

The Diabetic Foot–Pain–Depression Cycle A Multidisciplinary Cohort Study

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Background: More than 86,000 Americans with type 2 diabetes mellitus (T2DM) undergo nontraumatic lower-extremity amputations annually. The opioid-prescribing practice of podiatric surgeons remains understudied. We hypothesized that patients with T2DM who undergo any forefoot amputation while using antidepressant medication will have reduced odds of using opioids beyond 7 days.

Methods: We completed a retrospective cohort study examining patients with T2DM who underwent forefoot amputation (toe, ray, transmetatarsal). Data were restricted to patients with a hemoglobin A_{1c} level less than 8.0% and an ankle-brachial index greater than 0.8. The outcome was use of postoperative opioids beyond 7 days. Patients received an initial opioid prescription of 7 days or less. We developed simple logistic regression models to identify the odds of a patient using opioids beyond 7 days by patient variables: age, race, sex, amputation level, body mass index, antidepressant medication use, and marital status. Variables with $P < .1$ in the univariate analysis were included in the multiple logistic regression model.

Results: Fifty patients met the inclusion criteria. Antidepressant use and marital status were the only statistically significant variables. Adjusting for marital status, patients with antidepressant use had decreased odds (odds ratio, 0.018; 95% confidence interval, 0.001–0.229; $P = .002$) of using opioids beyond 7 days after a diabetic forefoot amputation.

Conclusions: Patients with T2DM who used antidepressants had significantly reduced odds of using opioids beyond 1 week after forefoot amputations compared with those without antidepressant use. We proposed an underlying diabetic foot–pain–depression cycle. To break the cycle, podiatric surgeons should screen this population for depression preoperatively and postoperatively and not hesitate to make a mental health referral if warranted. Nontraumatic amputations can be a traumatic experience for patients; psychiatrists and other mental health providers should be members of limb preservation teams. (J Am Podiatr Med Assoc 113(3), 2023)

The current opioid epidemic in the United States is a severe public health crisis that has substantially worsened during the COVID-19 pandemic.¹ In 2020,

Larach et al² found that prescription opioids after surgery is one of the most common paths for opioid addiction among opioid-naive patients and a leading cause of the opioid epidemic. In 2021, Brooks et al³ were the first to demonstrate that

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significant opioid-prescribing variation exists on the national level among podiatric surgeons. In 2022, Brooks et al⁴ were the first to describe the effect of cognitive bias on postoperative opioid-prescribing practice; the so-called Saint Leo effect describes the following phenomenon: in the absence of procedure-specific guidelines for postoperative opioid prescribing, podiatric surgeons, more often than not, are unaware of how their own opioid-prescribing habit measures up to that of other podiatric surgeons.⁴ The Saint Leo effect can likely be extrapolated to all surgeons.⁴ Therefore, guidelines, protocols, and further understanding of factors contributing to excessive postoperative opioid prescribing may be warranted in surgery.⁴

More than 86,000 patients annually undergo nontraumatic lower-extremity amputations in the United States attributable to diabetes mellitus.⁵ Podiatric physicians and surgeons perform many nontraumatic lower-extremity amputations, particularly toe, ray, and transmetatarsal amputations.⁶ Many of these patients present with altered epicritic and protopathic sensation and other comorbidities, including depression.⁷ A significant association exists between depression and diabetes-related complications^{7,8}; however, the impact of antidepressant medication use on postoperative opioid-prescribing practice has not been well-studied in this population. As a result, the balance between effective pain management and prevention of opioid dependence can be a difficult ethical dilemma in this patient population.^{3,9} Given that depression is associated with an increase in opioid use,¹⁰ it is important for clinicians to recognize that the risk of depression is elevated with chronic illnesses.

Further understanding the postoperative opioid-prescribing habits of podiatric physicians and surgeons treating patients with type 2 diabetes mellitus (T2DM) undergoing forefoot amputation may be useful in refining prescribing protocols to effectively control postoperative pain and minimize unused opioid distribution after diabetic forefoot amputations.³ We hypothesize that patients with T2DM who undergo any forefoot amputation while using antidepressant medication have reduced odds of using opioids beyond 7 days. We also aimed to determine the cause of such a phenomenon if we reject the null hypothesis and whether other associations exist between the patient characteristics and opioid use beyond 7 days, which is the Centers for Disease Control and Prevention's current recommendation for acute pain.¹¹

Methods

Research Design

We received institutional review board expedited approval for a retrospective cohort study design. The medical records of patients who underwent forefoot amputations were reviewed. Forefoot amputations were defined as toe amputation (partial or total), ray resection (partial or total), or transmetatarsal amputation. Patient characteristics were also recorded, including age, race, sex, type of procedure, body mass index, use of an antidepressant medication, and marital status. All of the patients received care at a large clinic in the Southern United States. The records that were reviewed were from 2017 to 2021. Patients without T2DM who had dehiscence after surgery, patients with a hemoglobin A_{1c} level greater than 8.0% or an ankle-brachial index less than 0.8, and patients who did not remain healed at the 2-month postoperative visit were excluded.

Outcome of Interest

The outcome variable of interest was opioid dosage units, which were dichotomized (made into two options) by the Centers for Disease Control and Prevention's recommendation of no more than 7 days of opioid prescribing for acute pain.¹¹ Because no more than 7 days of opioids were prescribed postoperatively at the time of surgery, using more than 7 days of opioids served as a proxy for an additional opioid prescription at the 1-week postoperative visit. Effectively, patients fell into one of two categories: "used 7 days of opioids or less" or "used more than 7 days of opioids" after forefoot amputation.

Statistical Analysis

We developed simple logistic regression models to identify the odds of a patient using postoperative opioids beyond 7 days by patient variables. The explanatory variables were patient-focused and included age, race, sex, level of amputation, body mass index, use of an antidepressant medication, and marital status. To adjust for confounding, we developed a multiple logistic regression model that included explanatory variables that achieved $P < .1$ with simple logistic regression. We analyzed the data with a statistical software program (Stata Statistical Software: Release 15.1; StataCorp LLC, College Station, Texas). In the multivariate model, statistical significance was predefined at $P < .05$.

Results

Descriptive Results

Fifty patients met the inclusion criteria. Patient demographics appear in Table 1. Most patients (n = 26) did not use opioids beyond 7 days; however, 24 did use postoperative opioids beyond 7 days.

Statistical Analysis Results

Use of an antidepressant medication and marital status were the only statistically significant variables in the univariate analysis. In the adjusted model, patients who used an antidepressant medication had decreased odds (odds ratio [OR], 0.018; 95% CI, 0.001–0.229; $P = .002$) of using postoperative opioids beyond 7 days after their diabetic forefoot amputation. Patients who were married had decreased odds (OR, 0.052; 95% CI, 0.005–0.526; $P = .012$) of using postoperative opioids beyond 7 days after their diabetic forefoot amputation.

Discussion

Summary of Findings

In this retrospective cohort study of 50 patients with T2DM who underwent forefoot amputation, married patients had reduced odds (OR, 0.052; 95% CI, 0.005–0.526; $P = .012$) of using opioids beyond 7 days postoperatively compared with unmarried patients (ie, single, widowed). An even stronger association (OR,

0.018; 95% CI, 0.001–0.229; $P = .002$) existed with patients treated with an antidepressant medication. Given the previously mentioned findings, we sought to understand the underlying factor or multifactorial explanation of these associations in this patient population commonly seen by podiatric physicians and surgeons; we postulated that a diabetic foot–pain–depression cycle exists and ultimately explains this phenomenon as to why more than 7 days of postoperative opioids are needed in patients with diabetes mellitus who lack severe and moderate peripheral vascular disease.

The Diabetic Foot–Pain–Depression Cycle

The diabetic patient population frequently presents with altered epicritic and protopathic sensation via peripheral neuropathy.¹² Amid the opioid crisis, opioid prescriptions for postoperative pain management of diabetic patients should be tailored to the specific needs of the individual patient.³ It is known that among patients with T2DM, depression is underdiagnosed.^{13,14} Addressing mental health, including depression, and the social determinants of health is key for postoperative success in both pain and compliance with the postoperative plan.^{12,15,16} We believe that podiatric physicians and surgeons stand to benefit by familiarizing themselves with the outer and inner portions of the diabetic foot–pain–depression cycle (Fig. 1).

The outer portion of the diabetic foot–pain–depression cycle includes what is more easily observed and readily tested for. Depression can lead to diabetic foot complications by weight gain, lack of self-care, and poor dietary choices (which may impact fructosamine, hemoglobin A_{1c}, and blood sugar levels).^{13,14,16} Wagner et al¹⁷ in 2010 noted that diabetic patients with depression (n = 153) may be less compliant with blood sugar control, self-care practices, health-care appointments, and dietary restrictions.¹⁸ In 2015, a meta-analysis of 88 prospective cohort studies totaling approximately 300,000 new cases of T2DM showed a clear dose-response with exposure to cigarette smoke over time (ie, pack-years)¹⁹; the same meta-analysis further estimated that at least 25 million cases of T2DM could be directly attributable to cigarette smoking alone.¹⁹

Despite the diabetic foot being viewed as insensate, both peripheral artery disease and amputation (s) have the potential to be painful.^{15,18,20,21} Nerve pain can impact the quality of a patient's sleep and result in the patient desiring additional postoperative opioids.²² Long-term prescription opioid use

Table 1. Demographic Characteristics of the 50 Study Patients

Characteristic	Patients (No.)
Level of amputation	
Toe (partial or total)	25
Ray (partial or total)	18
Transmetatarsal	7
Race	
Black	30
White	20
Body mass index	
Normal weight	7
Overweight	18
Obese	25
Marital status	
Married	32
Not married	18
Antidepressant use	
Yes	19
No	31

The Diabetic Foot – Pain – Depression Cycle

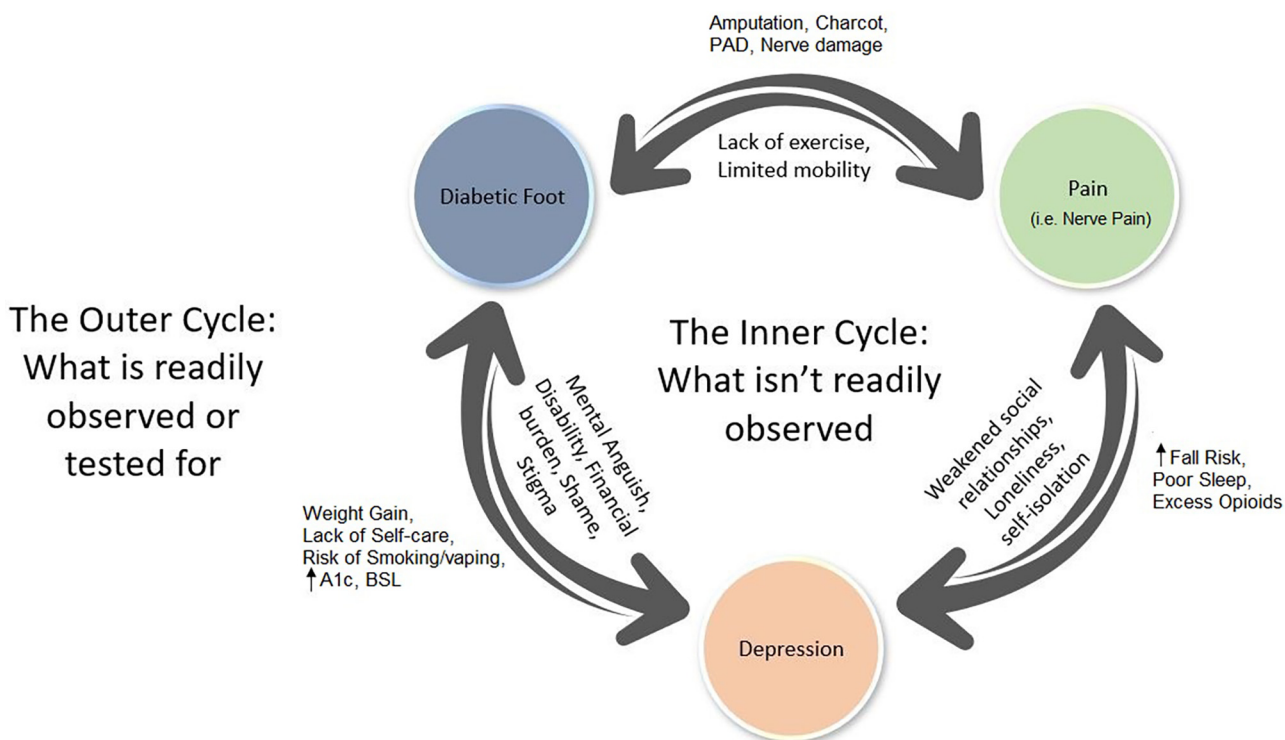


Figure 1. The diabetic foot–pain–depression cycle. BSL, blood sugar level; PAD, peripheral artery disease.

not only increases the risk of dependence but is also associated with new onset and recurrence of depression, which is highly prevalent among diabetic patients with peripheral neuropathy.²³ In addition, painful peripheral neuropathy has been recognized as a stronger predictor of depression compared with other complications and comorbidities related to diabetes.²⁴ Pain can also lead to limitation of physical activity, which contributes to muscle weakness and an increased risk of falls.²⁵ Unsteadiness is a strong predictor of depression that is often underreported by diabetic patients due to their association of it to the aging process rather than to peripheral neuropathy.²⁶⁻²⁸ For the diabetic patient with peripheral neuropathy, diminished afferent input from the lower extremities causes a slower reaction time and decreased proprioception.²⁶⁻²⁸ During gait and posture, this results in balance problems characterized by an increased amount of sway and impaired control of the knee and ankle.^{29,30} This instability results in a fear of falling that can restrict one's capacity to engage in daily activities and self-care, which in turn can diminish their self-worth.²⁷

The inner portion of the diabetic foot–pain–depression cycle contains what is not easily observed or tested for. The prevalence of depression is nearly twice as much in patients with T2DM.³¹ Depression can cause diabetic patients to have increased sensitivity to pain^{18,32}; consequently, diabetic patients with depression may find augmented relief from postoperative pain while taking opioids.³² Augmented relief can come in many forms; smoking cessation rates remain consistently lower for depressed smokers than for smokers in the general population.³³ Patients with depressive symptoms may experience self-isolation, loneliness, and weakened social relationships and, ultimately, may desire additional medication for their pain^{18,34}; positive and loving connections with others can help patients cope with stress and trauma and may be beneficial when dealing with a loss of part of the foot. Furthermore, Selvarajah et al³⁵ in 2014 (n = 142) reported that diabetic patients with painful neuropathy who have less social connection (young, single, and unemployed) experience more depressive symptoms and emotional distress. Patients with T2DM may also experience stigma and shame

associated with complications and amputations³⁶; there may also be financial burden associated with surgery, disability, and potential loss of income, which can impact depression.³⁷ Patients with foot pain may self-limit their mobility and experience a lack of exercise, which affects insulin tolerance and ultimately the diabetic foot.³⁸

Screening for Depression

Given that depression remains underdiagnosed and patients with T2DM are commonly seen by podiatric physicians and surgeons,¹³ podiatric physicians and surgeons should screen for depression preoperatively via the Patient Health Questionnaire (PHQ)-2 and the PHQ-9.³⁹ The purpose of the PHQ-2 is to screen for depression in a “first-step” approach.³⁹ If the patient scores 3 or more, then the podiatric physician should administer the PHQ-9. On the PHQ-9, scores of at least 5 indicate mild depression, 10 for moderate depression, 15 for moderate-severe depression, and 20 for severe depression.³⁹ Podiatric physicians and surgeons should make the appropriate mental health referral if there is a concern for depression.³⁹ Podiatric physicians and surgeons should consider bringing in psychiatrists and other mental health providers as members of multidisciplinary limb salvage teams.

Treatment of depression, when warranted, can result in decreased postoperative opioid use in diabetic patients. The initial treatment of a depressive disorder usually involves modalities such as psychotherapy or pharmacotherapy, either alone or in combination.⁴⁰ Antidepressant agents include a variety of different medications approved to treat depressive disorders.⁴⁰ Some select groups of antidepressants are considered first-line treatments for certain pain disorders.⁴¹ Of these, serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) hold analgesic properties largely due to their effect on norepinephrine.^{42,43} The SNRIs and TCAs deliver pain relief independent of their antidepressant effects, as analgesia is seen even in nondepressed patients. Furthermore, treatment of an underlying depressive disorder may also contribute to pain relief for some patients, irrespective of the medication’s analgesic quality. We also recommend that podiatric surgeons screen for depression postoperatively if postoperative opioid use extends beyond 7 days and other common etiologies have been ruled out, such as peripheral vascular disease.

The SNRIs and TCAs for multimodal pain management have effectively treated depression and addressed painful neuropathy.^{12,15} Among the

SNRIs, duloxetine has specific US Food and Drug Administration (FDA) indications for diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, and the most evidence to support its use for analgesic effect.^{44,45} Although TCAs are a central component of treatment for various chronic pain conditions,⁴¹ none carry an FDA-labeled indication for pain management. They, however, are routinely used and remain a viable off-label option.⁴¹ Because the antidepressant and analgesic effects of SNRIs and TCAs may take 2 to 4 weeks to manifest, multimodal postoperative pain management should involve a psychiatric consult or another mental health referral, ideally before the operation.^{12,15} The SNRIs and TCAs for multimodal pain management have effectively treated depression and addressed painful neuropathy.^{12,15} In addition, psychologic treatments such as cognitive behavioral therapy are widely used and have evidence supporting their application for patients with chronic pain, diabetic peripheral neuropathy, and depressive symptoms.^{12,22}

Screening for depression has several practice implications for the podiatric physician and surgeon. Screening for depression, along with documenting a follow-up plan, is a “preventative care and screening measure” for the Merit-based Incentive Payment System program (measure #134).⁴⁶ A referral to a mental health specialist, such as a psychiatrist or a clinical psychologist, fulfills the follow-up plan requirement and should be documented in the note.⁴⁶ Of note, this quality measure aligns with clinical guideline recommendations as well as the Healthy People 2020 recommendation for routine mental health screening.^{46,47} Although podiatric physicians should focus on screening preoperatively to avoid a delay in care, we also recommend that podiatric surgeons consider screening for depression postoperatively if postoperative opioid use extends beyond 7 days and other common etiologies have been ruled out, even if the patient screened negative preoperatively.

Marital Status as a Proxy for Enduring Connection

Marriage in this study was protective against prolonged pain and, therefore, opioid use; we view this variable as a proxy for enduring connection, social support, and possibly happiness. Patients with loneliness and emotional distress may, indeed, use more medication because their pain is more severe due to their psychosocial predicament.^{35,48} In primates, there is an association between brain size and social

group size.⁴⁹ Humans are inherently social creatures and require connection for fulfillment.^{50,51} Acclaimed connection researcher Brené Brown notes that “we are hardwired to connect with others, it’s what gives purpose and meaning to our lives, and without it there is suffering.”⁵² Being isolated from one’s tribe, especially tens of thousands of years ago, meant certain doom. Stress hormones, perhaps as an evolutionary advantage, could be protective against going it alone and allowed individuals to return to their tribe.^{50,53,54} Society in the past 200 years has drastically changed compared with the previous 200,000 years.⁵⁵ However, relationships remain important for our ability to survive and thrive. Despite being in the information age that is the 21st century, mere access and the ease of communication does not fulfill our need for meaningful and genuine connection.^{53,54,56} Social media is not a substitute for an actual friendship; avoiding social media when in distress or pain may even be beneficial because its use is associated with depressive symptoms.⁵⁷ The present study demonstrates that patients with some sort of support system, even if it is only a spouse, fare better in terms of postoperative pain compared with those without one. Happy people are noted to have more meaningful and long-lasting relationships compared with unhappy people, which has led psychologists and social scientists to note that human connection is the single biggest predictor of happiness and well-being.^{58,59}

Antidepressants Can Be Protective

Diabetic patients may be taking TCAs or opioids at baseline to treat their neuropathy.⁶⁰ A retrospective cohort study by Fan et al⁶¹ in 2021 (n = 3,495) examining the first-line treatments for diabetic neuropathy reported that 43.8% of their cohort was prescribed opioids despite the ongoing opioid pandemic. Postoperatively, diabetic patients have been observed to have increased opioid use after being surgically treated for ankle fractures.⁶² The present study identified use of an antidepressant as a factor that was associated with significantly reduced odds of using postoperative opioids beyond 7 days after any diabetic forefoot amputation. However, the current literature regarding the concurrent use of antidepressants and opioids is limited. A retrospective cohort study by Scherrer et al⁶³ in 2018 (n = 2,821) observed increased cessation of opioid use in patients with newly diagnosed depression who adhere to taking antidepressants as a part of their treatment for noncancer, non-human immunodeficiency virus pain. Further research, including longitudinal studies, is needed to better understand how

antidepressant use may affect opioid use in specific populations.

How to Break the Cycle: Adequately Treat Painful Peripheral Neuropathy

Every podiatric physician should use their clinical judgment to assess whether their patient’s postoperative pain stems from painful peripheral neuropathy. Conventionally, painful peripheral neuropathy in the diabetic patient population has been managed via oral or topical medications⁶⁴; these medication include gabapentin and amitriptyline for first-line therapy, as well as venlafaxine, lidocaine patches, and capsaicin cream for second-line therapy.⁶⁵ Gabapentin has been one of the most common oral medications prescribed for the treatment of painful peripheral neuropathy, but it is not without adverse effects.⁶⁴ In a Cochrane systematic review of the effects of gabapentin for chronic neuropathic pain in adults, one in ten patients (n = 5,914) experienced dizziness, sleepiness, peripheral edema, and gait disturbances.⁶⁶ Similarly, pregabalin has adverse effects of increased dizziness, blurred vision, and headaches with increased dosage.⁶⁷ In patients with a history of substance use disorder, ideally gabapentinoids (notably pregabalin) should be avoided.⁶⁸

Alternatively, other topical medications, such as capsaicin cream, may lessen the concern of drug-drug interaction for neuropathic analgesia.⁶⁹ However, these medications may require multiple applications daily and can result in skin irritation for patients with sensitive skin.⁶⁹ One study evaluated the effectiveness of a 5% lidocaine patch for diabetic polyneuropathy and demonstrated significant pain reduction and improved quality of life⁷⁰; of note, two-thirds of the patients had at least a mean 30% reduction in pain.⁷¹ Lidocaine use is not without risks; the parenteral form of lidocaine is the best-known source of lidocaine poisoning.⁷¹ In a case series over a 7-year period, 30 cases of acute lidocaine toxicity (mean ± SD patient age, 21.83 ± 6.57 years) occurred with either 6.5% lidocaine spray or 2% topical formulations of lidocaine.⁷¹ The ideal approach with managing your patient’s pain is to customize the pain management plan by taking a “patient-centric and procedure-focused” approach.

Limitations

The study’s sample (n = 50) is relatively small and may not entirely reflect the increasingly diverse and large population of Americans with T2DM who

undergo forefoot amputations. The explanatory variable “marriage” is also very broad; it remains unknown the impact of a happy marriage versus an unhappy one in this patient population or if just having some form of a social support system is protective in and of itself.

Conclusions

Patients with T2DM who used antidepressant drugs had significantly reduced odds of using postoperative opioids beyond 1 week after forefoot amputations compared with those who did not take antidepressants. We proposed an underlying and novel diabetic foot–pain–depression cycle. Considering the significant associations among diabetic foot complications, pain, and depression, it is imperative that podiatric physicians and surgeons pay attention to the clinical characteristics of coexisting depression and diabetes during their examination. To break the diabetic foot–pain–depression cycle, podiatric physicians and surgeons should screen this patient population for depression and not hesitate to make a mental health referral if warranted. Nontraumatic amputations can be a traumatic experience for patients; psychiatrists and other mental health providers should be considered members of limb salvage teams. Future research is warranted to understand the impact of the diabetic foot–pain–depression cycle.

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Note: The first author was inspired to undertake this project after reading about the life of Saint Mariam Baouardy; consequently, he prefers to refer to this causal pathway as the Saint Mariam Baouardy Cycle.

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