Topical Oxygen Wound Therapy

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Overview

Chronic wounds are a common and costly condition in the U.S. (Sen et al., 2009). Chronic wounds are defined as wounds that do not progress through the normal healing process in a timely manner and can be categorized based on etiology (e.g., pressure, diabetes, vascular, surgical, injury) (Frykberg & Banks, 2015). Underlying issues such as systemic disorders, nutritional deficiencies, or a compromised vascular system can affect blood supply to an area and limit oxygen delivery to tissues (Brimson & Nigam, 2013). Topical oxygen wound therapy (TOWT), also called topical hyperbaric oxygen wound therapy, is the local application of 100% oxygen, either through pressurized devices or transdermal application, to the surface of a wound (Brimson & Nigam, 2013; Dissemond, Kroger, Storck, Risse, & Engels, 2015).

Key Findings

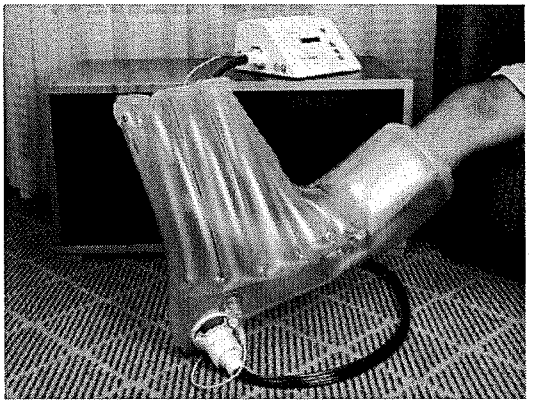
- The evidence base on TOWT consists largely of small, nonrandomized studies of poor methodological quality that suggest greater complete wound healing and shorter time to complete healing compared with standard wound care or other active treatments for chronic wounds. However, the report authors have very low confidence in the estimates of effectiveness given the overall poor methodological quality of the current evidence. The limitations of the body of evidence strongly suggest that future research of higher methodological quality could produce different results. Limitations of the available evidence include small sample sizes, absence of blinding of study staff and participants, and populations with different underlying medical conditions or wound types.
- Identified clinical practice guidelines range from good to poor methodological quality with best practice recommendations on the use of TOWT stating that the available evidence is insufficient, limited, or that "controversy exists as to the therapeutic value of topical pressurized oxygen delivery to local tissues/wounds" (Wounds Canada, 2017, p. 55).
- In 2006, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination (NCD) stating that topical oxygen is not an established effective therapy and thus not covered. In April 2017, the agency issued a decision memo reporting that the original determination would be amended to state that coverage decisions of TOWT would be made at the local contractor level through a local coverage determination (LCD). However, as of August 2017, the original determination language is unchanged and the two identified LCDs do not cover TOWT, using the original language of the 2006 NCD.
- The majority of private insurers and Medicaid programs explicitly do not cover TOWT, several describing the therapy as investigational or not medically necessary.

Background

Clinical Overview

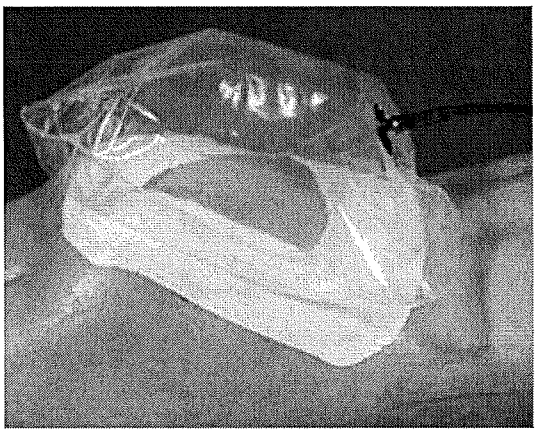
- Hypoxia, low oxygen levels in the tissue, is often a key limiting factor in wound healing. Oxygen is an essential component in the body's tissue healing process because it aids in collagen synthesis (i.e., creation of a fibrous protein in connective tissues), immune response (e.g., leukocyte activation), and angiogenesis (i.e., development of new blood vessels) associated with tissue repair (Rodriguez, Felix, Woodley, & Shim, 2008).
- Wounds are commonly categorized by the attributable systemic condition (e.g., diabetes, venous, or arterial insufficiency) or localized insult (e.g., burn, trauma, pressure). Tools to assess the severity of the underlying condition or concomitant ulcer (if present) include but are not limited to: the ankle brachial index (ABI) for arterial insufficiency in the legs; the CEAP (clinical, etiology, anatomy, pathophysiology) system for venous insufficiency; and the Wagner Ulcer Classification for diabetic foot ulcers. See Appendix A for additional information on the wound classification rating systems.
- There are several treatment modalities available for chronic wounds including debridement (i.e., removal of damaged tissue or foreign substances from the wound), offloading (e.g., removable foot cast), compression therapy, topical wound therapies and dressings, and advanced therapies such as negative pressure wound therapy, hyperbaric oxygen therapy, biophysical wound care, acellular matrix tissues, growth factors, bioengineered allogeneic cellular therapies, and stem cell therapies (Frykberg & Banks, 2015).
- In TOWT, oxygen, from a portable unit, is applied to the wound through either a re-usable chamber, a single-use bag, or continuously through portable units used in conjunction with an occlusive dressing and oxygen-supplying tubes, such as EPIFLO (see Figure 1). While the oxygen delivered through a chamber or bag is pressurized, it does not reach as high of a pressure as full-body hyperbaric oxygen therapy and varies by device (Greer et al., 2012).
- Figure 2 provides an overview of the spectrum of approaches to increase oxygen delivery to chronic wounds including different topical and hyperbaric oxygen modalities.
- Topical oxygen chambers are classified as a Class II device (special controls) by the U.S. Food and Drug Administration (FDA). Under this classification, the FDA has identified risks to health associated with the use of topical oxygen chambers such as infection, fire and explosion, local tissue damage, adverse tissue reaction, and electrical shock (FDA, 2011). The FDA has indicated that it will rely on "well-designed bench and/or animal testing, rather than clinical studies" for approval of any new topical oxygen chambers (FDA, 2011).

Figure 1. Topical Oxygen Wound Therapy



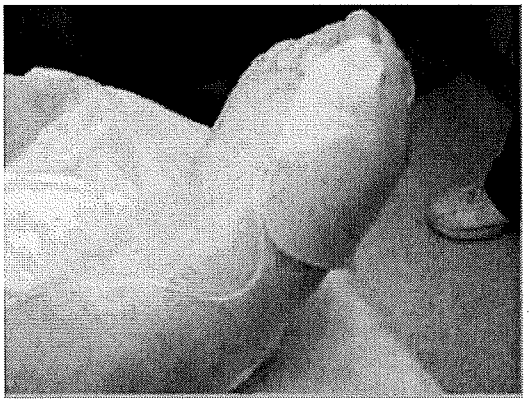
Pressurized Single Use Bag (e.g., AOTI device)

Source. http://www.birminghammail.co.uk/news/local-news/oxygen-therapy-used-to-treat-patients-182578



Pressurized Single Use Bag (e.g., GWR Medical, Inc. device)

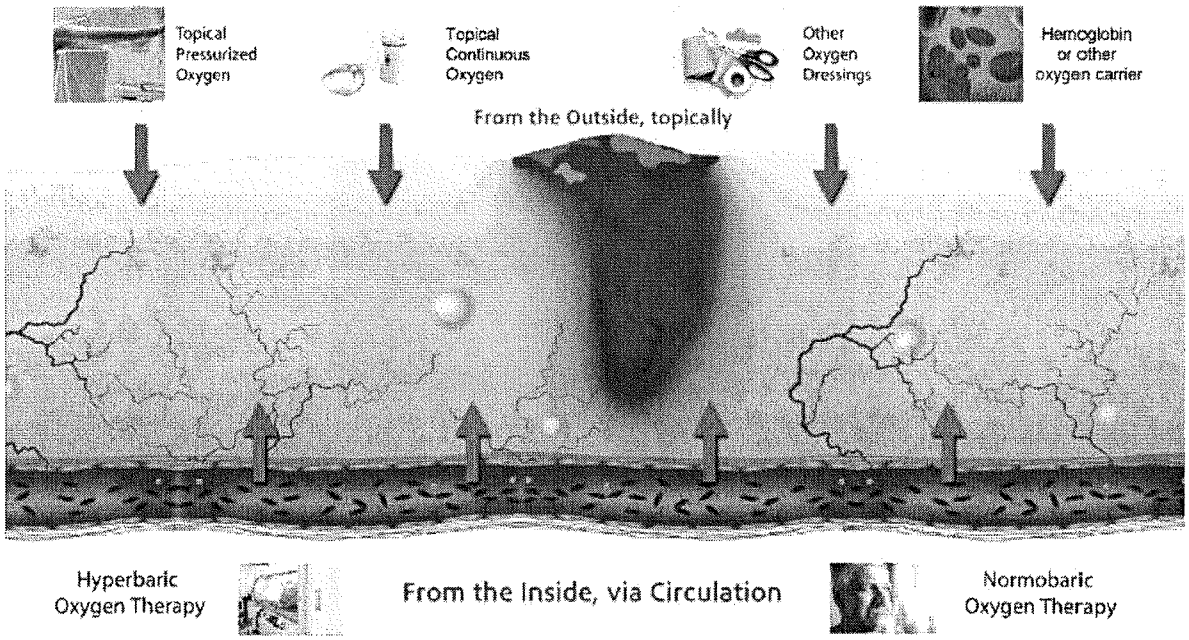
Source. http://www.topicaloxygen.com/products



Transdermal (EPIFLO)

Source. http://www.ogenix.com/wp-content/themes/ogenix/images/ECN3.PDF

Figure 2. Topical and Systemic Approaches of Oxygen Therapy for Chronic Wounds



Source. Dissemond, Kroger, Storck, Risse, and Engels (2015, p. 54)

Prevalence

Chronic wounds affect upwards of 6.5 million people in the U.S., with over $25 billion spent on wound care in the U.S. each year (Sen et al., 2009).

PICO

Population: Individuals with non-healing wounds (e.g., pressure ulcers, diabetic ulcers, venous ulcers, arterial insufficiency ulcers, surgical wounds, skin grafts, gangrenous lesions, frostbite, or burns)

Intervention: TOWT (e.g., continuous diffusion of oxygen, transdermal/transcutaneous continuous oxygen, topical oxygen)

Comparators: Standard wound care (e.g., debridement) or other active treatments (e.g., hyperbaric oxygen, negative pressure wound therapy)

Outcomes: Reduction in wound size; complete wound healing; time to wound healing; amputation; function; quality of life; harms of treatment; cost and cost-effectiveness; need for retreatment. Pain will be included as an outcome only if quality of life or function outcomes are not available.

Key Questions

1. How does TOWT differ from standard treatment or other treatment options for individuals with non-healing wounds?
2. What is the effectiveness of TOWT for non-healing wounds?
    a. How does effectiveness vary by wound stage or type?
3. What harms and adverse events are associated with the use of TOWT?
4. What are the costs and cost-effectiveness of TOWT compared to standard or other therapies?
5. What are current clinical practice guidelines on the use of TOWT for non-healing wounds?
6. What are Medicare, state Medicaid, and private payer coverage criteria for TOWT?

Methods

Center for Evidence-based Policy (Center) researchers searched Center core evidence and guidelines sources and Ovid MEDLINE for systematic reviews (with or without meta-analysis), technology assessments, and individual studies on TOWT published within the last 10 years and clinical practice guidelines published within the last five years. Center researchers evaluated the methodological quality of systematic reviews, individual studies, and clinical practice guidelines eligible for this report using the methodology described in detail in Appendix B and quality assessment tools included with the New York State Department of Health dossier process

(available on the New York State Department of Health website). Center researchers also searched Medicare, several state Medicaid programs, and private payers for coverage policies on the use of TOWT for the treatment of wounds. See Appendix B for a full list of payers searched.

Center researchers excluded systematic reviews if all of the included studies were also summarized by a more comprehensive systematic review, a systematic review of a higher methodological quality, and/or a more recently published systematic review. In addition, because only patient-important outcomes have relevance for the New York State Medicaid program the following outcomes were excluded from this review: animal studies, in-vitro studies, and studies that only reported on laboratory biological markers. Case series were only included if they addressed harms. Exclusion criteria were selected prior to review of the studies, and study methods were assessed before review of outcomes to eliminate bias. See Appendix B for a full description of methods.

Authors of studies usually report on the statistical significance of findings, but it is not always clear how relevant a statistically significant finding is in clinical practice. Reports from within the wound care research community highlight the challenges of translating evidence to practice in this field. Real-world wound care practices often involve heterogeneous populations, co-occurring interventions, and longer timeframes than feasible for many wound care researchers (Carter & Warriner, 2008).

Center researchers summarized the evidence as reported by the included systematic reviews. Center researchers did not review the individual studies included in the systematic reviews unless necessary for clarification of information reported in the systematic review.

Evidence Review

Findings

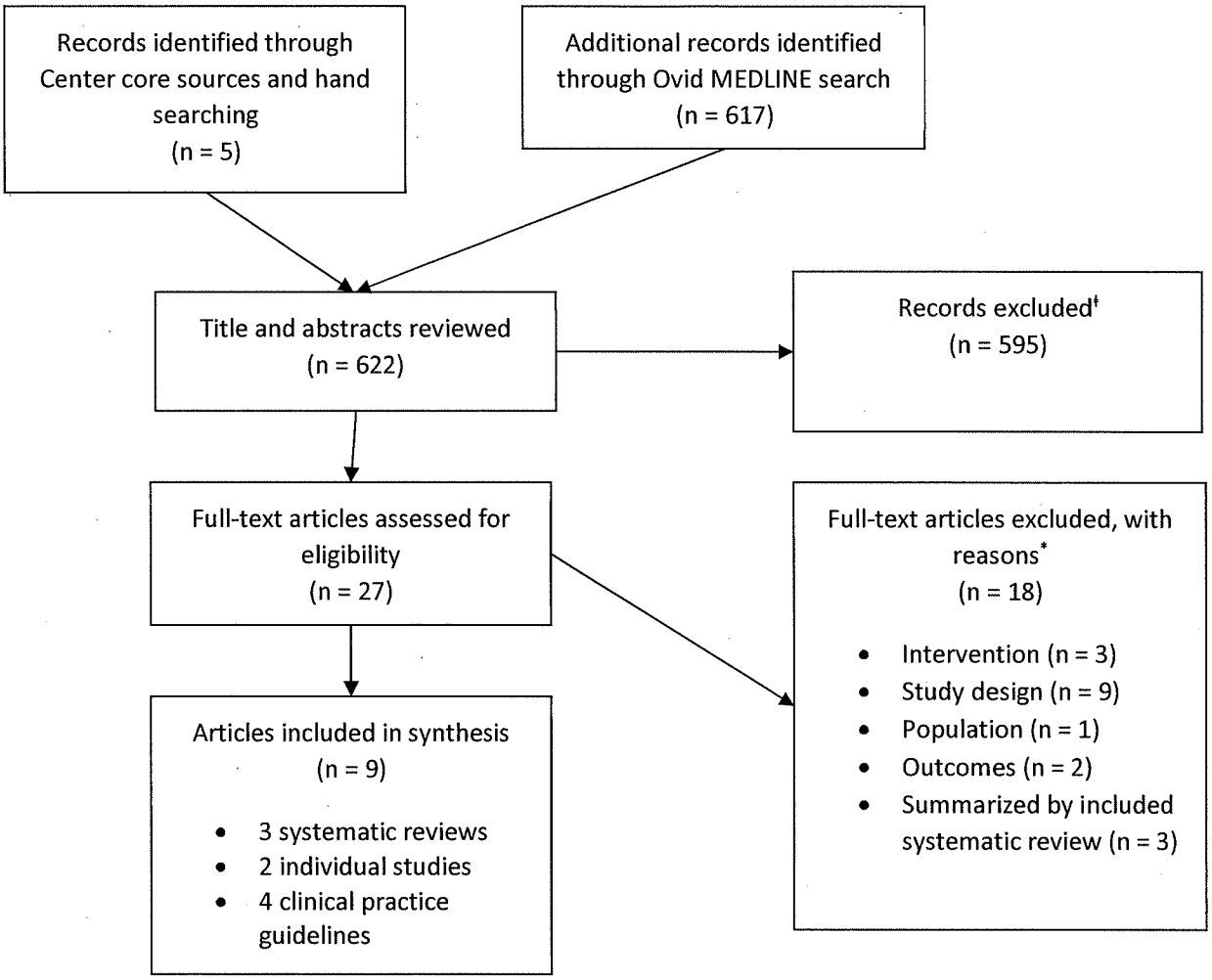
The Ovid MEDLINE database search identified 617 studies. Center researchers identified four additional studies in the Center core sources and one study from hand searching reference lists. Figure 3 outlines the number of articles identified by each search and the total number of studies included in this evidence synthesis. The search strategies and list of studies reviewed in full with reasons for exclusion are in Appendices B and C, respectively.

Overview of Evidence Sources

Center staff identified three recent systematic reviews (Brimson & Nigam, 2013; Canadian Agency for Drugs and Technologies in Health, 2012; Greer et al., 2012) and two individual studies (Driver et al., 2013; Tawfick & Sultan, 2013) relevant to the effectiveness and/or harms of TOWT for the treatment of wounds that met inclusion criteria.

Table 1 provides an overview of findings from the included systematic reviews and individual studies.

Figure 3. Search Results



‡ Articles were excluded if they did not meet pre-determined inclusion criteria (e.g., PICO, study design).
* Exclusion rationale provided in Appendix C.

Systematic Reviews

Brimson and Nigam (2013)

Brimson and Nigam (2013) conducted a poor methodological quality systematic review that evaluated the effectiveness of TOWT in the treatment of chronic wounds. The systematic review included a comprehensive database literature search for citations, but the authors restricted their screening process to "relevant seminal texts" from 2001 to 2012 (Brimson & Nigam, 2013). This review did not include a description of the included study characteristics nor did the study

authors assess the risk of bias of the included studies. The review authors cited seven articles in their discussion of evidence of effectiveness for TOWT (Brimson & Nigam, 2013). Center researchers reviewed the included citiations and determined that three were narrative reviews, not primary studies. The remaining citations included two non-comparative case series (Heng, Harker, Bardakjian, & Ayvazian, 2000a; Kalliainen, Gordillo, Schlanger, & Sen, 2003) and two cohorts (Blackman, Moore, Hyatt, Railton, & Frye, 2010; Tawfick & Sultan, 2009) which are both reviewed in-depth in the CADTH (2012) systematic review summarized below.

CADTH (2012)

CADTH (2012) conducted a good methodological quality systematic review that evaluated the clinical and cost-effectiveness of TOWT for wound healing. The systematic review included a comprehensive database literature seach for citations published between January 1, 2006, and December 19, 2011; reviewed gray literature; and hand-searched reference lists of identified articles (CADTH, 2012). The review included randomized and nonrandomized study designs. The authors included three observational studies consisting of 168 participants that compared TOWT with advanced moist wound therapy, conventional compression dressing, or hyperbaric oxygen therapy (CADTH, 2012). Two studies used an extremity chamber with pressurized and humidified medical grade oxygen, (i.e., Hyper-Box [AOTI Ltd]). The third used a single-use disposable device with a portable oxygen supply (e.g. TWO_2 (GWR Medical, Inc.)). One study evaluated TOWT for diabetic foot ulcers, another focused on refractory venous ulcers, and the third study involved individuals with chronic wounds (CADTH, 2012). Interventions varied by frequency and duration across the three studies. One study occurred in an inpatient setting, and two studies were conducted in an outpatient clinic. The authors note the inpatient treatment setting may include greater intensity of general wound care. The authors did not identify any economic evaluations of TOWT.

Greer et al. (2012)

Greer et al. (2012), on behalf of the U.S. Department of Veterans Affairs, conducted a good methodological quality systematic review on advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers. The review authors searched for RCTs published between 1995 and August 2012 in the Ovid MEDLINE and Cochrane Library databases. The authors did not identify any RCTs that evaluated TOWT for the aforementioned conditions.

Individual Studies

Driver et al. (2013)

Driver et al. (2013) conducted a poor methodological quality RCT (n = 17) that evaluated the comparative effectiveness of standard of care plus TOWT (via EPIFLO, distributed in the U.S. by Ogenix as of August 2017) to standard of care alone in patients with chronic diabetic foot ulcers. Standard of care included weekly debridement, boot offloading, and moisture (details not

provided) (Driver et al., 2013). The authors reported that there were no statistically significant differences in characteristics between groups at baseline (Driver et al., 2013). The outcomes reported included percentage of reduction in wound size from baseline and several biological markers (Driver et al., 2013).

Tawfick and Sultan (2013)

Tawfick and Sultan (2013) conducted a poor methodological quality cohort study that compared TOWT with conventional compression dressings for individuals with chronic refractory venous ulcers. The application of TOWT occurred via a pressurized chamber from AOTI Ltd. (referred to as both the HyperBox and Hyper-Box within the article). The venous ulcer was required to be over two years old, without improvement in the past year. The study enrolled 132 patients from October 2006 to December 2011 from a tertiary referral leg ulcer clinic in Ireland (Tawfick & Sultan, 2013). Patients were allowed to self-select treatment groups: 67 selected TOWT and 65 selected conventional compression dressings (Tawfick & Sultan, 2013). The primary outcomes included percentage of ulcers that showed signs of healing at three weeks, the percentage of ulcers that were completely healed at three months, time to complete wound healing, and methicillin-resistant *Staphylococcus aureus* elimination (Tawfick & Sultan, 2013).

Quality and Limitations

Center researchers rated two of the systematic reviews as having good methodological quality (CADTH, 2012; Greer et al., 2012), and one as having poor methodological quality (Brimson & Nigam, 2013). None of the systematic reviews identified RCTs on TOWT. Center researchers assessed the methodological quality of the included systematic reviews and not the individual studies within them. The individual studies in the systematic reviews were assessed by the respective review authors. References to individual study quality are taken directly from the systematic reviews, and are not assessments made by Center researchers.

Center researchers assessed the methodological quality of individual studies not included in the systematic reviews using standard quality assessment methods (see Appendix B for further details). Of the two additional included studies, Center researchers rated both as poor methodological quality (Driver et al., 2013; Tawfick & Sultan, 2013).

The systematic review authors and Center researchers (upon evaluation of individual studies published after the last systematic review) noted several common biases. The majority of studies were conducted outside of the U.S., thus limiting the generalizability of results for the U.S. health care system. The evidence base draws largely from small nonrandomized studies, without blinding, that often relied on patient or provider preference to allocate treatment. The single randomized study on TOWT identified in the current search enrolled 17 individuals (Driver et al., 2013). Together, these factors increase the risk of bias in these studies. The limitations of the

body of evidence strongly suggest that future research of higher methodological quality could produce different results.

Summary of the Evidence

Evidence is summarized in Table 1 by comparator and then by outcomes of effectiveness and harms. Table 1 provides a high-level summary of the evidence listed by systematic review and included studies.

Table 1. Overview of Included Studies

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Systematic Reviews with Meta-analysis			
Center researchers did not identify any systematic reviews with meta-analysis on this topic.			
Systematic Reviews (without Meta-analysis)			
Brimson and Nigam (2013) Search Dates 2001 to 2012 Eligible Study Designs *Not specified* Methodological Quality Poor	k = *Not reported* total n = *Not reported* *SR's quality assessment of individual studies: Not assessed*	Authors' Conclusions The use of TOWT for chronic wound healing is a promising area; more research needed to determine effectiveness	Center researchers rated this systematic review as having poor methodological quality because the authors provided little information on the review methods, such as study inclusion/exclusion criteria, and no specific details on included studies
CADTH (2012) Search Dates January 2006 to December 2011 Eligible Study Designs Technology assessments, SRs, meta-analyses, RCTs nonrandomized studies, economic studies	k = 3 nonrandomized studies total n = 168 *SR's quality assessment of individual studies:* Concern about the possibility of selection bias, lack of randomization and blinding	TOWT (via Hyper-Box from AOTI) vs. Conventional Compression Dressing *(Inpatient with refractory venous ulcers in Ireland)* *Complete Wound Healing at 12 Weeks* 80% vs. 35% ($p < .0001$) *Median Time to Full Wound Healing* 45 days vs. 182 days ($p < .001$)	Included studies also cited in the Brimson and Nigam (2013) systematic review Included studies utilized different types of TOWT (i.e., transdermal, pressurized via chamber), different treatment protocols limiting direct comparisons In studies using a chamber, the duration and frequency of

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Methodological Quality Good		*Wound Recurrence* 0/37 vs. 5/13 (no formal statistical test conducted) *Quality-adjusted time without symptoms* 12.5 vs. 4.5 months (p < .0001) TOWT (via single use bag from GWR Medical, Inc.) vs. Hyperbaric Oxygen Therapy *(Outpatient with chronic wounds > 4 weeks in U.S.)* *Wound Volume* TOWT statistically significantly reduced wound volume (p = .001), whereas hyperbaric oxygen therapy did not (p = .15) TOWT (via chamber from AOTI) vs. Advanced Moist Wound Therapy *(Outpatient with diabetic foot ulcers in Canada)* *Complete Wound Healing* 14/17 vs. 5/11 (p = .04) *Median Time to Wound Closure* 56 days vs. 93 days (no formal statistical test conducted)	treatments was not the same, limiting direct comparisons Included studies occurred in different treatment settings (e.g., inpatient) that may not be applicable to U.S. practices and may have given greater attention to basic wound care No studies on cost-effectiveness for TOWT were identified through their extensive search

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		Adverse Events None reported at 24-month follow-up Authors' Conclusions "While [TOWT] improves the healing of [diabetic foot ulcers, refractory venous ulcers,] and chronic wounds, its place in therapy cannot be fully determined as the absence of randomization and blinding prevent direct comparison between groups" (CADTH, 2012, p. 6)	
Greer et al. (2012) Search Dates 1995 to August 2012 Eligible Study Designs RCTs Methodological Quality Good	*The authors did not identify any relevant RCTs that met the authors' inclusion criteria.*		

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Randomized Controlled Trials			
Driver et al. (2013) Study Length 5 weeks Location U.S. Methodological Quality Poor	n = 17 individuals with chronic, non-healing diabetic foot ulcers; 9 received TOWT, 8 received SOC Inclusion criteria: Adults (age 18-90 years), diabetes mellitus (type 1 or 2), chronic diabetic foot wound (0.5 to 15 cm^2), Wagner grade 1 or 2, $TcPO_2$ > 30 mm Hg or ankle brachial index > 0.6 Exclusion criteria: noncontact ultrasound within previous 4 weeks, lower extremity malignancy, critical limb ischemia, local infection of limb with target ulcer, systemic infection, pregnancy, end stage renal disease, severe congestive heart disease, severe liver disease, venous leg ulcer with or without diabetes, known/suspected lidocaine allergy	Comparators Transdermal continuous oxygen therapy (via EPIFLO) plus standard of care (SOC) vs. SOC (i.e., debridement, boot offloading, moisture) Outcomes *Wound Size (% wound volume at week 5 compared to week 1)* TOWT: 21.8% ± 20.0% SOC: 49.2% ± 52.3% ($p < .05$)	Actual wound size not provided The outcome reported in this table is directly from the text of the article but differs from the supporting figure for this outcome which differs in standard deviation. It is unclear which estimate is correct. Actual wound size not reported, thus it is not possible to determine the actual clinical significance of the reported differences Study limitations include small sample size, lack of description of concealment and blinding methods, and direct funding support from the manufacturer
Other Study Designs			
Tawfick and Sultan (2013)	n = 132 individuals with chronic refractory venous ulceration	Comparators	Wounds treated with TOWT had significantly shorter duration to full

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Study Design Cohort Location Ireland Methodological Quality Poor	(chronic defined as more than 2 years); 67 received TOWT, 65 received CCDs Inclusion criteria: adults (≥ 18 years) with venous ulcers greater than 2 years in duration, no improvement over past 1 year in dedicated veins unit with $C_{6,s}$ CEAP classification, normal ankle-brachial index with normal digital pressure Exclusion criteria: bedridden, ischemic ulcers, osteomyelitis, malignant ulcers Intervention required 180 minutes within the Hyper-Box twice a day Comparison group received home nursing dressing changes 1 to 3 times per week	TOWT (via Hyper-Box) vs. conventional compression dressings (CCDs) Outcomes *Complete Healing (at 12 weeks follow-up)* 76% vs. 46% (p < .0001) *Median Time to Full Healing* 57 days vs. 107 days (p < .0001) *MRSA Elimination* 11/24 vs. 0/19 (p < .001) *Ulcers Showing Signs of Healing in 3 Weeks* 86% vs. 72% (p < .021) Harms *Wound Recurrence (fully healed wounds)* 3/51 vs. 14/30 (p < .0001)	healing than those treated with CCD, regardless of ulcer surface area or ulcer duration for the TOWT group Median follow-up was 36 months Treatment setting not described Patients allocated to treatment groups based on their preference Unclear whether groups received the same wound care aside from intervention Appears to be follow-up data from a study included in CADTH 2012 by same authors but not clear from manuscript

Abbreviations. CCD: conventional compression dressing; CEAP: clinical, etiological, anatomical, and pathophysiological; MRSA: methicillin-resistant Staphylococcus aureus; RCT: randomized controlled trial; SOC: standard of care; SR: systematic review; $TcPO_2$: transcutaneous oximetry; TOWT: topical oxygen wound therapy. Note: a indicates assessed by review authors.

Effectiveness: Reduction in Wound Size

Systematic Reviews

A single systematic review reported on this outcome for adults with chronic wounds comparing TOWT to hyperbaric oxygen therapy, but the original study did not make comparisons by treatment groups (CADTH, 2012). Recipients of TOWT experienced statistically significant reductions in wound volume, whereas hyperbaric oxygen recipients did not ($p = .001$ and $p = .15$, respectively) (CADTH, 2012). The absolute magnitude of the reduction is unknown, as is the clinical relevance of a statistically significant reduction in the size of a chronic wound.

Individual Studies

In their RCT of 17 participants with diabetic foot ulcers, Driver et al. (2013) observed a greater percentage reduction in wound volume from baseline for TOWT recipients (via EPIFLO) compared to standard of care. The absolute magnitude of the reduction in size was not reported, nor were complete wound healing rates. This study also lacked a description on concealment and blinding, and was financially supported by the manufacturer.

In their cohort study of 132 adults with refractory venous ulcers (>2 years in duration), Tawfick and Sultan (2013) found that a greater proportion of individuals had reduced wound surface area at three weeks for TOWT (via Hyper-Box) compared to compression dressings (86% vs. 72%, $p = .02$).

Effectiveness: Complete Wound Healing

Systematic Reviews

A single systematic review reported on this outcome for several comparators (CADTH, 2012). Compared to conventional compression dressings in adults with refractory venous ulcers, a greater proportion of TOWT recipients experienced complete wound healing (80% vs. 35%, $p < .0001$). The results were from a single study based in Ireland that tracked ulcers, not specific individuals, such that a single individual could contribute multiple data points if they had more than one ulcer.

In a separate study included in the CADTH (2012) review, TOWT recipients demonstrated greater complete wound healing compared to advanced moist wound therapy in adults with diabetic foot ulcers (14/17 vs. 5/11, $p = .04$).

Individual Studies

In their cohort study of 132 adults with refractory venous ulcers that had lasted more than two years, Tawfick and Sultan (2013) observed that a greater proportion of individuals had complete wound healing at 12-week follow-up for TOWT (via Hyper-Box) compared to conventional compression dressings (76% vs. 46%, $p < .0001$). Individuals self-selected their treatment. The

intervention required individuals to place the affected limb in the Hyper-Box for 180 minutes twice a day. The compression group received outpatient home nursing for dressing changes one to three times per week depending on the drainage rate from the wound. It is unclear whether all participants received the same level of attention to their wounds. It is also unclear whether the Hyper-Box was used at home or at a facility because previous work from this group (as cited in CADTH, 2012) involved inpatient use of the Hyper-Box.

Effectiveness: Time to Wound Healing

Systematic Reviews

A single systematic review reported on this outcome for several comparators (CADTH, 2012). Compared to conventional compression dressings in adults with refractory venous ulcers, the median time to complete wound healing was shorter for TOWT recipients (45 days vs. 182 days, $p < .001$). As mentioned above, this estimate is from a single Ireland-based study that allowed individuals with multiple ulcers to be counted repeatedly because the unit of analysis was an ulcer, not a person.

In a separate study in the CADTH (2012) review, TOWT recipients demonstrated shorter mean times to wound healing compared to advanced moist wound therapy in adults with diabetic foot ulcers (56 days vs. 93 days, no formal statistical test conducted).

Individual Studies

Compared to conventional compression dressings in adults with refractory venous ulcers that had lasted for more than two years, the median time to full healing was shorter for TOWT recipients (via Hyper-Box) (57 days vs. 107 days, $p < .0001$) (Tawfick & Sultan, 2013). As mentioned above, individuals self-selected their treatment. It is unclear whether all participants received similar attention to their wounds and it is unclear where individuals received TOWT treatment.

Effectiveness: Recurrence of Ulcer

Systematic Reviews

A single systematic review reported on this outcome for TOWT compared to conventional compression dressings for adults with refractory venous ulcers (CADTH, 2012). None of the ulcers receiving TOWT recurred (0/37) compared to 5/13 for ulcers receiving compression. The statistical significance of this finding was not reported in the CADTH (2012) review.

Individual Studies

In their cohort study of 132 adults with refractory venous ulcers that had lasted for more than two years, Tawfick and Sultan (2013) observed decreased recurrences for TOWT recipients (via Hyper-Box) compared to conventional compression dressings (3/15 vs. 14/30, $p < .0001$). Limitations of this study have been addressed above.

Effectiveness: Other Outcomes

Systematic Reviews

A single systematic review reported on the quality-adjusted time spent without symptoms for adults with refractory venous ulcers (CADTH, 2012). A single study observed greater quality-adjusted time spent without symptoms for TOWT compared to compression dressings (12.5 vs. 4.5 months, $p < .0001$).

Center researchers did not identify any studies that reported on amputation, function, quality of life, or pain.

Effectiveness: Cost and Cost-Effectiveness

Center researchers did not identify any studies reporting on the cost or evaluating the cost-effectiveness of TOWT.

Harms: Need for Retreatment

Center researchers did not identify any studies reporting on the need for retreatment after receiving TOWT.

Clinical Practice Guidelines

Center researchers identified four clinical practice guidelines that address the use of TOWT for the treatment of wounds (Gottrup et al., 2017; National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, & Pan Pacific Pressure Injury Alliance, 2014; Orsted et al., 2012; Wounds Canada, 2017). Center researchers rated three of the guidelines as having poor methodological quality (Gottrup et al., 2017; Orsted et al., 2012; Wounds Canada, 2017) and one as having good methodological quality (National Pressure Ulcer Advisory Panel et al., 2014). Table 2 provides a summary of guideline recommendations for TOWT. The strength of underlying evidence noted in the table for guideline recommendations is an assessment by guideline authors, not Center researchers.

In a joint good methodological quality guideline from the Australian National Pressure Ulcer Advisory Panel, the European Pressure Ulcer Advisory Panel, and the Pan Pacific Pressure Injury Alliance, TOWT is not recommended for routine use in the treatment of pressure ulcers (National Pressure Ulcer Advisory Panel et al., 2014). This guideline used a robust recommendation development process that was based on a comprehensive systematic review of the literature, and used clear rationale for study inclusion and exclusion. Included studies were assessed for risk of bias, and the guideline authors directly linked the strength of each recommendation to the underlying evidence base.

Orsted et al. (2012) developed a poor methodological quality guideline from Canada that provides best practices on the use of TOWT. To establish recommendations, the guideline

authors used the Delphi process, which the distributor of TOWT in Canada convened, and the role of the distributor in this process is unclear. The authors stated that the Delphi process was based on a systematic review of the literature, however, very little detail was provided on the methods used in the systematic review. Orsted et al. (2012) recommended that TOWT be used in the treatment of chronic wounds and noted that TOWT could be contraindicated for patients with untreated acute deep venous thrombosis or untreated acute thrombophlebitis. The guideline authors further recommended that if 20% to 40% of wound closure is not achieved in two to four weeks, TOWT should be discontinued (Orsted et al., 2012).

The Canadian Association of Wound Care (also known as Wounds Canada) guideline provides best-practice recommendations for the prevention and management of wounds (Wounds Canada, 2017). Center researchers rated this best practice guideline as having poor methodological quality because it lacked a description of how the recommendations and care pathways were developed. The Wounds Canada guidelines authors did not provide a recommendation on TOWT, but noted that there is controversy regarding the therapeutic value of TOWT in the treatment of wounds (Wounds Canada, 2017, p. 55).

The European Wound Management Association, in conjunction with Wounds Australia, recently released a poor methodological quality guideline specific to the use of hyperbaric and topical oxygen to treat wounds (Gottrup et al., 2017). Although the guideline stated that it is based on a comprehensive literature search, guideline authors do not provide any details about the underlying evidence search, nor how the evidence findings were used to develop recommendations. Gottrup et al. (2017) recommended the use of TOWT as an adjunctive therapy for non-healing chronic wounds, but cautioned that more research is needed that evaluates the clinical efficacy of TOWT.

Table 2. Summary of Clinical Practice Guidelines Recommendations for TOWT

Citation Methodological Quality	Recommendation (Evidence Rating)
European Wound Management Association and Wounds Australia (Gottrup et al., 2017) Poor	"There is a limited but expanding evidence base for successful healing after treatment with [TOWT] products, especially in a subset of non-healing patients who failed to achieve an adequate healing response in standard treatment settings. Although the authors endorse the adjunctive administration of [TOWT] therapies for non-healing chronic wounds, more robust data from multi-centre prospective placebo-controlled trials affirming their clinical efficacy will be required before this promising therapy can be given a stronger recommendation" (Gottrup et al., 2017, p. S22).

Citation Methodological Quality	Recommendation (Evidence Rating)
National Pressure Ulcer Advisory Panel et al. (2014) Good	"Due to insufficient evidence to support or refute the use of topical oxygen in the treatment of pressure ulcers, topical oxygen is not recommended for routine use at this time. (Strength of Evidence = C; Strength of Recommendation: No specific recommendation)"* (National Pressure Ulcer Advisory Panel et al., 2014, p. 43)
Orsted et al. (2012) Poor	"[TOWT] is indicated for the treatment of chronic wounds such as diabetic/neuropathic foot ulcers, venous stasis ulcers and pressure ulcers, Level IIa"‡ (Orsted et al., 2012, p. 279) "[TOWT] is contraindicated if the patient has an untreated acute deep venous thrombosis or untreated acute thrombophlebitis, Level IV"‡ (Orsted et al., 2012, p. 280) "The frequency and duration of [TOWT] is dependent on wound aetiology, wound response and patient tolerance, Level IV"‡ (Orsted et al., 2012, p. 281) "If wound closure is the goal and the wound is not reduced by 20–40% after 2–4 weeks of [TOWT], despite efforts to address the underlying causes and cofactors, [TOWT] should be discontinued and alternate methods sought, Level IV"‡ (Orsted et al., 2012, p. 282) "A low recurrence rate may be expected in venous leg ulcers and diabetic foot ulcers following [TOWT], Level III"‡ (Orsted et al., 2012, p. 282) "[TOWT] may reduce wound-related pain in venous leg ulcers, Level III"‡ (Orsted et al., 2012, p. 282) "Preliminary studies have shown that [TOWT] has the potential for cost savings, Level IV"‡ (Orsted et al., 2012, p. 283)
Wounds Canada (2017) Poor	"Controversy exists as to the therapeutic value of topical pressurized oxygen delivery to local tissues/wounds." (Wounds Canada, 2017, p. 55)

Abbreviations. TOWT: topical oxygen wound therapy

*Notes: *Determined by guideline authors. C = The recommendation is supported by indirect evidence (e.g., studies in healthy humans, humans with other types of chronic wounds, animal models) and/or expert opinion. ‡Determined by guideline authors. Level IIa = Evidence obtained from at least one well-designed controlled study without randomization. Level III = Evidence obtained from well-designed non experimental*

descriptive studies, such as comparative studies, correlation studies, and case studies. Level IV = Evidence obtained from expert committee reports or opinions and/or clinical experiences from respected authorities.

Payer Policies

Center researchers searched for policies on the coverage of TOWT from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians' Health Plan, CMS, Cigna, EmblemHealth, Empire Blue Cross Blue Shield (BCBS), Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, and WA). Table 3 provides a comparison of identified coverage criteria for all payers searched.

TOWT is billed using the combination of the Healthcare Common Procedure Coding System (HCPCS) codes A4575 (topical hyperbaric oxygen chamber, disposable) and E1390 (oxygen concentrator, single delivery port, capable of delivering 85% or greater oxygen concentration at the prescribed flow rate) or the single code E0446 (topical oxygen delivery system, not otherwise specified, includes all supplies and accessories).

Medicare

CMS recently addressed the coverage of TOWT in a decision memo released in April 2017 (CMS, 2017). In the memo, CMS stated that an NCD for TOWT is "not appropriate at this time" and that reference to TOWT in the NCD on hyperbaric oxygen therapy (section C) will be amended to state that Medicare coverage determinations of TOWT will be made by local contractors (CMS, 2017). However, as of August 2017, the hyperbaric oxygen therapy NCD (20.29) had not yet been updated and still stated that Medicare will not reimburse for TOWT (CMS, 2006).

Two LCDs incorporate the coverage of TOWT under hyperbaric oxygen coverage criteria. Both LCDs (L36504, L35021) state that TOWT is "not reasonable and necessary" and therefore not reimbursed by Medicare (CMS, 2015; CMS, 2016).

Private Payers

Eight of the nine private payers reviewed do not cover the use of TOWT. EmblemHealth was the only private payer searched that allows coverage of TOWT, and the coverage criteria mirror those of the New York State Medicaid program. The full coverage criteria are outlined in Table 3. Center researchers did not identify any coverage criteria from the Capital District Physicians' Health Plan.

State Medicaid Agencies

California, Oregon, and Texas Medicaid programs explicitly do not cover TOWT. Center researchers could not identify coverage criteria of TOWT in five state Medicaid programs (FL, MA, NJ, PA, and WA). However, Massachusetts and New Jersey Medicaid agencies provide pricing information for the associated HCPCS codes. The Massachusetts Medicaid provider fee schedule lists A4575 as reimbursable at the actual acquisition cost (AAC) plus 20%, E0446

reimbursable at the AAC plus 30%, and E1390 reimbursable at $158.21 (MassHealth, 2010). Similarly, the New Jersey Medicaid fee schedule lists A4575 as being priced by report, does not list E0446, and reimburses E1390 at $250 per month as a rental unit (New Jersey Medicaid Management Information System, 2017).

New York State Medicaid covers the use of TOWT for Stage IV pressure ulcers, neuropathic ulcers, venous insufficiency ulcers, non-healing surgical or traumatic wounds, or non-healing wounds of mixed etiology after trial of a complete wound-healing therapy program has failed (New York State Medicaid, 2017b). The New York State Medicaid fee schedule does not list a price for A4575, does not list E0446, and allows a reimbursement of $190.00 for E1390 as a rental unit (New York State Medicaid, 2017a). Additional coverage criteria are in Table 3.

Table 3. TOWT Coverage Policies

Payer	Coverage Criteria
Medicare	
Decision Memo CAG-00060R (*4/3/2017*)	"After examining the evidence, CMS has decided that no National Coverage Determination is appropriate at this time concerning the use of topical oxygen for the treatment of chronic wounds. We will amend NCD 20.29 by removing Section C, Topical Application of Oxygen and Medicare coverage of topical oxygen for the treatment of chronic wounds will be determined by the local contractors" (CMS, 2017).
NCD 20.29 (*effective 6/19/2006*)	"Topical Application of Oxygen: This method of administering oxygen does not meet the definition of HBO therapy as stated above. Also, its clinical efficacy has not been established. Therefore, no Medicare reimbursement may be made for the topical application of oxygen" (CMS, 2006). Reimbursement: *A4575 is not priced at the national or the New York localities rates. E0446 and E1390 are not listed under the national or the New York localities list.*
LCD 36504 (*effective 4/11/2016, applies to FL, Puerto Rico, Virgin Islands*)	"Topical Application of Oxygen: This method of administering oxygen does not meet the definition of HBO therapy as stated above, as its clinical efficacy has not been established. Therefore, Medicare considers the topical application of oxygen not reasonable and necessary. Medicare reimbursement will be limited to therapy that is administered in a chamber (including single or multi-place units)" (CMS, 2016).
LCD 35021 (*effective 10/1/2015, applies to AR, CO, DE, D.C., LA, MD, MN, MS, NJ, OK, PA, TX*)	"Topical Application of Oxygen: This method of administering oxygen does not meet the definition of HBO therapy as stated above as its clinical efficacy has not been established. Therefore, Medicare considers the topical application of oxygen not reasonable and necessary. Medicare reimbursement will be limited to therapy that is administered in a chamber (including single or multi-place units)" (CMS, 2015).
Private Payers	

Payer	Coverage Criteria
Aetna (*last review 7/2017*)	Considered experimental and investigational (Aetna, 2017)
Anthem (*last review 8/2016*)	Considered investigational and not medically necessary (Anthem, 2016)
Blue Shield of Northeastern New York (*last review 3/2017*)	Considered investigational (Blue Shield of Northeastern New York, 2017)
Capital District Physicians' Health Plan	*No coverage criteria identified.*
Cigna (*last review 5/2017*)	"Considered experimental, investigational or unproven for any indication" (Cigna, 2017)
EmblemHealth (*last review 9/2016*)	"Medicaid/Family Health Plus members are eligible for coverage of topical oxygen wound therapy when criteria 1 and any of criteria 2–6 are met: 1. A complete wound therapy program as applicable, depending on the type of wound, has been attempted prior to application of TOWT, including: • Documentation in the patient's medical record of evaluation, care, compliance and wound measurements by the treating physician, and • Application of dressings to maintain a moist wound environment, and • Debridement of necrotic tissue if present, and • Evaluation of and provision for adequate nutritional status, and 2. Stage IV pressure ulcers: • The patient has been appropriately turned and positioned, and • The patient has used a support surface for pressure ulcers on the posterior trunk or pelvis (not required if the ulcer is not on the trunk or pelvis), and • The patient's moisture and incontinence have been appropriately managed, or 3. Neuropathic (for example, diabetic) ulcers: • The patient has been on a comprehensive diabetic management program, and • Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities, or 4. Venous insufficiency ulcers:

Payer	Coverage Criteria
	• Compression bandages and/or garments have been consistently applied, and • Leg elevation and ambulation have been encouraged, or 5. For non-healing surgically created or traumatic wounds, documentation of medical necessity for accelerated formation of granulated tissue as a result of which cannot be achieved by other topical wound treatments, or 6. A chronic (being present for at least 30 days) ulcer of mixed etiology. Limitations/Exclusions TOWT is considered investigational, not medically necessary, medically contraindicated and not covered for all other indications, including but not limited to, the following: 1. The presence in the wound of necrotic tissue with eschar, if debridement is not attempted. 2. Untreated osteomyelitis within the vicinity of the wound. 3. Cancer present in the wound. 4. The presence of a fistula to an organ or body cavity within the vicinity of the wound. 5. Stage I, II or III pressure ulcers. An initial electronic prior authorization (DVS) will be granted for A4575 for a maximum of 16 days in a 28 day period, as treatment is 4 days on, 3 days off. The provider should request authorization once for the number of days (units) based on the written order. Prior approval is required for treatment exceeding 4 weeks. E1390 is not prior authorized and is billed monthly. TOWT should be attempted first in a hospital or another health care facility prior to discharge to the home setting. In these continuing cases, documentation should reflect patient compliance and pain management during application of TOWT. If TOWT has not been attempted, providers must obtain an initial prior authorization of two weeks (8 days or units) only. Prior approval may then be requested for an extension of the treatment"(EmblemHealth, 2016).
Empire BCBS (*last review 8/2016*)	Considered investigational and not medically necessary (Empire BCBS, 2016)
Excellus BCBS (*last review 4/2017*)	Considered investigational (Excellus BCBS, 2017)
Tufts Health Plan (*last review 4/2017*)	Not covered (Tufts Health Plan, 2017)

Payer	Coverage Criteria
UnitedHealthcare (*effective 4/2017*)	Coverage in compliance with LCDs above. For states without an applicable LCD, refer to LCD L35021 for coverage guidelines (UnitedHealthcare, 2017).
State Medicaid	
California (*effective 7/15/2017*)	"Topical oxygen therapy is not considered HBO therapy and is not a covered benefit of the Medi-Cal program" (California Department of Health Care Services, n.d.). Reimbursement: *HCPCS codes A4575 and E0446 not listed*
Florida (*effective 1/1/2017*)	*No coverage criteria identified* Reimbursement: *HCPCS codes A4575 and E0446 not listed*
Massachusetts (*effective 2/25/2010*)	*No coverage criteria identified* Reimbursement: A4575: average acquisition cost (AAC) + 20%; E0446: AAC + 30%; E1390: $158.21
New Jersey (*effective 9/1/2017*)	*No coverage criteria identified* Reimbursement: A4575: pricing by report, cannot be rented, requires prior authorization; *E0446 not listed;* E1390: $250/month, prior authorization required
New York (*effective 5/1/2017*)	TOWT (A4575 with E1390) is covered when criteria 1 and any of criteria 2-6 are met: 1. A complete wound therapy program as applicable, depending on the type of wound, has been attempted prior to the application of TOWT, including: (a) Documentation in the member's medical record of evaluation, care, compliance and wound measurements by the treating physician, and (b) Application of dressings to maintain a moist wound environment, and (c) Debridement of necrotic tissue if present, and (d) Evaluation of and provision for adequate nutritional status, and 2. Stage IV pressure ulcers: (a) The member has been appropriately turned and positioned, and (b) The member has used a support surface for pressure ulcers on the posterior trunk or pelvis (not required if the ulcer is not on the trunk or pelvis), and (c) The member's moisture and incontinence have been appropriately managed, or

Payer	Coverage Criteria
	3. Neuropathic (for example, diabetic) ulcers: (a) The member has been on a comprehensive diabetic management program, and (b) Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities, or 4. Venous insufficiency ulcers: (a) Compression bandages and/or garments have been consistently applied, and (b) Leg elevation and ambulation have been encouraged, or 5. For non-healing surgically created or traumatic wounds, documentation of medical necessity for accelerated formation of granulation tissue that cannot be achieved by other topical wound treatments, or 6. A chronic (being present for at least 30 days) ulcer of mixed etiology. <u>Non-Covered Indications</u> TOWT is considered investigational, not medically necessary, medically contraindicated and not covered for all other indications, including but not limited to, the following: 1. The presence in the wound of necrotic tissue with eschar, if debridement is not attempted; 2. Untreated osteomyelitis within the vicinity of the wound; 3. Cancer present in the wound; 4. The presence of a fistula to an organ or body cavity within the vicinity of the wound; 5. Stage I, II or III pressure ulcers. <u>General Guidelines</u> The procedure codes for billing TOWT are A4575 Topical oxygen chamber, disposable and E1390 Oxygen concentrator, single delivery port, capable of delivering 85% or greater oxygen concentration at the prescribed flow rate. Payment for E1390 includes all necessary equipment, delivery, maintenance and repair costs, parts, supplies and services for equipment set-up, maintenance and replacement of worn essential accessories and parts. Payment for A4575 includes the dressing set and canister set used in conjunction with E1390 and contains all necessary components, including but not limited to an occlusive dressing which creates a seal around the wound site for maintaining the desired concentration of oxygen at the wound.

Payer	Coverage Criteria
	Payment for E1390 and A4575 are considered payment in full for TOWT. An initial electronic prior authorization (DVS) will be granted for A4575 for a maximum of 16 days in a 28 day period, as treatment is 4 days on, 3 days off. The DMEPOS provider should request authorization once for the number of days (units) based on the written order. Prior approval is required for treatment exceeding 4 weeks. E1390 is prior authorized (DVS) and is billed monthly. TOWT should be attempted first in a hospital or another health care facility prior to discharge to the home setting. In these continuing cases, documentation should reflect member compliance and pain management during application of TOWT. If TOWT has not been attempted, DMEPOS providers must obtain an initial electronic prior authorization of two weeks (8 days or units) only. Prior approval may then be requested for an extension of the treatment (NYS DOH2017b, pp. 103-105). Reimbursement: A4575: *price not listed*, 16 max units, prior authorization required; *E0446 not listed*; E1390: $190.00, rental, prior authorization required
Oregon (*effective 4/1/2016*)	Topical hyperbaric oxygen chambers (A4575) not covered Reimbursement: *A4575 and E0446 not listed*; E1390: $145.43, rental only
Pennsylvania (*effective 12/12/2005*)	*No coverage criteria identified* Reimbursement: *A4575 and E0446 not listed*; E1390: $173.17, rental only
Texas (*effective 7/31/2017*)	Portable hyperbaric oxygen chambers (A4575) not covered Reimbursement: *A4575 and E0446 not listed*; E1390: $148.76
Washington (*effective 1/1/2017*)	*No coverage criteria identified* Reimbursement: *A4575, E0446, E1390 not listed*

Abbreviations. ACC: average acquisition cost; BCBS: Blue Cross Blue Shield; CPT: Current Procedural Terminology; HBO: hyperbaric oxygen therapy

Discussion

There is very limited evidence on the use of TOWT for chronic wounds, regardless of etiology. Three observational studies were identified through inclusion in systematic reviews and one RCT and one cohort study were identified from searches for additional individual studies. Although the identified studies suggest that TOWT might be an effective treatment, the significant biases noted for each study make it difficult to determine the overall validity of the findings. Center researchers identified only one randomized trial that compared TOWT with standard of care, and no studies that compared TOWT to a sham treatment. The available evidence draws from small studies across disparate populations with different interventions (e.g., transdermal oxygen, pressurized oxygen), limiting the ability to assess the effect of TOWT on wound healing and limiting generalizability of the results to the Medicaid population. Without higher

methodological quality studies, it is not possible to discern the true effect of TOWT on wound healing.

There are a limited number of best practice recommendations on the appropriate use of TOWT for chronic wounds. An older consensus guideline from Canada recommended the use of TOWT to treat chronic wounds, but to discontinue treatment if 20% to 40% improvement was not observed within two to four weeks. Newer guidelines from Canada stated that there is significant controversy regarding the therapeutic value of TOWT as a wound treatment modality but did not provide evidence in support of that statement. Newer guidelines from Australia and Europe did not recommend the use of TOWT because of insufficient evidence of effectiveness for individuals with pressure ulcers. A 2017 guideline from the European Wound Management Association recommended the use of TOWT as an adjunctive therapy for chronic non-healing wounds, but noted that additional research on the clinical efficacy of the therapy is needed.

The vast majority of payer policies identified do not provide coverage of TOWT. New York State Medicaid and EmblemHealth have detailed coverage criteria for the use of TOWT for chronic wounds, including non-covered indications. Some state Medicaid programs, such as Massachusetts and New Jersey, do not outline coverage criteria in their provider manuals, but do allow for coverage as listed in program fee schedules using the combination of codes A4575 and E1390 or the separate code E0446.

Although the current search did not identify any evidence on harms of TOWT, the FDA *Class II Special Controls Guidance* document for TOWT addressed several potential issues with the various TOWT devices related to the use of oxygen, including fire, explosion, and electrical shock (FDA, 2011).

The current search did not identify any evidence on cost or cost-effectiveness for TOWT. Given the high prevalence of chronic wounds and cost burden in the U.S., additional research in this area is strongly needed.

Strength of Evidence

The Center uses the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group approach to enhance consistency in grading the strength of evidence. RCTs are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength rating is downgraded depending on the severity of the bias, based on limitations including study risk of bias; inconsistency (i.e., differences between study findings indicated by statistical or clinical heterogeneity); indirectness (i.e., limited generalizability of the findings from the study sample to another population); imprecision (i.e., wide confidence intervals); and high probability of reporting bias, also known as publication bias. The rating can be increased from low for evidence from observational studies if there is a strong association,[1] a very strong association,[2] or a dose-response gradient. The rating is also increased if all plausible confounders have reduced the estimate (Schünemann, Brozek, Guyatt, & Oxman, 2014). Tables 4 to 6 provide an overview of the strength of evidence by wound etiology, outcome, and associated rationale for the strength of evidence rating.

[1] Significant relative risk of >2 or <0.5 with no plausible confounders in two or more observational studies.

[2] Significant relative risk of >5 or <0.2 based on direct evidence with no major threats to validity.

Table 4. Strength of Evidence for TOWT for Chronic Diabetic Foot Ulcers

Outcome	Strength of Evidence Assessment	Rationale
Effectiveness		
Wound Size	Very low	One small RCT suggests TOWT plus standard of care might be more effective at reducing wound size than standard of care alone. Unable to determine whether difference in wound size is clinically significant. • Downgraded for imprecision • Downgraded for risk of bias (two levels)
Complete Healing	Very low	Based on one small observation study, TOWT might be more effective at achieving complete healing than advanced moist wound healing. • Downgraded for risk of bias
Time to Full Healing	Very low	Based on one small observation study, TOWT might be more effective than advanced moist wound therapy at reducing the time to full wound healing. • Downgraded for risk of bias
Amputation, Function, Quality of Life, Pain	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Harms		
Adverse Events, Wound Recurrence	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Cost-Effectiveness		
Center researchers did not identify any studies that reported on cost or evaluated the cost-effectiveness of TOWT.		

Abbreviations. TOWT: topical oxygen wound therapy

Table 5. Strength of Evidence for TOWT for Chronic Ulcers (Mixed Etiology or Not Defined)

Outcome	Strength of Evidence Assessment	Rationale
Effectiveness		
Wound Size	Very low	One small cohort study suggests TOWT might be more effective at reducing wound size compared to hyperbaric oxygen therapy. Unable to determine whether difference in wound size is clinically significant. • Downgraded for risk of bias
Complete Healing	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Time to Full Healing	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Amputation, Function, Quality of Life, Pain	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Harms		
Adverse Events, Wound Recurrence	No evidence	*Center researchers did not identify any studies that reported on these outcomes for this population.*
Cost-Effectiveness		
Center researchers did not identify any studies that reported on cost or evaluated the cost-effectiveness of TOWT.		

Abbreviations. TOWT: topical oxygen wound therapy

Table 6. Strength of Evidence for TOWT for Refractory Venous Leg Ulcers

Outcome	Strength of Evidence Assessment	Rationale
Effectiveness		
Wound Size	No evidence	*Center researchers did not identify any studies that reported on these outcomes.*
Complete Healing	Very low	Based on two small cohort studies, TOWT might be more effective than conventional compression dressing in the percentage of complete wound healing. • Downgraded for risk of bias
Time to Full Healing	Very low	Based on two small cohort studies, TOWT might be more effective than conventional compression dressing in the time to complete wound healing. • Downgraded for risk of bias
Quality-adjusted Time Spent Without Symptoms	Very low	Based on one small cohort study, TOWT might be more effective than conventional compression dressing in the time spent without symptoms. • Downgraded for risk of bias
Amputation, Function, Quality of Life, Pain	No evidence	*Center researchers did not identify any studies that reported on these outcomes.*
Harms		
Wound Recurrence	Very low	Based on two small cohort studies, TOWT might be more effective than conventional compression dressing at reducing the incidence of wound recurrence. • Downgraded for risk of bias
Other Adverse Events	No evidence	*Center researchers did not identify any studies that reported on these outcomes.*
Cost-Effectiveness		
Center researchers did not identify any studies that reported on cost or evaluated the cost-effectiveness of TOWT.		

Abbreviations. TOWT: topical oxygen wound therapy

2014 TOWT Dossier Response Summary

In April 2014, Center researchers summarized and responded to a dossier on TOWT submitted to the New York State Department of Health by GWR Medical, Inc. The dossier submission included 24 articles published between 2000 and 2014. Center researchers independently assessed the submitted articles for inclusion, methodological quality, and reported results. In addition, Center researchers conducted independent literature searches of the Ovid MEDLINE database (no date limit) and the Center's core sources (as described in Appendix B).

Center researchers identified three systematic reviews and one case series in addition to the articles submitted in the dossier. Upon review of the provided dossier materials, 12 of the submitted articles were excluded based on study design (e.g., narrative review, animal study). A total of four systematic reviews, four RCTs, four cohort studies, and four case series were reviewed as part of the dossier response. See Appendix E for a full list of included studies from the dossier response.

Of the studies reviewed in the dossier, three individual studies evaluated the use of Hyper-Box from AOTI, two evaluated TOWT devices from GWR Medical, Inc., two individual studies evaluated the use of EPIFLO from Ogenix, and one individual study evaluated Topox from Topox Therapeutic Rentals, Inc. The remaining included studies did not report on the specific device used in the evaluation of TOWT, nor did any of the studies excluded from the dossier submission.

This current report did not identify any additional studies from what was identified in the 2014 dossier summary and response. However, there are slight methodical differences between the current report and the 2014 dossier response. The dossier response summarized and assessed the methodological quality of included systematic reviews and the individual studies included within them. The dossier response also included two systematic reviews that are not publically accessible and thus not included in this current report (ECRI Institute, 2013; Hayes Inc., 2002). See Appendix E for a comparison of specific inclusion/exclusion rationale for studies included in the 2014 dossier summary and response and this report.

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Appendix A. Wound Classification and Rating Systems

Ankle Brachial Index (ABI)

"ABI is a noninvasive vascular screening test to identify large vessel, peripheral arterial disease by comparing systolic blood pressures in the ankle to the higher of the brachial systolic blood pressures, which is the best estimate of central systolic blood pressure. ABI is performed using a continuous wave Doppler, a sphygmomanometer and pressure cuffs to measure brachial and ankle systolic pressures" (Wound Ostomy and Continence Nurses Society Clinical Practice Wound Subcommittee, 2012, p. S21). Table 7 provides a description of ABI scores and perfusion status.

Table 7. Ankle Brachial Index

Ratio of Brachial to Ankle Pressure (i.e., ABI)	Perfusion Status
>1.3	Elevated, incompressible vessels
>1.0	Normal
≤0.9	Lower extremity arterial disease
≤0.6 to 0.8	Borderline
≤0.5	Severe ischemia
≤0.4	Critical ischemia, limb threatened

Source. Adapted from (Wound Ostomy and Continence Nurses Society Clinical Practice Wound Subcommittee, 2012, p. S26)

Clinical, Etiology, Anatomy, Pathophysiology (CEAP)

The CEAP is a classification system designed to establish standard terminology to discuss and classify venous disorders (American College of Phlebology, n.d.). The clinical section (C), outlined in Table 8 is the most commonly used portion of the CEAP system (American College of Phlebology, n.d.) and is outlined in Table 8.

Table 8. CEAP – Clinical Section

Clinical Classification	Description
C0	No sign of venous disease
C1	Spider or reticular veins
C2	Varicose veins
C3	Presence of edema of the ankle
C4 (a and b)	Pigmentation (darkening) of the skin, eczema (redness, itching), lipodermatosclerosis

Clinical Classification	Description
	(hardening of the soft tissue), and atrophie blance (whitish skin area)
C5	Healed venous ulcer present
C6	Active open venous ulcer

Source. Adapted from (American College of Phlebology, n.d.)

Wagner Ulcer Classification System

The Wagner ulcer classification is the most widely accepted classification system for diabetic foot ulcers (Frykberg, 2002) and is detailed in Table 9.

Table 9. Wagner Ulcer Classification System

Grade	Lesion
0	No open lesions, may have deformity or cellulitis
1	Superficial diabetic ulcer (partial or full thickness)
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
4	Gangrene localized to portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

Source. Adapted from (Frykberg, 2002, p. 1657)

Appendix B. Methods

General Search Strategy

Evidence

A full search of the Center's core clinical evidence primary sources was conducted to identify systematic reviews, meta-analyses, and technology assessments using the search terms *topical oxygen* and *oxygen wound*. Searches of core sources were limited to citations published after 2006. Center researchers also searched the Ovid MEDLINE database for relevant systematic reviews and meta-analyses, technology assessments, individual studies, and cost-effectiveness studies published after 2006.

The core sources searched included the following:

Agency for Healthcare Research and Quality (AHRQ)

BMJ – Clinical Evidence

Cochrane Library (Wiley Interscience)

National Institute for Health and Care Excellence (NICE)

PubMed Health

Tufts Cost-Effectiveness Analysis Registry

Veterans Administration Evidence-based Synthesis Program (ESP)

Washington State Health Technology Assessment Program

Clinical Practice Guidelines

Center researchers conducted a full search of Center clinical practice guidelines primary sources to identify clinical practice guidelines using the terms *topical oxygen* and *oxygen wound*. Searches were limited to citations published within the last five years.

The guideline sources included the following:

Australian Government National Health and Medical Research Council (NHMRC)

National Guidelines Clearinghouse

National Institute for Health and Care Excellence (NICE)

New Zealand Guidelines Group

Scottish Intercollegiate Guidelines Network (SIGN)

Veterans Administration/Department of Defense (VA/DOD)

World Health Organization (WHO)

Center researchers searched Google 10 pages deep using the terms *topical oxygen* and *guideline or position or practice*.

Coverage Policies

Center researchers searched for policies on the coverage of TOWT for the treatment of wounds from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physicians' Health Plan, CMS, Cigna, Emblem Health, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, and WA).

General Inclusion/Exclusion Criteria

Two Center researchers independently reviewed the results from the Center core sources and Ovid MEDLINE database searches at each stage of review (e.g., title and abstract, full text). Any study that was identified by at least one researcher as potentially meeting inclusion criteria was advanced to the next review level. All excluded studies were determined by two Center researchers as not meeting the pre-determined inclusion criteria. Any disagreement between study reviewers regarding the inclusion of a study was arbitrated by a third Center researcher. Center researchers excluded studies that were not systematic reviews, meta-analyses, or technology assessments, or individual studies (as applicable by topic) that were published before 2007, or were published in a language other than English.

Specific Search Details

The search terms *topical oxygen* and *oxygen wound* were used in the remaining core source searches. Archived government reports were not included.

Inclusion Criteria

Population: Individuals with non-healing wounds (e.g., pressure ulcers, diabetic ulcers, venous ulcers, arterial insufficiency ulcers, surgical wounds, skin grafts, gangrenous lesions, frostbite, or burns)

Intervention: TOWT (e.g., continuous diffusion of oxygen, transdermal/transcutaneous continuous oxygen, topical oxygen)

Comparators: Standard wound care (e.g., debridement) or other active treatments (e.g., hyperbaric oxygen, negative pressure wound therapy)

Outcomes: Reduction in wound size, complete wound healing; time to wound healing; amputation; function; quality of life; harms of treatment; cost and cost-effectiveness; need for retreatment. Pain will be included as an outcome only if quality of life or function outcomes are not available.

Exclusion Criteria

Study exclusion criteria included the following:

- Animal and in-vitro studies
- Studies only reporting on laboratory biological markers
- Case series that did not report on harms
- Case reports, letters, editorials, comments
- Duplicate information from a research study published in more than one source (only the highest quality, most recent publication with outcome of interest was included)
- Systematic reviews that included only studies that were summarized by more comprehensive systematic reviews or systematic reviews of higher quality and/or that were more recently published
- Studies identified that were included in a summarized systematic review or technology assessment

Ovid MEDLINE Search

The Ovid MEDLINE search strategy was developed for broad inclusion of relevant systematic reviews and individual studies. Individual studies published after the search dates of the included systematic review or studies that were eligible and not included in the systematic review were included to update the systematic review.

Database: Ovid MEDLINE <1946 to August Week 1 2017>, Ovid MEDLINE In-Process & Other Non-Indexed Citations <August 09, 2017>

Search Strategy:

1 exp Skin Ulcer/
2 exp Foot Ulcer/
3 exp Leg Ulcer/
4 exp Varicose Ulcer/
5 exp Diabetic Foot/
6 exp Skin Transplantation/
7 exp Wound Healing/
8 exp Venous Insufficiency/
9 exp "Wounds and Injuries"/
10 exp Gangrene/
11 exp Burns/
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 exp Oxygen/
14 (topica$ adj3 oxygen).ti,ab.
15 topical oxygen.mp.
16 13 or 14 or 15
17 12 and 16
18 limit 17 to english language
19 (animals not animals, humans).mp.

20 18 not 19
21 limit 20 to yr="2007 -Current"
22 limit 21 to (case reports or comment or editorial or letter)
23 21 not 22
24 remove duplicates from 23

Quality Assessment

Center researchers assessed the methodological quality of the included studies using standard instruments developed and adapted by the Center that are modifications of the systems in use by the Campbell Collaboration, Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) (Campbell Collaboration, 2015; Moher, Liberati, Tetzlaff, & Altman, 2009; NICE, 2014; SIGN, 2015). Two Center researchers independently rated all studies. In cases where there was not agreement about the quality of a study, consensus was reached through discussion.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine whether a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Appendix C. Articles Selected for Full-Text Review: Exclusion Rationale

Citation	Exclusion Rationale
Anonymous (2015)	Exclude: Intervention (hemoglobin spray)
Bakri et al. (2008)	Exclude: Outcome (tissue oxygen tension)
Basilico et al. (2015)	Exclude: Intervention (nanodroplets)
Blackman et al. (2010)	Exclude: Included in Brimson and Nigam (2013) systematic review
Braun, Fisk, Lev-Tov, Kirsner, and Isseroff (2014)	Exclude: Intervention (does not include a review of TOWT)
Chambers and Leaper (2011)	Exclude: Study design (narrative review)
Davis (2007)	Exclude: Study design (narrative review)
Dissemond et al. (2015)	Exclude: Study design (narrative review)
Eisenbud (2012)	Exclude: Study design (narrative review)
U.S. Food and Drug Administration (2011)	Exclude: Study design (narrative review)
Gordillo et al. (2008)	Exclude: Included in Brimson and Nigam (2013) systematic review
Gordillo and Sen (2009)	Exclude: Study design (narrative review)
Howard, Asmis, Evans, and Mustoe (2013)	Exclude: Study design (narrative review)
Roe, Gibbins, and Ladizinsky (2010)	Exclude: Population (human donor skin samples)
Schreml et al. (2010)	Exclude: Study design (narrative review)
Tawfick and Sultan (2009)	Exclude: Included in CADTH (2012) systematic review
Woo, Coutts, and Sibbald (2012)	Exclude: Study design/outcome (case series not reporting harms)
Yip (2015)	Exclude: Study design (narrative review)

Appendix D. List of Ongoing Trials

Trial Name ClinicalTrials.gov Identifier	Status	Notes
Topical Oxygen Therapy for Diabetic Wounds (TOFU) NCT02313428	Recruiting	Device: Topical oxygen chamber for extremities Completion Date: June 2018
Can Topical Oxygen Therapy (Natrox™) Improve Wound Healing in Diabetic Foot Ulcers? NCT02599805	Not yet open for recruitment	Device: Natrox Oxygen Delivery System (ODS) Completion Date: December 2016
Evaluation of Topical Wound Oxygen (two2) Therapy NCT00871312	Terminated	Device: Topical wound oxygen therapy Device: Topical wound oxygen placebo Completion Date: December 2009
Transdermal Continuous Oxygen Therapy for Infection Prophylaxis in High-Risk Patients Undergoing Colon Surgery NCT02617706	Study withdrawn prior to enrollment	Device: EPIFLO Completion Date: January 2019
Efficacy, Safety and Economic Benefits of Topical Wound Oxygen Therapy in the Treatment of Chronic Diabetic Foot Ulcers (TWO2DFU) NCT02326337	Recruiting	Device: TWO2 device Device: Placebo device Completion Date: July 2018

Appendix E. 2014 TOWT Dossier Review: List of Included/Excluded Studies

Citation	TOWT Device / Manufacturer	Inclusion / Exclusion Criteria	
		2014 Dossier Review	Current Report
Blackman et al. (2010)	AOTI devices	Included	Excluded: Included in CADTH (2012) systematic review
Brem and Tomic-Canic (2007)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (TOWT not discussed in article)*
Brimson and Nigam (2013)	*Not reported*	Included	Included
CADTH (2012)	AOTI devices, TWO2 from GWR Medical, Inc	Included	Included
Driver et al. (2013)	EPIFLO	Included	Included
ECRI Institute (2013)	*Not reported*	Included	*Not identified (not publically available)*
Eisenbud (2012)	*Not reported*	Excluded: Study design (narrative review)	Excluded: Study design (narrative review)
Feldmeier et al. (2005)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (published outside of search date range)*
Fries et al. (2005)	*Not reported*	Excluded: Study design (animal study)	*Not identified (published outside of search date range)*
Gordillo et al. (2008)	Device from GWR Medical, Inc.	Included	Excluded: Included in CADTH (2012) systematic review
Gordillo and Sen (2003)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (published outside of search date range)*
Gordillo and Sen (2009)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (published outside of search date range)*
Hayes Inc. (2002)	*Not reported*	Included	*Not identified (not publically available)*
Heng et al. (2000a)	*Not reported*	Included	Excluded: Included in Brimson et al. (2013) systematic review
Heng et al. (2000b))	*Not reported*	Included	*Not identified (published outside of search date range)*
Hunt, Ellison, and Sen (2004)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (published outside of search date range)*

Citation	TOWT Device / Manufacturer	Inclusion / Exclusion Criteria	
		2014 Dossier Review	Current Report
Ignacio, Pavot, Azer, and Wisotsky (1985)	*Not reported*	Included	*Not identified (published outside of search date range)*
Japour (2003)	*Not reported*	Excluded: Study design (case report)	*Not identified (published outside of search date range)*
Kalliainen et al. (2003)	Device from GWR Medical, Inc.	Included	Excluded: Included in Brimsom et al. (2013) systematic review
Leslie, Sapico, Ginunas, and Adkins (1988)	Topox (Topox Therapeutic Rentals, Inc.)	Included	*Not identified (published outside of search date range)*
Nie et al. (2010)	*Not reported*	Included	*Not identified (not published in English)*
Orsted et al. (2012)	*Not reported*	Excluded: Study design (guideline without supporting systematic review)	Included
Sen (2010)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (TOWT not discussed in article)*
Sen et al. (2002)	*Not reported*	Excluded: Study design (narrative review)	*Not identified (published outside of search date range)*
Sheikh et al. (2000)	*Not reported*	Exclude: Study design (animal study)	*Not identified (published outside of search date range)*
Tawfick and Sultan (2009)	AOTI Hyper-box	Included	Excluded: Included in CADTH (2012) systematic review
Tawfick and Sultan (2013)	AOTI Hyper-box	Included	Included
Woo et al. (2012)	EPIFLO	Included	Excluded: Study design (case series does not report on harms)

Abbreviations. CADTH: Canadian Agency for Drugs and Technologies in Health; TOWT: topical oxygen wound therapy.

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