

### Technology Assessment/Guidance

The National Institute for Health and Care Excellence (NICE) Medtech Innovation Briefing (MIB208) on “NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds” summarised evidence from three studies: one randomised controlled trial (RCT) and two observational studies. The three studies included a total of 172 adults: 20 patients were included in the RCT and the remainder in the observational studies. The latter studies did not include a control group. The evidence suggests that NATROX can effectively treat a range of chronic wounds and may be more effective than standard care in people with grade 2 or 3 diabetic foot ulcers (DFU). However, NICE concluded that there were key uncertainties around the evidence and the technology due to the small sample size of the RCT and the heterogeneity of the population in the other two studies (NICE 2020).

### Evidence reviews

Multiple systematic reviews evaluating TOT have been identified. The following list includes the most recent and relevant published reviews :

- Connaghan et al. (2021) aimed to determine the impact of topical oxygen therapy (TOT) on DFU healing rates. The authors reported eight studies undertaken in different settings and a meta-analysis of four studies. The overall findings suggested that TOT enhances the likelihood of wound healing for patients with hard-to-heal DFUs when used in addition to standard care.
- Thanigaimani et al. (2021) summarised evidence on the effect of TOT on wound healing in participants with DFU. Findings from six eligible RCTs were reported and the meta-analysis suggested that TOT significantly increased the likelihood of ulcer healing compared to the controls (either standard care or sham treatment).
- Nataraj et al. (2019) reported five studies which used different modes of topical oxygen administration to investigate the healing dynamics of diabetic foot ulcer. The authors concluded that TOT facilitates wound healing dynamics among individuals with chronic DFUs, with higher rate of complete wound healing in low-grade ulcers than in high grade ulcers.
- de Smet et al. (2017) summarises studies conducted on various types of oxygen therapies on wound healing. Within this review, seven studies tested the use of TOT on chronic wounds, two studies on acute wounds and one study tested the technology on both acute and chronic wounds. Seven studies reported at least one or more significant positive outcome. However, this review had a broad scope and included both animal-based and human research. Only six

studies included in the review were conducted on humans and only one employed the use of continuous TOT. This study reported that out of the six wounds investigated in patients with diabetes, that were previously non-responsive to treatments, five wounds completely healed within 20 weeks after continuous TOT.

### Primary studies

The two clinical trials previously reported as ongoing research in an earlier version of this report have now been completed and the results made available. These are a multicentre RCT by Serena et al. (2021) and an observational study Tang et al. (2021); however, for the purpose of this TER, only RCTs will be discussed in detail here.

Serena et al. (2021) compared continuous TOT in addition to standard of care (SOC) to SOC alone for a period of 12 weeks in patients with DFUs or minor amputation wounds. In the intention-to-treat analysis, a significantly greater proportion of patients treated with SOC plus TOT healed compared to those treated with SOC alone: 18/64 (28.1%) patients healed in the SOC group compared with 36/81 (44.4%) in the SOC plus TOT group. The authors also reported a statistically significant reduction in wound area between the groups (40% in the SOC group compared to 70% in the SOC plus TOT) but this did not reach statistical significance in the intent-to-treat analysis.

Additionally, through the searches conducted, another primary study conducted by Song et al. (2021) has been identified and it evaluated the effects of TOT on granulation tissue in patients with chronic traumatic wounds. The authors conclude that TOT used in combination with negative pressure wound therapy is more effective in treating patients with chronic traumatic wounds than negative pressure wound therapy alone.

### Areas of uncertainty

The evidence identified studies the use of TOT for a range of different wound types, predominantly DFUs or other types of chronic, non-healing wounds. Further assessment would be needed to establish whether there are specific wound types in which this technology is most likely to be beneficial. The evidence also varied in terms of the device used to deliver TOT, its application method, duration of treatment, and whether it was used in addition to or as a replacement for other types of wound care. We also did not identify any assessments of the cost-effectiveness of TOT.

## Literature search results

### Health technology assessments and guidance

NICE. (2020). NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds [MIB208]. National Institute for Health and Care Excellence. Available at: <https://www.nice.org.uk/advice/mib208> [Accessed 04.11.2021].

### Evidence reviews

Connaghan F, Avsar P, Patton D, et al. (2021). Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review. *Journal of wound care*. 30(10): 823-9. <https://doi.org/10.12968/jowc.2021.30.10.823>

de Smet GH, Kroese LF, Menon AG, et al. (2017). Oxygen therapies and their effects on wound healing. *Wound Repair and Regeneration*. 25(4): 591-608. <https://doi.org/10.1111/wrr.12561>

Nataraj M, Maiya AG, Karkada G, et al. (2019). Application of Topical Oxygen Therapy in Healing Dynamics of Diabetic Foot Ulcers - A Systematic Review. *The review of diabetic studies : RDS*. 15: 74-82. <https://doi.org/10.1900/RDS.2019.15.74>

Thanigaimani S, Singh T, Golledge J. (2021). Topical oxygen therapy for diabetes-related foot ulcers: A systematic review and meta-analysis. *Diabetic medicine : a journal of the British Diabetic Association*. e14585. <https://doi.org/10.1111/dme.14585>

### Individual studies

Serena TE, Bullock NM, Cole W, et al. (2021). Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *Journal of wound care*. 30(Sup5): S7-S14. <https://doi.org/10.12968/jowc.2021.30.Sup5.S7>

Song Z, Guo X, Zhang X. (2021). Effects of topical oxygen therapy on chronic traumatic wounds and its impact on granulation tissue. *American journal of translational research*. 13(6): 7294-9. <https://www.ncbi.nlm.nih.gov/pubmed/34306496>

Tang TY, Mak MY, Yap C, et al. (2021). An Observational Clinical Trial Examining the Effect of Topical Oxygen Therapy (Natrox™) on the Rates of Healing of Chronic Diabetic Foot Ulcers (OTONAL Trial). *The International Journal of Lower Extremity Wounds*. 15347346211053694. <https://doi.org/10.1177/15347346211053694>

**Date of search:**

December 2021

**Concepts used:**

NATROX, (topical oxygen therapy) AND (wound OR leg ulcer OR diabetic foot ulcer)