

How CDO Works

The following is a summary overview of how Continuous Diffusion of Oxygen (CDO) therapy works. Additional information/details can be found in the following pages. Literature references are included at the end. Additional evidence as to how oxygen is effective in wound healing can be found in the EO₂ guidance document “How Oxygen Works in Wound Healing”.¹

How Oxygen Penetrates Wounds



Moist Wounds “Breathe” Similar to Alveoli in Lungs – By Diffusion

- Oxygen diffuses into moist tissue in the same way it penetrates alveoli during breathing (external respiration), or at the cellular level (internal respiration)
- Oxygen does not diffuse into dry tissues very well



Using Pure Oxygen Increases Tissue Levels

- Henry’s Law - concentration in tissue is proportional to concentration above tissue²
- Pure oxygen results in four-fold increase at 2 mm depth in tissue³



Process is Rapid

- As evidenced during breathing, oxygen diffuses into the moist tissues rapidly
- Results in moist tissues show rapid and deep penetration³

How CDO Differs from Topical (TOT, TWO) and Hyperbaric Oxygen (HBO) Therapies⁴



Silent, Wearable & Discreet

- CDO is small & lightweight, others are not



24/7 Continuous Treatment

- CDO treats continuously (24/7), others are only 90 minutes per day



Cost Effective

- CDO is a fraction of the cost of others

Clinical Evidence Supporting CDO



Fully-Blinded RCT with Sham/Placebo in Diabetic Foot Ulcers: 100 Patients⁵

- CDO leads to significantly higher rates of closure (2x to 3x; P = .02 to .006)
- CDO works better as wounds become more chronic
- CDO results in significantly faster time to closure (P < 0.001)



Retrospective Review Chronic Toe Ulcers: 20 Patients⁶

- 74% full closure on ulcers that were unresponsive to other treatments
- High degree of patient compliance with therapy (95%)

Retrospective Review of Ulcers in Veterans Healthcare: 25 Patients⁷

- 68% full closure on ulcers that were unresponsive to other treatments
- Demonstrated adjunctive use with advanced tissue / skin substitutes



Prospective RCT with MWT Control Group: 9 CDO & 8 MWT Patients⁸

- 87% volume reduction in 4 weeks vs. 46% with MWT (P < .05)

Prospective RCT with MWT Control Group in DFUs: 9 CDO & 9 MWT Patients⁹

- 90% closure in 8 weeks vs. 30% with MWT
- Differences became more notable in more advanced ulcers



Case Report of Pain Reduction and Wound Closure in Venous Ulcer¹⁰

- Patient served as own control, pain reduced from 10 to 2 in 3 days



Pain Reduction in Uncontrolled Study of Venous Ulcers: 10 Patients¹¹

- Significant (P < .009) pain reduction during six weeks with 58.9% size reduction

Case Series Review of Severe, Painful Wounds: 4 Patients¹²

- Significant pain reduction in all cases and all closed fully

Case Series Review of Painful Lower Extremity Wounds: 6 Patients¹³

- Significant pain reduction in all cases

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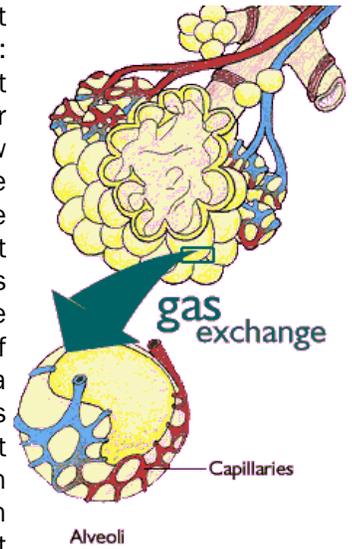
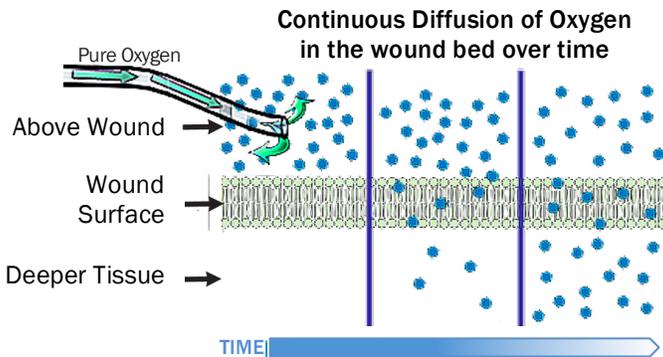
How Oxygen Penetrates Wounds



Moist Wounds “Breathe” Similar to Alveoli in Lungs – By Diffusion

Oxygen transport into a clean, moist wound occurs via the same transport processes that govern oxygen absorption into the alveoli in lungs during breathing: diffusion. Oxygen is transported from the surrounding air to cells in a clean, moist wound (or alveoli) via the physical driving force of diffusion. In diffusion, gases (or liquids) move from an area of high concentration (partial pressure) to areas of low concentration (partial pressure). If there is a mixture of gases in a container, the pressure of each gas (partial pressure or concentration) is equal to the pressure

that each gas would produce if it occupied the container alone. This applies equally well to the concentration of a gas in a liquid. If a gas (oxygen) is present above a liquid (open moist wound), the gas will diffuse into the liquid until it reaches equilibrium in concentration (partial pressure) in the liquid in proportion to that present in the gas above it.



Using Pure Oxygen Increases Tissue Levels

Henry's law states that at a constant temperature, the amount of a gas that dissolves in a liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid. Oxygen in water obeys Henry's law rather well; the solubility is roughly proportional to the partial pressure of oxygen in the air: $pO_2 = KO_2 \cdot xO_2$, where pO_2 is the partial pressure of oxygen in Torr, xO_2 is the mole fraction of oxygen in oxygen-saturated water, and KO_2 is the Henry's law constant for oxygen in water (about 3.30×10^7 K/Torr at 298 K).²

In human tissue, oxygen levels contain approximately 50 mmHg pO_2 at 3-4 mm below the wound for moist wounds exposed to air which has 21% oxygen ($pO_2 = 159$ mmHg). By increasing the oxygen concentration above the wound from 21% ($pO_2 = 159$ mmHg) to 100% ($pO_2 = 760$ mmHg), as is the case with CDO, the resulting oxygen levels in the tissue can increase to as high as 250 mmHg pO_2 . These levels have been found experimentally to be optimal for many of the enzymatic pathways involved in fibroblast proliferation, collagen synthesis, phagocytic (antibacterial) activity, angiogenesis (new blood vessel formation) and growth factor signaling transduction in wound repair. For more information, refer to the “How Oxygen Works in Wound Healing” guidance document.¹



Supplemental Oxygen Rapidly Raises Tissue Oxygen Levels

Oxygen therapies have been shown to rapidly raise oxygen levels in the wound bed, in both clinical and preclinical settings, when pure oxygen is applied directly to the surface of a moist wound at near-atmospheric pressures (not hyperbaric). Preclinically, pure oxygen applied to an open wound has been shown to increase the pO_2 of the superficial wound tissue in pigs³. In this study, an increase of pO_2 from less than 10 mmHg to 40 mmHg at a depth of 2 mm in the center of the wound bed was observed in as little as 4 minutes using an implanted probe.

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How CDO Differs from Topical (TOT, TWO) and Hyperbaric Oxygen (HBO)

There are three primary different methods of oxygen-based therapies that are used to treat wounds: Hyperbaric Oxygen, Topical Oxygen and Continuous Diffusion of Oxygen.⁴ All three technologies are similar in that they use pure oxygen as an aid to wound healing. Hyperbaric Oxygen Therapy is used to treat a patient systemically with pure oxygen at elevated pressures. Topical Oxygen Therapy is used to treat an area directly surrounding a patient's wound using pure oxygen at pressures slightly above atmospheric. Both of these technologies only offer treatment for a relatively short period of time (typically 90 minutes per day, 4 or 5 days per week), which means that the wound only receives supplemental oxygen for a few hours a day. Furthermore, neither of these technologies allows for patient mobility during treatment and can require significant time and expense associated with travel and preparation time for the patient.

CDO Therapy offers several breakthroughs in oxygen therapy in that it:

-  Provides continuous oxygen therapy, which is about 25x the therapy time of competing technologies
-  Is lightweight (nine ounces)
-  Is wearable, which enables full patient mobility and restoration of lifestyle
-  Is rechargeable
-  Is silent
-  Incorporates continuous monitoring of oxygen flow rates and pressures to ensure efficacious delivery of the oxygen

Table 1. Advantages of CDO

Modality	Continuous Diffusion of Oxygen Therapy (CDO)	Topical Oxygen Therapy ^A (TOT)	Hyperbaric Oxygen Therapy (HBO)
Treatment at Home	Yes	Yes ^B	No
Patient Mobility	Yes	No	No
Maintains Moist Wound Bed	Yes	No	Possible
Direct Wound Treatment	Yes	Yes ^C	No
Therapy Time	Continuous	~90 min/day	~90 min/day
Flow Rate	3-15 ml/hr	5-60 L/min	Up to 600 L/min

Notes: A - also referred to as Topical Hyperbaric Oxygen Therapy (THOT) or Topical Wound Oxygen (TWO) therapy

B - can be treated at home, yet patient immobile during treatment

C - treatment typically treats portion of limb, not just wound: limb may be constricted

CDO



TOT



HBO



CDO Therapy continuously diffuses pure oxygen into an oxygen-compromised wound to aid in wound healing while maintaining a moist wound healing environment, maintaining patient mobility and significantly reducing costs.

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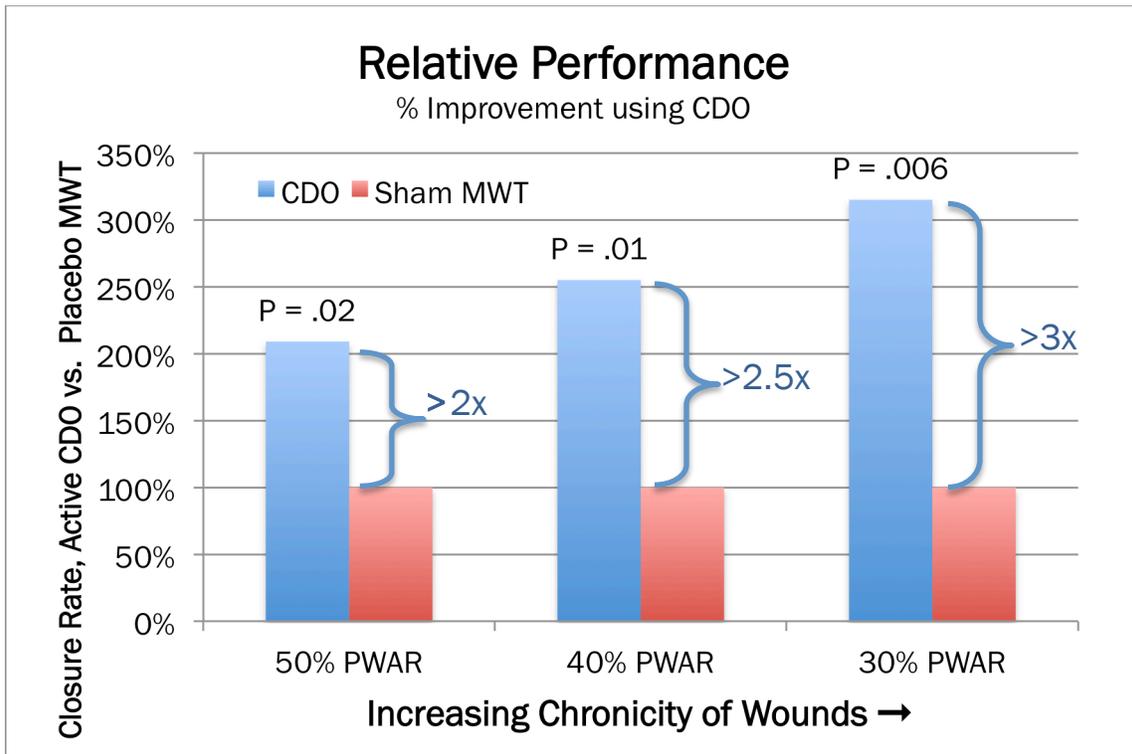
Clinical Evidence Supporting CDO



Fully-Blinded RCT with Sham/Placebo in Diabetic Foot Ulcers: 100 Patients⁵

Results from a **unique** Tier 1A Diabetic Foot Ulcer clinical trial involving 100 patients, which show Continuous Diffusion of Oxygen (CDO) therapy to be statistically significant compared to a sham (placebo) arm, have been published online in Journal of Diabetes Science and Technology in February of 2017 (<http://dx.doi.org/10.1177/1932296817695574>). The rigor of this study is rare in the medical device world: it is a double-blind, prospective, randomly-controlled trial with a sham and an active arm. Both arms received identical treatment (device, dressings, etc.) and the devices were functional in both arms. However, the oxygen did not flow to the wound in the sham arm. In essence, this is on par with a pharmaceutical trial where the patients and clinicians do not know the treatment arm.

A significantly higher proportion of people, more than twice as many (209%), healed in the active CDO arm compared to sham (46% vs 22%, $P = .02$). This relative effect became greater in more chronic wounds: in the most chronic wounds, more than three times (315%) as many wounds closed in the active CDO arm (42.5% vs 13.5%, $P = .006$). Patients randomized to the active device experienced significantly faster rates of closure relative to the sham ($P < .001$). As the wound size increased, the relative positive effect of CDO remained similar or became greater. Dr. David Armstrong of the SALSA Clinic, University of Arizona, is the overall principal investigator for this study.



Clinical Registry

These results are bolstered by those from our post-market surveillance registry that demonstrates a success rate of 74% in 59 days in the field for a wide variety of wounds. These wounds range from small, persistent ulcers to large Stage IV ulcers and include dehisced surgical wounds, large venous ulcers, and acute surgical incisions, to name a few. It is important to note that this success rate is on very difficult wounds that have already been unresponsive to other advanced therapies such as NPWT and HBO and had been open for an average of 359 days (as a new technology, CDO is typically first tried on challenging, unresponsive wounds). More details of the current registry results can be found on our website (eo2.com).



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Retrospective Review Chronic Toe Ulcers: 20 Patients⁶

A retrospective analysis on the impact of CDO in chronic toe ulcer healing for 20 patients showed an overall success rate (full closure) of 74% on wounds that were unresponsive to other therapies. The author highlighted a chief benefit being that of high patient compliance (95%), which he attributed to the device's ease of use, the noticeability of improvement within a short period of time, and the reduction of pain.



Retrospective Review of Ulcers in Veterans Healthcare: 25 Patients⁷

Another retrospective analysis of 25 patients in a Veteran's Healthcare Administration environment showed 68% full closure, both as a stand-alone and adjunctive therapy. The author found that CDO improves wound healing potential, including in wounds receiving advanced tissue/ skin substitute applications.



Prospective RCT with MWT Control Group: 9 CDO & 8 MWT Patients⁸

A prospective, randomized clinical trial of CDO versus MWT followed 17 patients (9 CDO, 8 MWT) for 4 weeks and found significant differences in wound volume reduction. The CDO group had an average volume reduction of 87%, whereas the MWT group had an average volume reduction of 46% ($P < .05$).



Prospective RCT with MWT Control Group in DFUs: 9 CDO & 9 MWT Patients⁹

Significant differences in the healing rate of CDO as compared to MWT were recently demonstrated in a prospective, randomized pilot clinical trial with 9 patients receiving MWT and 9 receiving CDO. The study focused on smaller DFUs (approx. 1.5 cm²), UT Grade I-III, over an 8-week period. CDO was shown to close 90% of the wounds by the end of the study, whereas the MWT group experienced 30% closure. The authors also noted significantly faster wound closure rates in the CDO arm and more noticeable differences from CDO in the more advanced ulcers (Grades II and III).



Case Report of Pain Reduction and Wound Closure in Venous Ulcer¹⁰

For a patient who served as her own control during CDO therapy treatment, her pain levels were reported as high as 8/10 on a visual analogue score (VAS), with pain medications taken as needed, during the 5-month duration of the ulcer prior to CDO therapy. After 20 days of CDO therapy, the patient reported a pain level of 2/10 and was no longer taking pain medications. At this time, CDO therapy was temporarily discontinued since the patient was leaving town for a holiday. Six days later the patient returned to the clinic with a pain level of 10/10 and reported difficulty sleeping. CDO therapy was reapplied and, within three days, the patient's pain level was controlled (VAS 2/10) and she ceased taking narcotics.



Pain Reduction in Uncontrolled Study of Venous Ulcers: 10 Patients¹¹

In an uncontrolled, nonrandomized study of 10 patients with venous ulcers, CDO therapy was reported to significantly ($P < .009$) reduce pain in a six-week period. The corresponding mean reduction in wound size was 58.9%.



Case Series Review of Severe, Painful Wounds: 4 Patients¹²

In a case series review, four patients with severe, very painful wounds were successfully closed and the pain was significantly reduced in all cases.



Case Series Review of Painful Lower Extremity Wounds: 6 Patients¹³

A six patient case review of CDO in patients with diabetes and chronic lower extremity wounds reported significant pain reduction.

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