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CASE REPORT

Daily Application of Transdermal Fentanyl Patches in Patients Receiving Hyperbaric Oxygen Therapy

Jayne Pawasauskas and George Perdrizet

ABSTRACT

Hyperbaric oxygen therapy (HBOT) is a treatment for a variety of conditions, particularly nonhealing wounds. The treatment requires the inhalation of pure oxygen in a sealed chamber that is pressurized to 1.5 to 3 times that of normal atmospheric pressure. HBOT safety protocols require all transdermal products to be removed prior to entrance into the hyperbaric chamber, and many institutional policies state that removed patches are not to be reapplied. Limited data are available regarding the use of transdermal fentanyl patches in patients undergoing HBOT. For such patients, the patch would need to be changed on a daily basis. Although the recommended dosing interval is 72 hours, many references discuss the use of 48-hour intervals in select patients, and no published reference recommends dosing intervals shorter than 48 hours. The authors evaluated the clinical safety and efficacy parameters for two patients receiving daily application of transdermal fentanyl while receiving HBOT. Patient 1 was a 47-year-old female with diabetes mellitus, sepsis, and left foot wound with toe necrosis. Complicating her management was the presence of chronic pain syndrome secondary to fibromyalgia. Patient 2 was a 70-year-old female with paralysis secondary to spinal fracture who presented with a stage IV sacral pressure ulcer, who was later diagnosed with osteomyelitis. Both patients were successfully managed with daily application of fentanyl transdermal patch.

KEYWORDS fentanyl, hyperbaric, oxygen, transdermal

INTRODUCTION

Hyperbaric oxygen therapy (HBOT) can pose challenges in pain management when a patient's drug regimen involves topical drug delivery. Safety protocols require that topically applied medications be removed from patients prior to entrance in the hyperbaric chamber, and many institutional policies state that removed patches are not to be reapplied. Ideally, a patient's analgesic regimen would be changed to oral or parenteral analgesics while HBOT is underway. However, in certain instances this is not feasible; therefore, clinicians must seek safe methods of providing adequate analgesia to support patient adherence to HBOT. Transdermal fentanyl has a specialized drug delivery mechanism and provides an advantage in terms of selecting favorable routes of administration while considering patient ease of use. Coupled with the favorable route of administration is the risk of patient harm due to various factors: use of a narcotic analgesic with potent activity, equianalgesic dosing ranges, clinician unfamiliarity with pharmacokinetics specific to this formulation, or patient uncertainty about dosing schedule or factors that may alter drug absorption. Although the recommended dosing interval is 72 hours, many references discuss the use of 48-hour intervals in select patients, and no published reference recommends dosing intervals shorter than 48 hours. This case series discusses the use of transdermal fentanyl, applied every 24 hours, in patients undergoing hyperbaric oxygen therapy for wound care.

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CASE 1

A 47-year-old female with diabetes mellitus presented to the hospital with a 1-week history of severe pain in left foot pain, accompanied by poor oral intake and vomiting. The patient demonstrated a long-standing history of peripheral arterial disease and ischemia of the left leg, complicated by a nonhealing diabetic ulcer of her left foot (Wagner grade 3). One week prior to admission, she noticed that her foot began to "peel" and the increasing pain was impairing ambulation. She was also experiencing severe nausea with vomiting, which led to poor oral intake. This resulted in difficulty controlling her blood glucose levels, and at this time she sought medical attention.

The patient's past medical history was significant for coronary artery disease, myocardial infarction, type I insulin-dependent diabetes mellitus for 30 years, peripheral vascular disease, hypertension, gastroesophageal reflux disease, fibromyalgia, rheumatoid arthritis, migraine headache, neuropathy, irritable bowel syndrome, hypothyroidism, dyslipidemia, and gingival and periodontal diseases. Her past surgical history included femoral to popliteal arterial bypass procedure of the left lower leg, multiple wound debridements, cholecystectomy, tubal ligation, and tonsillectomy.

Her medications prior to admission included fentanyl transdermal patch 50 μg every 72 hours, gabapentin 600 mg by mouth (PO) three times daily, hydromorphone 4 mg PO four times daily, ondansetron 4 mg PO every 6 hours as needed (PRN), gemfibrozil 600 mg PO twice daily, levothyroxine 125 μg PO daily, lansoprazole 30 mg PO twice daily, paroxetine 40 mg PO daily, metoprolol 25 mg PO twice daily, hydroxyzine 25 mg PO three times daily, diphenhydramine 25 mg PO every 6 hours PRN itch, glargine insulin 16 units at bedtime, lispro insulin 4 units before breakfast and 7 units before lunch and dinner, and one multivitamin tablet daily. She was allergic to vancomycin, esomeprazole, morphine, niacin, valsartan, and topical silver.

She was diagnosed with Wagner grade 3 ulceration of her left foot, peripheral arterial disease status post arterial bypass with ongoing left lower extremity ischemia, and poorly controlled diabetes mellitus. A surgical consult was obtained, as were consults for pain management, infectious disease, and wound care. The patient was admitted and treated with opioid analgesics, antiemetics, and antimicrobials. She was prescribed meropenem 500 mg intravenous (IV) every 6 hours, moist normal saline dressings every 12 hours, tight glucose control (levels <150 mg/dL), and hyperbaric oxygen therapy at 2.4 atmospheres absolute (ATA) 100% O_2 for 40 treatments. Her fentanyl patch was increased to 100 μg every 72 hours, and her hydromorphone was increased from four times daily to every 4 hours as needed.

HBOT was initiated on hospital day 6. By day 15, the patient had developed acute kidney injury secondary to antimicrobial regimen and did not receive HBOT for approximately 1 week. On hospital day 40, nursing staff discovered a used fentanyl patch in the patient's room, as the patient had been removing the patch herself and leaving it in her hospital room prior to transport to the scheduled HBOT. To address this situation, nursing staff began documenting the daily removal and disposal of the transdermal fentanyl (TDF) patch Mondays through Fridays. The TDF patch was then reapplied by nursing upon patient return from HBOT. Therefore, on day 41, the dosing interval was changed to daily, Mondays through Fridays. The patient was discharged on day 72. (Figure 1).

To consider any impact of the effects attributed to the change in dosing schedule, we monitored the patient for the safety and efficacy parameters outlined in Table 1. Prior to the dosing change, the patient was reporting pain scores on a 0 to 10 verbal rating scale of 6 to 10, she had been requiring breakthrough doses of hydromorphone approximately four times per day, and required tramadol sporadically. Her appetite was baseline, and she was not experiencing nausea, vomiting, or constipation. Her sleep patterns were also baseline. She was using diphenhydramine approximately once to twice daily as needed for itching.

Following the change to the daily dosing schedule, the patient continued to report pain scores ranging from 6 to 10 out of 10, her use of PRN hydromorphone and tramadol was unchanged, and she did not exhibit any notable changes in her appetite, sleep, or gastrointestinal symptoms. From a safety perspective, she had no changes in level of consciousness, drowsiness, or sedation. She did have one behavioral episode in which she became agitated and removed her central line. She did not experience respiratory depression, hypoxemia, or hypercarbia. She continued to use diphenhydramine once to twice daily for itching.

TABLE 1. Monitoring Considerations

Safety	Efficacy
Drowsiness, confusion, sedation	Pain intensity
Nausea, vomiting	Changes in mood or behavior
Respiratory depression	Changes in appetite, nausea
Constipation	Physiologic signs of acute pain/exacerbation
	Changes in sleep pattern

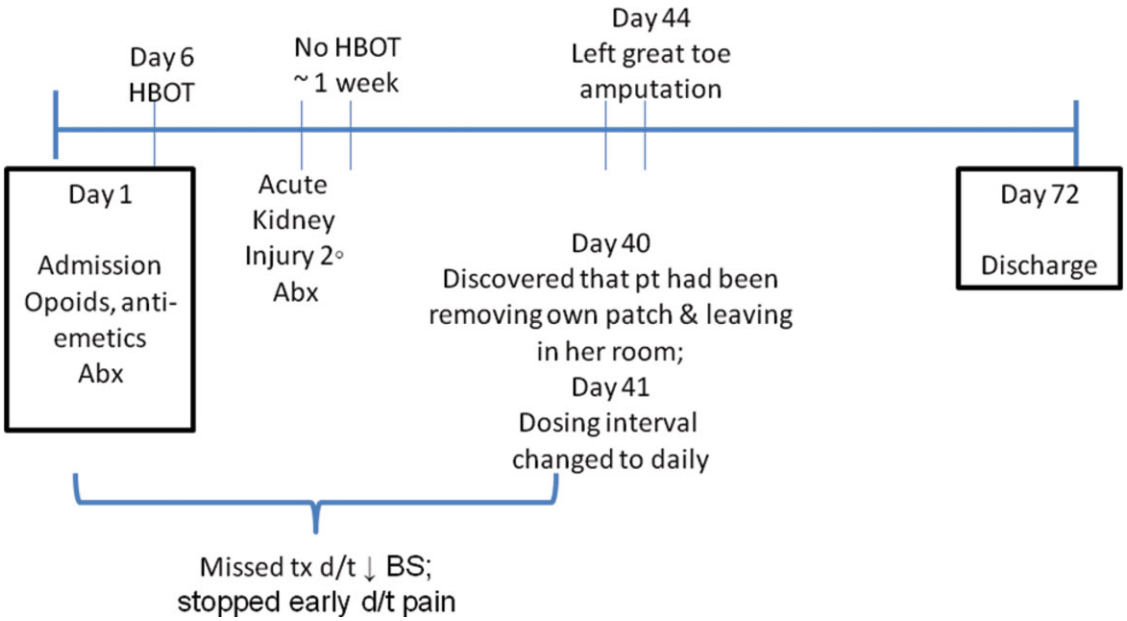

FIGURE 1. Hospital course: Case 1.

CASE 2

A 70-year-old female was admitted to the hospital for a stage IV sacral pressure ulcer complicated by osteomyelitis. She had a previous admission for spinal surgery for repair of vertebral fracture, with subsequent development of a stage II sacral pressure ulcer. The ulceration was noted to worsen during rehabilitation in an extended care facility. Past medical history included quadriplegia due to a C-5 spinal cord injury, bowel incontinence, chronic diarrhea secondary to dumping syndrome, long-standing *Clostridium difficile* colitis, type II insulin-dependent diabetes mellitus for 20 years, anemia, oxygen-dependent chronic obstructive pulmonary disease, gastroesophageal reflux disease, rheumatoid arthritis (steroid-dependent), congestive heart failure, history of gastrointestinal bleeding, small bowel obstruction, and recurrent urinary tract infections. The patient was bedridden.

She had documented allergies to codeine, aspirin, sulfa-containing drugs, cephalosporins, penicillin, erythromycin, metaproterenol, tetracycline, albuterol, zolpidem, fluticasone, fluoxetine, meperidine, ciprofloxacin, contrast dye, seafood, and tape.

Medications upon admission included prednisone 10 mg PO daily, quetiapine 25 mg PO at bedtime, montelukast 10 mg PO daily, vitamin D 5000 international units by mouth weekly, alprazolam 0.25 mg PO daily and twice daily PRN, sertraline 100 mg PO daily, metoprolol 12.5 mg PO twice daily, ipratropium 4 puffs inhaled every 6 hours, sucralfate 1 g PO before meals and at bedtime, insulin 70/30 34 units each morning + 30 units each evening.

She was diagnosed with a stage IV sacral decubitus ulcer, measuring 7 cm and extending to bone. Her chronic bowel incontinence complicated wound management. She had declined a diverting colostomy on several occasions. Multiple consultations were obtained to fashion a comprehensive plan of care, including surgical, infectious disease, nutrition, and wound care services. It was elected to débride and cover this large wound with a gluteal myocutaneous flap procedure. A bone biopsy for bacterial culture was obtained to guide antimicrobial therapy, which proved problematic due to the patient's multiple drug allergies. On hospital day 2, débridement, bone biopsy, and gluteal flap procedure were performed without complication. On hospital day 3, the following regimen was started: TDF patch 12.5 μg, oxycodone/acetaminophen 5/325 mg PO 2 tablets every 4 hours PRN, and ondansetron 4 mg IV every 6 hours PRN for nausea/vomiting. The patient had begun to exhibit systemic signs of infection (white blood cell count = 15.7, temperature = 38.7°C); therefore, acetaminophen 650 mg PO every 6 hours PRN fever was added. On postoperative day 5, the gluteal flap appeared ischemic. Wound care consultation recommended that she undergo daily HBOT for 10 treatments for flap preservation. She was transferred to the intensive care unit to undergo desensitization for meropenem, due to documented anaphylaxis to penicilliins and cephalosporins. HBOT was begun on

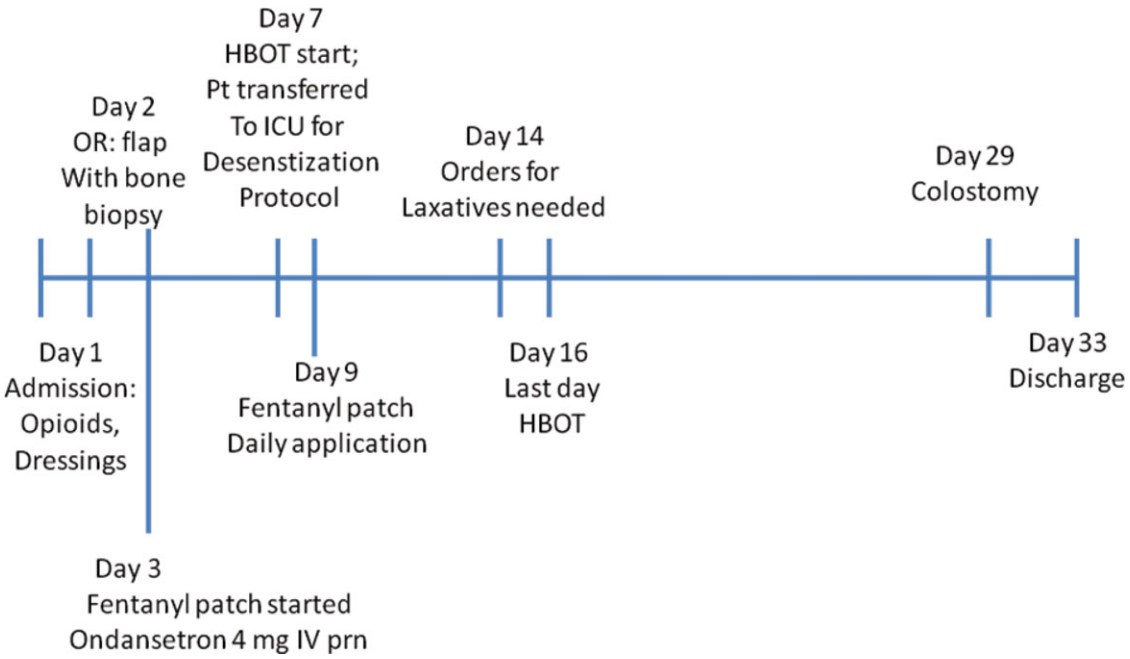

FIGURE 2. Hospital course: Case 2.

hospital day 7. By hospital day 9, she was switched to a daily dosing schedule for the TDF patch. By day 14, she was experiencing constipation, requiring twice daily doses of docusate and polyethylene glycol daily. On day 16, she received her final session of HBOT, her dosing schedule of transdermal fentanyl was switched back to every 72 hours, and her laxatives were discontinued. Over the next few days, her diarrhea returned, further complicating wound healing, and finally on day 29 she underwent successful creation of a diverting colostomy (Figure 2).

Prior to the change in her TDF patch dosing schedule, the patient reported pain scores averaging 8 out of 10. She used the PRN oxycodone/acetaminophen approximately once to twice daily and was exhibiting normal appetite and sleep patterns, with no complaints related to nausea, vomiting, or constipation.

Following the change in dosing schedule, her pain scores were noted to be 0 at times, and 10 at other times. Her use of PRN oxycodone/acetaminophen increased to three to four times daily. She did not exhibit any changes to her appetite or sleep patterns, nor report nausea or vomiting. She did develop constipation approximately 5 days following the dosing interval change. She had no documented changes in level of consciousness, drowsiness, or sedation. She did not experience respiratory depression and did not require naloxone administration. She did increase use of PRN alprazolam from once daily prior to dosing interval change to twice daily afterwards. This was attributed to anxiety about the transport procedure to and from the hyperbaric facility.

DISCUSSION

Hyperbaric oxygen therapy (HBOT) is a treatment for a variety of conditions, including carbon monoxide poisoning, gas gangrene, nonhealing wounds related to diabetes mellitus, radiation tissue injury, chronic osteomyelitis, decompression sickness, and arterial gas embolism.[1–6] HBOT requires the inhalation of pure oxygen in a sealed chamber that is pressurized to 1.5 to 3 times that of normal atmospheric pressure. Duration of each treatment ranges from 60 to 120 minutes. Once or twice a day treatments are administered for a duration of 30 to 60 total treatments. Patients who are prescribed HBOT often require special considerations for their comorbid conditions, including pain management. Special consideration arises when the drug or route of administration has the potential to be altered by the HBOT in a manner that could either increase the risk for toxicity or compromise efficacy.

Transdermal fentanyl delivery systems have provided a mechanism to deliver analgesia for patients who, for one reason or another, require or prefer nonoral, injectable, or rectal routes of administration. Transdermal delivery causes the drug to bypass first-pass hepatic extraction, therefore allowing improved bioavailability. This route of delivery has

particular advantages for patients with chronic disease or illness, for whom oral routes of administration may be compromised during times of disease exacerbation, and for those who receive most of their care at home or in settings where injectable routes of administration are less practical. Additionally, many drugs that are formulated as transdermal medications have extended dosing intervals due to the delivery mechanism built into the transdermal patch system. This is a potential advantage for patients who may have difficulty remembering to take medications, difficulty with fine motor skills, or those with compliance concerns. In the currently available product, the μ-opioid agonist fentanyl is incorporated into an inert matrix that releases drug at a nearly constant rate.[7] Release of drug is determined by the concentration gradient between the matrix and the skin, where fentanyl travels toward the area of lower concentration (i.e., passive delivery).[8] Following initial application, a depot of fentanyl forms in the upper layers of skin, after which the drug releases into systemic circulation. Serum concentrations will increase initially, then reach a relatively constant level, usually between 12 and 24 hours. When used continuously, serum levels will increase with the first few patch applications and reach a steady-state level by the end of the third 72-hour dosing interval. This level is maintained as long as the patient continues to apply the same patch strength, and in the same clinical conditions and dosing interval. If a patch is removed, serum levels will gradually decline, demonstrating a half-life of 20 to 27 hours.[8]

HBOT policy mandates that all transdermal products be removed prior to entrance into the hyperbaric chamber. From a safety perspective, a primary concern focuses on the risk of fire. In general, transdermal drug patches are not believed to contribute significantly to the risk of fire during HBOT,[9] and the ingredients in the transdermal fentanyl patch (TDF) are considered nonignitable.[8] Safety standards that determine how HBOT is delivered to humans have a long track record of being very effective. There is one example of a clinical hyperbaric chamber in the United States catching fire during use and this was the result of gross negligence by the facility staff.[10]

A second safety concern relates to the potential for altered drug effect during HBOT. The direct effect of pressure changes on transdermal fentanyl was demonstrated by in vitro testing. Release of fentanyl from the patch was significantly increased when the patch was placed in hyperbaric conditions at room temperature 2.5 ATA for 90 minutes[11] and when compared with untreated patches at increased temperatures.[12] The variables of oxygen and pressure have not been studied independently. It is also possible that in vivo physiologic alterations in skin perfusion due to HBOT-associated vasoconstriction may affect transdermal drug absorption, although this has never been directly tested.

There are possible interactions between opioids and HBOT that may, in theory, cause concerns for drug safety or efficacy. Respiratory rate and tidal volume are regulated by systems in the ventrolateral medulla. These create a respiratory rhythm that is mediated by afferent input reflecting the partial pressure of arterial O_2.[13] Opioids depress all phases of respiration and produce irregular breathing through effects on μ and δ receptors, with resulting effects on rhythm believed to be greater than those on tidal volume.[14] Opioids decrease ventilatory response to increased CO_2 by decreasing excitability of brainstem neurons.[13] When respiration is decreased, there is an increase in alveolar and arterial pCO_2. Oxygen therapy may contribute to a further depression of ventilation, especially in a subset of chronic obstructive pulmonary disease (COPD) patients whose ventilator drive is hypoxemia. Removal of this hypoxic ventilator drive potentially could cause additive effects in the setting of concurrent opioid administration.[15] This additive depression of ventilation may contribute to a great enough rise in arterial pCO_2 and result in apnea. Fentanyl is one of the most potent opioid analgesics available for clinical use; therefore, patient monitoring for adverse effects should be heightened when used in conjunction with HBOT. Although these pharmacologic principles of both opioid analgesics and HBOT are hypothesized and speculative, there is very little published on clinical outcomes and adverse events for patients who receive these treatments concurrently.

At our institution, hospital policy states that removed patches are not to be reapplied to the patient. Considering that patients will receive HBOT on a daily basis (either continuously or on a "Monday through Friday" schedule), this would require removal of the TDF prior to HBOT and application of a new patch following each treatment. Since the typical dosing regimen for TDF is every 72 hours, a change to a 24-hour dosing interval would require careful consideration. Review of literature that addresses daily dosing of TDF in any clinical scenario yielded few results. One observational study found a small percentage of patients who reported daily use of TDF. These patients reported mild adverse reactions of drowsiness, constipation, and nausea, although these effects did not lead to drug discontinuation.[16] A survey of physicians treating cancer patients reported 5% of their patients used alternate dosing schedules, including daily application.[17] The use of more frequent dosing of TDF is not recommended by

TABLE 2. Dosing Schedules

	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su
TDF patch	X	x	x	X	x		X	x	x	X	x	x	X		x	X	x	x	X		
HBOT session	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		

Note. "x" indicates additional applications due to HBOT.

national guidelines or consensus statements.[18] Although it is acknowledged that some patients may require application every 48 hours, it's generally recommended never to reapply a patch at shorter intervals.[18,19]

Thus, per current hospital policy, the daily removal, disposal, and application of a new TDF patch would be required for all patients receiving HBOT. The amount of time from patch removal to new patch application is estimated to be 3 hours. Based on this scenario, we considered two aspects of pharmacotherapy related to our management of the patient's analgesic coverage if the TDF patch therapy is continued:

1. Would interruption in a drug that's provided by 24-hour continuous delivery cause loss of analgesia?
2. Would more frequent dosing lead to drug accumulation and potential toxicity?

Since routine monitoring of fentanyl levels is not readily available in our hospital, nor is it well correlated with efficacy or toxicity, we examined clinical parameters pertinent to safety and efficacy in two of our patients to answer these questions (Table 1). From the safety perspective, we monitored the patient for emergence of opioid-related adverse events such as drowsiness, confusion, sedation, nausea, vomiting, constipation, or respiratory depression. From the efficacy perspective, we monitored the patient for any signs of loss of analgesic efficacy, including pain ratings on appropriate intensity scales, changes in mood, behavior, sleep patterns or appetite, or physiologic signs of acute pain or exacerbation of pain symptoms.

The patients reviewed in this report were using TDF for pain related to chronic nonhealing wounds. The first patient had attempted to find pain relief with various opioid and nonopioid analgesics, over several years, and found that the only drug that offered sufficient relief was TDF. Although we attempted to switch her to an alternate opioid for the duration of her HBOT, she adamantly refused. Therefore, the decision was made to continue with her existing pain regimen. The second patient had started using TDF for a relatively short time before she started receiving HBOT. In this case, the HBOT was considered an emergent situation, and since the patient was only expected to receive a short course of treatments, it was decided that she would continue the TDF.

Both patients tolerated the switch to daily dosing of TDF well. The first patient had no significant adverse effects, or loss of efficacy. The second patient experienced constipation, which was interesting considering her history of chronic diarrhea. The constipation could have been due to the addition of oxycodone/acetaminophen; however, since it developed approximately 5 days after the change in TDF dosing interval, it is difficult to determine if one of these factors was the sole cause. Nonetheless, the patient did not require discontinuation of either medication, and upon discontinuation of TDF, the symptoms returned to baseline. This finding is consistent with published literature that noted that daily use of TDF was associated with mild adverse events such as drowsiness, constipation, and nausea, although these did not lead to drug discontinuation.[16]

A consideration that often challenges the hospital pharmacist is the cost associated with an unusual regimen. If we examine the case of the first patient, her dosing interval increased from every 3 days to every day (5 days per week) for 8 weeks. The cost for a 100 μg fentanyl patch is approximately $9.81; thus, during a 3-week time period, the cost would increase from $68.67 (72-hour application) to $147.15 (daily application) (Table 2). Although the amount is more than doubled for a 3-week period, the cost increase is reasonable and therefore would have a small role in determination of appropriateness of such a regimen.

In summary, daily dosing of transdermal fentanyl is not recommended in guidelines for pain management, nor by most pain management experts, and such regimens are associated with increased costs when compared with standard dosing. However, we present our limited experience of two patients undergoing concurrent HBOT and TDF therapy in which no compromise of efficacy or safety was observed. Further study will require pharmacokinetic analysis and increased

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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