



## 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:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	NATROX Oxygen Wound Therapy
Topic exploration report number:	TER122

### Introduction and aims

NATROX Oxygen Wound Therapy is a CE-marked medical device that delivers topically a continuous flow of pure, humidified oxygen (98%) over wound tissue. The device claims to promote healing of chronic wounds and Diabetic Foot Ulcers (DFU) by reversing the hypoxic environment surrounding the wound tissue. Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of continuous topical oxygen therapy (TOT) in comparison to standard care.

### Summary of findings

Evidence on the effectiveness of TOT to treat chronic non-healing wounds and diabetic foot ulcers is available from a small number of randomised trials. Some, but not all, trials suggest that continuous topical oxygen therapy might add benefit for the treatment of chronic wounds. A further two randomised trials are in progress. We did not identify any evidence regarding the cost-effectiveness of TOT, or any previous technology assessments studying this intervention.

### Evidence

#### *Secondary literature:*

In 2019, ECRI published a Hotline Response titled "Topical Oxygen Therapy for Diabetic Foot Ulcers." The document stated that there was inconclusive evidence on the use of the technology since data from 2 RCTs generated conflicting results, with one trial reporting that continuous TOT had a significant effect on DFU wounds healing when compared to sham, while the second trial suggested that no differences were observed between the TOT-treated group versus the sham device. Both studies treated patients for a period of 12 weeks.

A systematic review by de Smet *et al.* (2017) titled “Oxygen therapies and their effects on wound healing” summarizes clinical and experimental 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.

A second systematic review by Sayadi *et al.* 2018 titled “Topical oxygen therapy & micro/nanobubbles: a new modality for tissue oxygen delivery” examines the use of TOT for wound healing. Three clinical studies on continuous TOT were identified in the context of this review. All of the studies reported positive outcomes including improvement in wound healing in patients with stage IV pressure ulcers based on wound dimensions and volume (Banks *et al.* 2008), significant decrease in the mean wound surface area and wound infection checklist score after 4 weeks (Woo *et al.* 2012), and significantly decreased DFU wound size when compared to baseline measurements. 90% of ulcers receiving continuous TOT healed at 8 weeks compared to 30% of ulcers receiving standard care. Although the range of interventions covered in this review expand beyond the scope of this appraisal, some of the findings could be valuable for evaluating the technology in question.

#### *Primary Studies:*

“Topical oxygen therapy results in complete wound healing in diabetic foot ulcers” (Yu *et al.* 2016) is an interventional, parallel RCT (Clinical Trial number NCT02599805) conducted on 20 subjects that evaluated TOT as an adjuvant therapy in addition to standard care for chronic wounds including DFU. The use of TOT as an adjuvant therapy was found to have a significant effect on wound healing rate at 8 weeks for grade II and III ulcers. Furthermore, there was a significant decrease in the mean wound area size from baseline values in the TOT group at week 2, 3, 4, 5, 6, 7 and 8.

A study by Driver *et al.* 2017 titled “A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers” is an interventional, parallel, blinded, multicentre RCT (Clinical Trial number NCT0129160) conducted on 122 participants evaluating the use of continuous TOT as an adjuvant therapy in addition to moist wound therapy. Continuous TOT did not appear to offer any added benefit over moist wound therapy; although patients aged 65 years and over may benefit from adjuvant treatment with continuous TOT for wound healing.

“A prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to sham therapy in the treatment of diabetic foot ulcers” (Niederauer *et al.* 2017) is an interventional, double-blinded, multicentre RCT (Clinical Trial number NCT01645891) conducted on 100 subjects to evaluate the use of continuous diffusion of oxygen therapy in comparison to a sham device that provided moist wound therapy without oxygen delivery. A higher proportion of wound healing was observed with the continuous diffusion of oxygen therapy arm and relative effect was greater in more chronic wounds. Significantly faster rates of wound closures were attributed to the TOT device in comparison to controls.

### *Ongoing research:*

Two ongoing clinical trials were identified:

- The Effect of Natrox® Oxygen Wound Therapy on the Healing Rate of Chronic Diabetic Foot Ulcers. Interventional Clinical Trial, Randomised, Multicentre, Parallel, Open Label. Recruitment Status: Recruiting. Estimated Primary Completion Date: 25 January 2020. ClinicalTrials.gov Identifier: NCT03905863 - Primary outcomes measured: percentage of wound healed at 12 weeks and wound size change at 12 weeks.
- An Observational Clinical Trial Examining the Effect of Topical Oxygen Therapy (NATROX™) on the Rates of Healing of Chronic Diabetic Foot Ulcers. Observational Clinical Trial, Case-Only, Prospective, Single Centre. Recruitment Status: Recruiting. Estimated Primary Completion Date: December 2019. ClinicalTrials.gov Identifier: NCT03863054 - Primary outcome measured: percentage change in ulcer size at 12 weeks.

### Areas of uncertainty

NATROX is described as the first technology of its kind, but the evidence identified suggests that alternative methods of TOT are available. It is not clear if there is variation in, for example, method of application and duration of exposure to treatment. Additionally, since different types of oxygen therapies are available and already used for patients with chronic wounds and DFU (such as hyperbaric oxygen therapy), studies that directly compare the effectiveness of such alternatives could provide a better understanding of the best oxygen therapy for the treatment of chronic wounds.

The evidence identified suggests potential benefits of TOT for DFU but there is a lack of comparative evidence on the clinical effectiveness of TOT for chronic non-healing wounds. Lastly, there is a lack of cost-effectiveness studies in this field.

### Conclusions

The evidence found suggests the use of continuous TOT could be beneficial in the healing of chronic wounds and DFU. However, further investigation of the evidence is needed to quantify whether TOT is more effective than standard care, and whether its use is cost-effective.

## Brief literature search results

Resource	Results
HTA organisations	
<a href="#">Healthcare Improvement Scotland:</a>	We did not identify any relevant information from this source.
<a href="#">Health Technology Assessment Group</a>	We did not identify any relevant information from this source.
<a href="#">Health Information and Quality Authority</a>	We did not identify any relevant information from this source.
UK guidelines and guidance	
<a href="#">SIGN</a>	We did not identify any relevant information from this source.
<a href="#">NICE</a>	We did not identify any relevant information from this source.
Secondary literature and economic evaluations	
<a href="#">ECRI</a>	<ul style="list-style-type: none"> <li>• Topical Oxygen Therapy for Diabetic Foot Ulcers. Hotline Reponse, 2019.</li> </ul>
<a href="#">Cochrane library</a>	Only ongoing clinical trials identified (see ongoing research)
Medline	<ul style="list-style-type: none"> <li>• de Smet, G. H., Kroese, L. F., Menon, A. G., Jeekel, J., van Pelt, A. W., Kleinrensink, G. J., &amp; Lange, J. F. (2017). Oxygen therapies and their effects on wound healing. <i>Wound Repair and Regeneration</i>, 25(4), 591-608. (Six clinical studies, three RCTs and one prospective study; however, only six conducted on human and only one with a continuous oxygen flow)</li> <li>• Sayadi, L. R., Banyard, D. A., Ziegler, M. E., Obagi, Z., Prussak, J., Klopfer, M. J., &amp; Widgerow, A. D. (2018). Topical oxygen therapy &amp; micro/nanobubbles: a new modality for tissue oxygen delivery. <i>International wound journal</i>, 15(3), 363-374.</li> </ul>
Ongoing research	
<a href="#">Clinicaltrials.gov</a>	<ul style="list-style-type: none"> <li>• The Effect of Natrox® Oxygen Wound Therapy on the Healing Rate of Chronic Diabetic Foot Ulcers. Interventional Clinical Trial, Randomised, Multicentre, Parallel, Open Label. Recruitment Status: Recruiting. Estimated Primary Completion Date: 25<sup>th</sup> of January 2020. ClinicalTrials.gov Identifier: NCT03905863</li> <li>• An Observational Clinical Trial Examining the Effect of Topical Oxygen Therapy (NATROX™) on the Rates of Healing of Chronic Diabetic Foot Ulcers. Observational Clinical Trial, Case-Only, Prospective, Single Centre. Recruitment Status: Recruiting. Estimated Primary Completion Date: December 2019. ClinicalTrials.gov Identifier: NCT03863054.</li> </ul>
Primary studies	
Medline	<ul style="list-style-type: none"> <li>• Yu, Janelle, et al. "Topical oxygen therapy results in complete wound healing in diabetic foot ulcers." <i>Wound Repair and Regeneration</i> 24.6 (2016): 1066-1072. NCT02599805 - Randomised Clinical Trial, Interventional, Parallel.</li> <li>• Driver, V. R., Reyzelman, A., Kawalec, J., &amp; French, M. (2017). A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers. <i>Ostomy/wound management</i>, 63(4), 12-28. NCT0129160 - Randomised Clinical Trial, Multicentre, Interventional, Parallel</li> <li>• Niederauer, M. Q., Michalek, J. E., &amp; Armstrong, D. G. (2017). A prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to sham therapy in the treatment of</li> </ul>

	diabetic foot ulcers. <i>Journal of diabetes science and technology</i> , 11(5), 883-891. NCT01645891 - Randomised Controlled Trial, Multicentre, Double Blind, Interventional.
<a href="#">Cochrane library</a>	Only clinical trials identified (see ongoing research)

Date of search:	October 2019
Concepts used:	NATROX, topical oxygen wound therapy, leg ulcer