Gastroenterology 2022;163:403–410

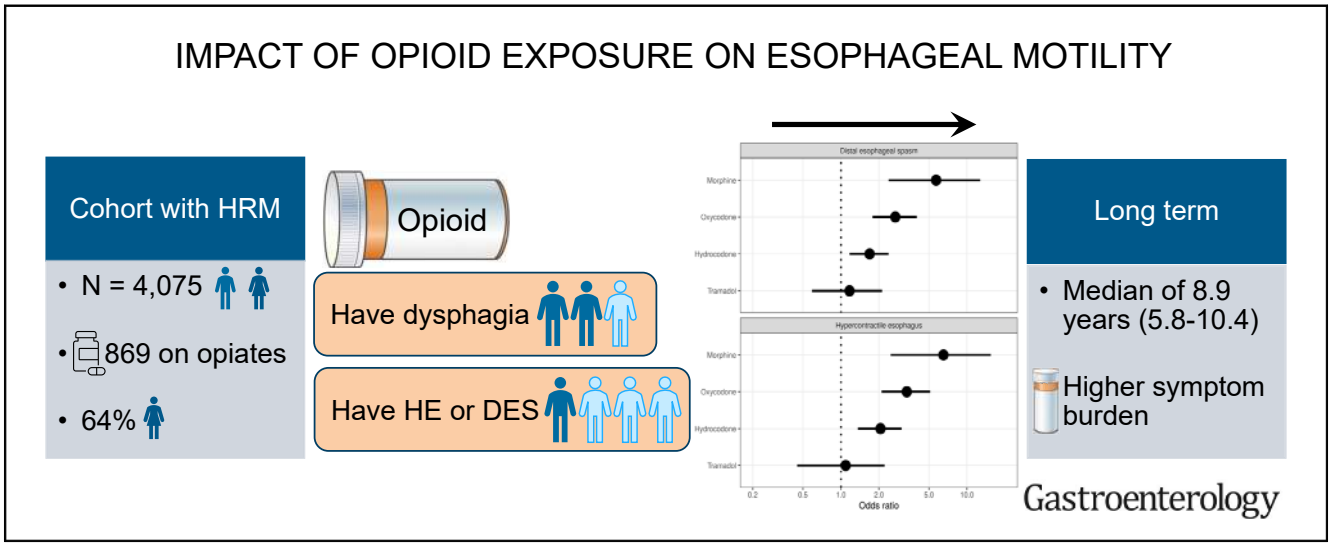
ESOPHAGUS

Opioid Exposure Differentially Impacts Esophageal Body Contraction Over the Lower Esophageal Sphincter

Dhyanesh A. Patel,[1] James Goss,[2] Muhammad Hayat,[3] Claudio Tombazzi,[3] Rishi D. Naik,[1] James C. Slaughter,[4] Muhammad Aslam,[1] Shabnam Sarker,[1] Tina Higginbotham,[1] and Michael F. Vaezi[1]

[1]Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, Tennessee; [2]School of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [3]Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; and [4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e19. Learning Objective: Upon completion of this CME activity, successful learners will be able to understand the effects of opioids on esophageal motility disorders.



BACKGROUND & AIMS: Studies with limited sample sizes have investigated association of chronic opioid use with motility disorders of esophagogastric junction and esophageal body peristalsis. Our aims were to use a large cohort of patients to assess (1) the impact of opioid exposure on clinical and manometric characteristics, and (2) the association of opioid exposure with higher long-term symptom burden. **METHODS:** Patients recruited from a tertiary medical center who underwent high-resolution manometry (HRM) between 2007 and 2018 were included. Demographics, opiate exposure, clinical symptoms, and HRM parameters were compared. Patient-Reported Outcomes Measurement Information System–Gastrointestinal swallowing domain (PROMIS-GI swallowing domain) and Eckardt score were administered via phone interviews in patients with hypercontractile esophagus (HE) or distal esophageal spasm (DES) to determine long-term symptom burden between opioid and nonopioid users. **RESULTS:** Our cohort included 4075 patients (869 with opiate exposure with median morphine milligram equivalent [interquartile range] of 30 [10–45]). Patients in the opioid group were significantly more likely to have dysphagia (65% vs 51%, $P < .01$) and diagnosis of DES (11% vs 5%, $P < .01$) and HE (9% vs 3%, $P < .01$). Partial opioid agonists were not associated with motility abnormalities. Patients on opioids had significantly higher symptom burden on median (interquartile range) follow-up of 8.9 years (5.8–10.4) post manometric diagnosis with median PROMIS-GI swallowing domain score of 21.5 (17–25) compared with the nonopioid group at 15 (9.8–21, $P = .03$). **CONCLUSIONS:** Nearly 2 of 3 patients with opioid exposure undergoing HRM have dysphagia and more than 25% of them with dysphagia as the primary symptom have a diagnosis of either DES or HE. Opioid users with spastic disorders have higher symptom burden long-term compared with nonopioid users.

Keywords: Opioid-induced Esophageal Dysfunction; Achalasia; Distal Esophageal Spasm; Hypercontractile Esophagus; Type of Opioid.

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; DES, distal esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IQR, interquartile range; IRP, integrated relaxation pressure; MME, morphine milligram equivalent; OIED, opioid-induced esophageal dysfunction; OR, odds ratio; POEM, per-oral endoscopic myotomy; PROMIS-GI, Patient-Reported Outcomes Measurement Information System–Gastrointestinal.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.04.051

Since the early 2000s, there has been a nationwide increase in opioid prescriptions with nearly 50% increase from 2000 to 2010; now, nearly 4% of the US population is under chronic opioid treatment for non–cancer-related chronic pain.[1,2] Although the detrimental effects of opioids on stomach, small bowel, and colon are well known, the opioid health crisis has increased awareness on the association of opioid use with major esophageal motility disorders.[3–6] The largest study to date included 200 patients on chronic opiates and found association with type III achalasia, esophagogastric junction outflow obstruction (EGJOO) and distal esophageal spasm (DES).[4] Studies of small sample sizes have shown that opioid effect on esophageal dysmotility may be reversible with discontinuation of the drug.[3] This observation has led to increased hesitance toward offering more definitive therapy (such as per-oral endoscopic myotomy [POEM] or heller myotomy) to patients with suspected opioid-induced esophageal dysfunction (OIED) as the cause of spastic achalasia.

Given the widespread treatment implications of OIED and potential for biases in studies with small sample sizes, we aimed to investigate the demographics, and clinical and manometric characteristics of patients with chronic opioid exposure in the largest cohort of patients studied to date at a tertiary care esophageal center to evaluate the following: (1) is chronic opioid exposure associated with disorders of the esophageal body or disorders of the esophagogastric junction, (2) what are predictors of abnormal manometric diagnosis in patients on chronic opioids, and (3) what types of opioids are associated with the highest odds of major motility disorders of the esophagus, and also to (4) prospectively assess if opioid exposure is associated with higher long-term symptom burden in patients with spastic esophageal motility disorders.

WHAT YOU NEED TO KNOW

BACKGROUND

The impact of opioid exposure on esophageal motility is being increasingly recognized, but current evidence is limited by studies with small sample sizes.

NEW FINDINGS

(1) Opioid exposure is associated with distal esophageal spasm and hypercontractile esophagus, but not disorders of the esophagogastric junction (type III achalasia or esophagogastric junction outflow obstruction). (2) Patients on opioids with spastic motor disorders have higher long-term symptom burden compared with nonopioid users.

LIMITATIONS

Retrospective cohort design.

IMPACT

(1) More than 1 in 4 patients with dysphagia and on opioids have a diagnosis of either distal esophageal spasm or hypercontractile esophagus. (2) Partial opioid agonist is not associated with motility abnormalities compared with full opioid agonist. (3) Given higher long-term symptom burden in opioid users, counseling patients on the impact of opioids on esophageal symptoms is critical.

Materials and Methods

Our single center cohort study included adult patients (age $\geq$18 years) who underwent high-resolution manometry (HRM) between 2007 and 2018. Baseline patient characteristics recorded in the database included age, gender (male/female), and ethnicity (Caucasian, African American, Hispanic, or other). Primary covariates, including opiate exposure (within 24 hours and 3 months, converted to morphine milligram equivalent [MME]), type of opiate, clinical symptoms, primary indication for the HRM study, endoscopy findings, and HRM parameters, were extracted from the electronic medical records. HRM studies that did not apply the Chicago Classification v3.0[7] motility diagnostic criteria were manually re-analyzed by 2 esophageal experts (D.P. and R.N.). Patients in our cohort did undergo medication reconciliation by a nurse 24 hours before the manometry procedure, which was used to note exposure at 24 hours. Electronic medical records were further reviewed to see if the same opioid was also present at 3 months before manometry. Only patients with the same opioid noted at 3 months and 24 hours before manometry were included to ensure chronic opioid exposure.

Prospective Phone Interview

Patients with hypercontractile esophagus or DES based on the previously described HRM findings underwent a phone interview and were administered standardized patient-reported outcome measures (Patient-Reported Outcomes Measurement Information System–Gastrointestinal [PROMIS-GI] swallowing domain[8] and Eckardt score[9]) to assess their long-term symptom burden.

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The Vanderbilt Institutional Review Board approved this study (IRB #181352).

Statistical Analysis

Data were collected and stored in the secure Web-based Vanderbilt Digestive Disease Center Research Electronic Data Capture (1 UL1 RR024975 National Center for Research Resources/National Institutes of Health). There was strict control and supervision of the data entry and access for this study.

Categorical variables were summarized using percentages, and continuous variables were summarized using the median, 25th, and 75th percentiles. Demographic and physiologic tests between those with and without opiate exposure were compared using the Kruskal-Wallis test for continuous variables or Pearson's $\chi 2$ tests for categorical variables. Multivariate logistic regression was used to estimate the association of age, MME, body mass index (BMI), and gender with the probability of abnormal manometry. To analyze the association of time since diagnosis and opioid exposure with symptom scores, we used multivariable proportional odds ordinal logistic regression for Eckardt score and multivariable linear regression for PROMIS-GI scores. All analyses were conducted using

the R statistical program (R Project for Statistical Computing, Vienna, Austria) at a .05 level of significance.

Results

Demographics and Clinical Symptoms

A total of 4075 patients (64% women, median [interquartile range (IQR)] age of 61 [50–71]) who underwent esophageal manometry were included for analysis. In this cohort, 21% (869 patients) were classified as chronic opioid users with a median MME (IQR) of 30 (10–45) based on opioid listed at both 3 months and 24 hours before esophageal manometry. Patients on opioids were older with median (IQR) age of 63 (54–71), had a higher BMI of 29 (25–34), and were more likely to be women (71%, $P < .01$) as shown in Table 1. Dysphagia was the primary symptom and indication for HRM in the opioid exposure group at 65% compared with 51% in the nonexposure group ($P < .01$). Heartburn was the second most common symptom. There were no differences in endoscopic findings between the 2 groups.

Table 1. Demographic Information, Primary Symptom, Type of Opioid of Patients Undergoing Esophageal HRM Categorized by Opioid Exposure (N = 4075)

	Opioid naïve (n = 3206)	Opioid user (n = 869)	*P* value
Age	61 (48–71)	63 (54–71)	<.01
Female (%)	62	71	<.01
Race (%)			.74
Caucasian	91	90	
African American	8	8	
Other	1	2	
BMI	28 (25–32)	29 (25–34)	<.01
Primary symptom (%)			<.01
Heartburn	19	16	
Regurgitation	7	6	
Dysphagia	51	65	
Cough	7	2	
Chest pain	12	8	
Hoarseness	1	1	
Pulmonary (asthma, IPF)	3	2	

NOTE. Age and BMI are presented as median and IQR.

Esophageal Motility

The most common motility diagnosis was normal esophageal motility in both groups (Table 2), but patients on opioids were significantly more likely to have DES (11% vs 5%, $P < .01$) and hypercontractile esophagus (9% vs 3%, $P < .01$). There were no differences in prevalence of achalasia (including type I, II, or III) or esophagogastric junction outflow obstruction. With regard to commonly used HRM parameters, the opioid exposure group had higher baseline lower esophageal sphincter pressure (IQR) of 21 (12–34), higher integrated relaxation pressure (IRP) of 8.2 (4.1–14.9), and distal contractile integral of 1803 (1068–3262, $P < .01$). There were no significant differences in median MME dose between the various esophageal motility disorders.

Predictors of Abnormal Manometric Diagnosis

Among patients on chronic opioids, 367 (42%) patients had abnormal manometric diagnosis based on Chicago Classification v3.0 and 502 (58%) patients had a normal manometry. Patients with an abnormal manometric diagnosis were older (64 [57–73] vs 61 [53–70], $P < .01$), more likely to have dysphagia (76% vs 56%, $P < .01$) as the presenting symptom, and included a higher proportion of patients on MME dose of >20 (62% vs 48%, $P < .01$). Age and MME were found to be independent predictors for an abnormal manometric diagnosis in patients with opioid exposure. The risk was highest (nearly 60%) for the older patients with the highest MME dose and lowest for young patients with low doses (about 20%) (Figure 1). Figure 2 shows a Forest plot showing likelihood of DES or hypercontractile esophagus using parameters of MME, age, and BMI.

Patients With Dysphagia as Primary Symptom

When we restricted the cohort to patients with only dysphagia as the primary symptom undergoing esophageal manometry (n = 1425), 26% were on opioids. In this subgroup, 16% of patients with dysphagia on opioids had DES (vs 8%, $P < .01$) and 10% had hypercontractile esophagus (vs 4%, $P < .01$) compared with nonopioid users. Overall, more than 1 in 4 patients with dysphagia and on opioids had a diagnosis of spastic disorder of the esophageal body. There were, again, no differences in prevalence of achalasia or EGJOO.

Type of Opioid

Most patients in the cohort were on full opioid agonists (80%). Patients on full opioid agonist were more likely to have DES (12% vs 7%, $P < .01$) and hypercontractile esophagus (9% vs 5%, $P < .01$) compared with patients on partial agonists. There were no differences between incidence of spastic disorders between partial agonists and the opioid-naïve group. Hydrocodone was the most used opioid (50%), followed by oxycodone (29%), tramadol (16%), and morphine (5%). The remaining patients were on fentanyl or codeine. Multivariable analysis showed that when compared with normal manometry, patients with DES and hypercontractile esophagus had the highest odds of being on morphine followed by oxycodone, and hydrocodone. For DES, odds ratios (ORs) were as follows: morphine (OR, 5.46; 95% confidence interval [CI], 2.25–12.5), oxycodone (OR, 2.66; 95% CI, 1.74–3.96), and hydrocodone (OR, 1.52; 95% CI, 1.04–2.16). For hypercontractile esophagus, ORs were as follows: morphine (OR, 6.44; 95% CI, 2.45–15.31),

Table 2. MME (24 Hour) and Esophageal Motility Diagnoses and Parameters Based on Chicago Classification v3.0 Categorized by Opioid Usage

	Opioid naïve (n = 3206)	Opioid user (n = 869)	*P* value
Morphine equivalents (24 hr)	0	30 (10–45)	<.01
Motility diagnosis (%)			
Normal	66	58	<.01
Achalasia	6	6	
Type I	1	1	
Type II	4	3	
Type III	1	2	
EGJ outflow obstruction	1	2	
Distal esophageal spasm	5	11	
Hypercontractile esophagus	3	9	
Ineffective motility	15	12	
Absent peristalsis	3	3	
HRM parameters			
Basal LES pressure (*mm Hg*)	19 (11–30)	21 (12–34)	<.01
IRP (*mm Hg*)	6.7 (3.0–12.0)	8.2 (4.1–14.9)	<.01
Distal contractile integral (*mm Hg/s/cm*)	1360 (731–2442)	1803 (1068–3262)	<.01

NOTE. Basal LES pressure, IRP, distal contractile integral, and MMEs (24 hour) are presented as median and IQR.
EGJ, esophagogastric junction.

oxycodone (OR, 3.31; 95% CI, 2.09–5.09), and hydrocodone (OR, 2.01; 95% CI, 1.33–2.96). Tramadol (partial agonist) was not associated with either manometric abnormalities of DES (OR, 0.99; 95% CI, 0.49–1.81) or hypercontractile esophagus (OR, 1.05; 95% CI, 0.44–2.14). Figure 3 shows a Forest plot of various opioid medications and risk of DES and hypercontractile esophagus.

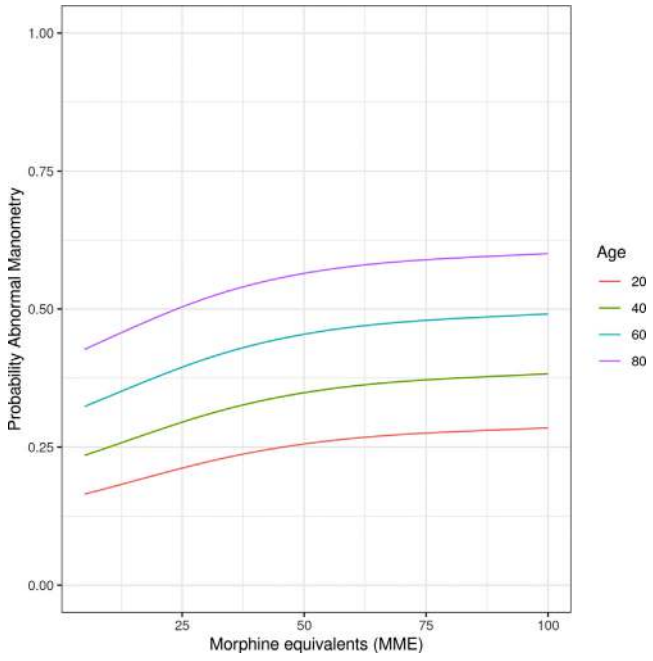


Figure 1. Model using age and MME predicting risk of abnormal manometric diagnosis in patients with opioid exposure.

Long-term Symptom Burden

A total of 454 patients (172 with chronic opioid exposure) underwent prospective assessment of clinical outcome. Standardized patient-reported outcomes (PROMIS-GI swallowing domain and Eckardt score) were successfully completed in 83 (18%) of the cohort (72% women, median [IQR] age of 65 [60–70]) and 27 (33%) of them were on chronic opioids with median MME (IQR) of 45 (22–60). There were no differences in endoscopic findings, gender, BMI, primary symptom, or manometric parameters (lower esophageal sphincter pressure, IRP, distal contractile integral) between the 2 groups. Endoscopy with esophageal dilation, Botox injection, acid suppressive medication, and neuromodulators were the commonly used interventions in this group. Phone interview was conducted at median (IQR) of 8.9 years (5.8–10.4) post manometric diagnosis. Patients on chronic opioids had significantly higher symptom burden on follow-up with median (IQR) PROMIS-GI score of 21.5 (17–25) compared with the nonopioid group at 15 (9.8–21, $P = .03$). There were no differences in the Eckardt score with median (IQR) of 3 (1–4) in the nonopioid group and 3 (2–5) in patients on chronic opioids ($P = .09$). Figure 4*A* (PROMIS-GI score) and Figure 4*B* (Eckardt score) show symptom scores in opioid and nonopioid users based on time since manometric diagnosis. Nonopioid users were more likely to have symptom improvement over time compared with opioid users.

Discussion

The detrimental effects of opioids on esophageal motility are increasingly recognized. Esophageal peristalsis is primarily driven by an inbuilt latency gradient controlled by the local inhibitory nerves that secrete nitric oxide and

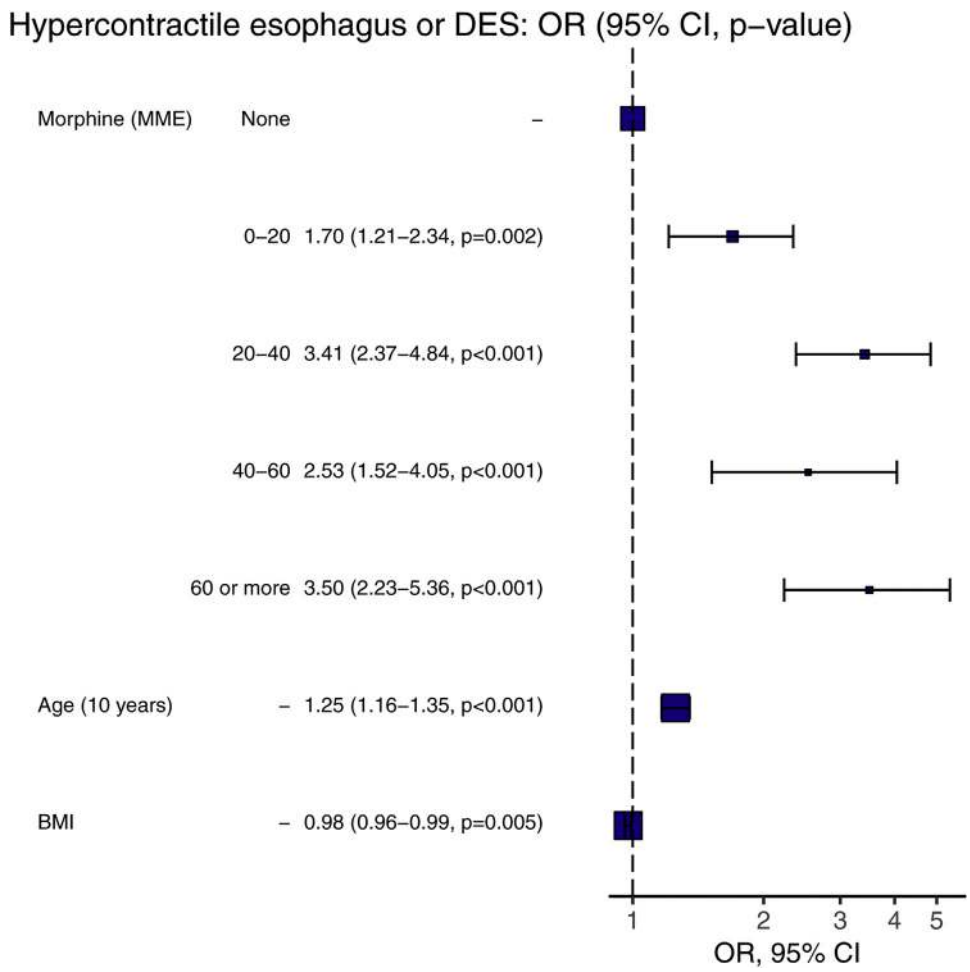


Figure 2. Forest plot looking at likelihood of hypercontractile esophagus or DES based on MME, age, and BMI.

vasoactive intestinal peptide.[10,11] Given that opioids suppress excitability of the inhibitory neurons, we had previously proposed that loss of latency gradient in the smooth muscle results in high-amplitude, simultaneous contractions in the distal esophagus of patients with OIED due to unopposed excitatory stimulation.[12] Provocative testing using amyl nitrite and cholecystokinin also have been shown to potentially differentiate between opioid-induced vs idiopathic type III achalasia.[13] One of the first studies to propose this association was in 2015, when a study of 66 patients ON opioids and 55 patients OFF opioids showed that patients on opioids were significantly more likely to have EGJOO (27% vs 7%), spastic peristalsis (lower distal latency), and higher IRP on manometry.[3] Prior report of 224 patients on opioids found a higher likelihood of manometric abnormalities including type III achalasia (13% vs 1%), EGJOO (13% vs 3%), and DES (3% vs 0.5%).[4] Given the potential for biases in small studies and the widespread treatment implications of OIED, larger studies were needed.

In our study, we analyzed the largest cohort to date of patients undergoing manometry at a tertiary care esophageal center with 4075 patients of whom 21% (869 patients) were on chronic opioids. We found that dysphagia was a significantly more common symptom in patients on chronic opioids (65%) compared with opioid-naïve (51%) patients. Chronic opioid use was associated with higher likelihood of DES (11% vs 5%, $P < .01$) and hypercontractile esophagus (9% vs 3%, $P < .01$), but we did not find any association with EGJOO or type III achalasia. Our results differ from the currently available smaller studies, which did find associations with type III achalasia and EGJOO.[3,4] The results from prior studies could be confounded by a smaller sample of opioid users studied, which might have led to a higher artificial representation of achalasia, but also could be due to dose effect. In the study by Babaei et al[4] that found association with type III achalasia and EGJOO, this association was primarily with very high doses of opioids with median MME of nearly 200 in type III achalasia and 100 in EGJOO. The median MME (IQR) in our cohort was 30 (10–45), which is more consistent with the national prescribing practices in the United States.[14] Only 6% of our achalasia cohort had MME >60. Hence, our cohort is more representative of the national prescribing practices in terms of opioid exposure and dose. Age and MME were independent predictors for risk of abnormal manometric diagnosis in patients on opioids.

We also found that type of opioid has a significant impact on risk of OIED. One prior study of 225 patients on

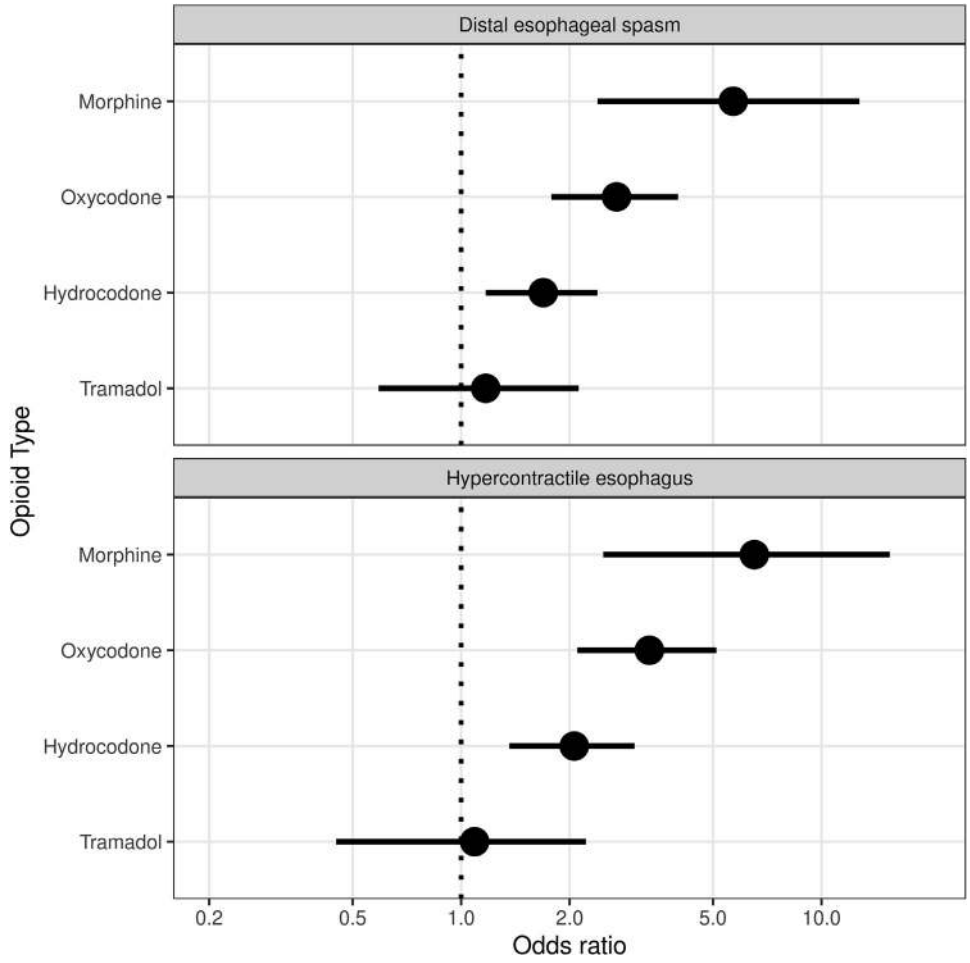


Figure 3. Forest plot of various opioid medications and risk of DES and hypercontractile esophagus.

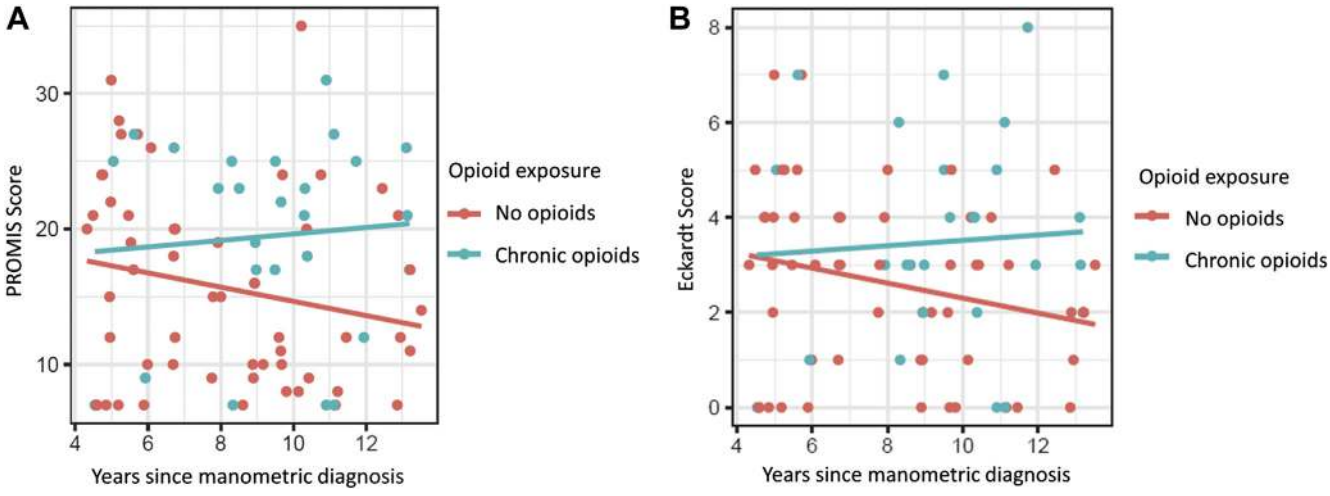


Figure 4. Relationship between PROMIS-GI (swallowing domain, *A*) and Eckard score (*B*) stratified by opioid exposure over time since diagnosis of DES or hypercontractile esophagus. Nonopioid users had improvement in symptom scores over time compared with opioid users.

oxycodone, hydrocodone, or tramadol found that OIED was more prevalent in patients on oxycodone or hydrocodone compared with tramadol, but was unable to determine the magnitude of impact with different opioids.[15] We found similar results in that patients on full opioid agonists were more likely to have DES (12% vs 7%, $P < .01$) and hypercontractile esophagus (9% vs 5%, $P < .01$) compared with patients on partial agonists. Partial opioid agonists (such as tramadol) were not associated with spastic disorders. We also found that the type of opioid might also determine magnitude of risk. Morphine had the highest odds of all the opiates, followed by oxycodone and hydrocodone.

Last, we performed prospective phone interviews in our cohort of patients with hypercontractile esophagus and DES to determine if there were differences in long-term symptom burden among opioid and nonopioid users. These manometric diagnoses were chosen based on our findings that opioid use was only associated with these disorders. We found that patients on chronic opioids had significantly higher symptom burden based on PROMIS-GI swallowing domain at a median (IQR) of 8.9 years (5.8–10.4) post manometric diagnosis. There were no differences between patients in the opioid and nonopioid groups who agreed to a phone interview in terms of manometric parameters, clinical characteristics, demographics, or interventions performed. This strengthens the finding that opioid exposure was the primary driver of higher symptom burden long-term compared with nonopioid users. There are currently no studies in the literature that have assessed long-term symptom burden between these cohorts, and our study uniquely highlights that patients on chronic opioid exposure with spastic motility disorders have persistent symptom burden long-term. We also assessed time since manometric diagnosis as a parameter and found that, although nonopioid users have improvement over time post-intervention, opioid users continue to be symptomatic despite therapy.

Overall, our data strengthens the findings from previous studies by providing more accurate estimates on impact of OIED in the largest cohort to date and raises several important observations. First, chronic opioid use was associated with spastic disorders of the esophageal body, but not the esophagogastric junction. This is a very critical observation compared with prior small studies, as it has massive treatment implications. Prior reports showing association of opioids with type III achalasia and EGJOO had led to increased hesitance toward offering more definitive therapy, such as POEM to this group, as small case reports noted opioid effect might be reversible with withdrawal of the drug.[3] However, it should be noted that there are no current studies showing that the type III achalasia pattern suspected from opioids reverses with opioid cessation. A limited number of studies have shown reversal of EGJOO, which as an entity has come under significant scrutiny recently, as 21% to 28% of patients had artifactual elevation of IRP from either structural abnormality (such as fundoplication, bariatric surgery, hiatal hernia) or from HRM-related catheter artifact.[16–20] This led to overdiagnosis of clinically insignificant EGJOO with prior iterations of the Chicago Classification and led to key change in the Chicago Classification v4.0.[21] Given that POEM has high efficacy in treatment of type III achalasia (nearly 90% response rate)[22] and patients on chronic opioids have long-term symptomatic burden (with most being unable to discontinue opioids), our study would support a more definitive therapeutic approach for this group. However, we should warn against the use of pain as the driving force for more invasive therapy in this group. Long-term outcome studies are needed comparing opioid and nonopioid users and recurrence of symptoms after definitive therapy.

Second, because chronic opioid exposure is associated with DES and hypercontractile esophagus, our study suggests that switching from full to partial agonist (tramadol) may mitigate the adverse motility outcome in this group of patients. Furthermore, type of opioid dictates the magnitude and risk of OIED. Given that morphine had the highest odds of all the opiates, followed by oxycodone and hydrocodone, switching to a lower potency or dose might also be a reasonable strategy in order to assess potential symptom improvements.

Third, this is the first study to show that chronic opioid exposure in patients with hypercontractile esophagus and DES lead to persistent symptom burden long-term. Although nonopioid users have improvement over time post-intervention, opioid users continue to be symptomatic despite therapy. This might further highlight the importance of trying opioid cessation or partial opioid agonist (if feasible) in patients with persistent symptoms. Furthermore, this study also provides data to clinicians about the importance of education and counseling to patients on chronic opioids and how it might affect their symptoms long-term.

In conclusion, nearly 2 of 3 patients with opioid exposure undergoing manometry have dysphagia as the primary symptom. Opioid exposure is associated with DES and hypercontractile esophagus, but not disorders of the esophagogastric junction (type III achalasia or EGJOO). More than 1 in 4 patients with dysphagia and on opioids had a diagnosis of either DES or hypercontractile esophagus. Type of opioid, age, and MME may predict risk of abnormal manometric diagnosis in this group of patients. Patients on opioids with spastic motor disorders have higher long-term symptom burden compared with nonopioid users.

References

1. Soelberg CD, Brown RE Jr, Du Vivier D, et al. The US opioid crisis: current federal and state legal issues. Anesth Analg 2017;125:1675–1681.
2. Gomes T, Mamdani MM, Dhalla IA, et al. The burden of premature opioid-related mortality. Addiction 2014; 109:1482–1488.
3. Ratuapli SK, Crowell MD, DiBaise JK, et al. Opioid-induced esophageal dysfunction (OIED) in patients on chronic opioids. Am J Gastroenterol 2015;110:979–984.
4. Babaei A, Szabo A, Shad S, et al. Chronic daily opioid exposure is associated with dysphagia, esophageal outflow obstruction, and disordered peristalsis. Neurogastroenterol Motil 2019;31:e13601.

5. Kraichely RE, Arora AS, Murray JA. Opiate-induced oesophageal dysmotility. Aliment Pharmacol Ther 2010; 31:601–606.
6. Ravi K, Murray JA, Geno DM, et al. Achalasia and chronic opiate use: innocent bystanders or associated conditions? Dis Esophagus 2016;29:15–21.
7. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160–174.
8. Spiegel BM, Hays RD, Bolus R, et al. Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal symptom scales. Am J Gastroenterol 2014;109:1804–1814.
9. Taft TH, Carlson DA, Triggs J, et al. Evaluating the reliability and construct validity of the Eckardt symptom score as a measure of achalasia severity. Neurogastroenterol Motil 2018;30:e13287.
10. Goyal RK, Chaudhury A. Physiology of normal esophageal motility. J Clin Gastroenterol 2008;42:610–619.
11. Weisbrodt NW, Christensen J. Gradients of contractions in the opossum esophagus. Gastroenterology 1972; 62:1159–1166.
12. Patel D, Callaway J, Vaezi M. Opioid-induced foregut dysfunction. Am J Gastroenterol 2019;114:1716–1725.
13. Babaei A, Shad S, Massey BT. Motility patterns following esophageal pharmacologic provocation with amyl nitrite or cholecystokinin during high-resolution manometry distinguish idiopathic vs opioid-induced type 3 achalasia. Clin Gastroenterol Hepatol 2020;18:813–821.e1.
14. Kiang MV, Humphreys K, Cullen MR, et al. Opioid prescribing patterns among medical providers in the United States, 2003–17: retrospective, observational study. BMJ 2020;368:l6968.
15. Snyder D, Crowell MD, Horsley-Silva J, et al. Opioid-induced esophageal dysfunction: differential effects of type and dose. Am J Gastroenterol 2019;114:1464–1469.
16. Scherer JR, Kwiatek MA, Soper NJ, et al. Functional esophagogastric junction obstruction with intact peristalsis: a heterogeneous syndrome sometimes akin to achalasia. J Gastrointest Surg 2009;13:2219–2225.
17. van Hoeij FB, Smout AJ, Bredenoord AJ. Characterization of idiopathic esophagogastric junction outflow obstruction. Neurogastroenterol Motil 2015;27:1310–1316.
18. DeLay K, Austin GL, Menard-Katcher P. Anatomic abnormalities are common potential explanations of manometric esophagogastric junction outflow obstruction. Neurogastroenterol Motil 2016;28:1166–1171.
19. Clayton SB, Patel R, Richter JE. Functional and anatomic esophagogastric junction outflow obstruction: manometry, timed barium esophagram findings, and treatment outcomes. Clin Gastroenterol Hepatol 2016; 14:907–911.
20. Lynch KL, Yang YX, Metz DC, et al. Clinical presentation and disease course of patients with esophagogastric junction outflow obstruction. Dis Esophagus 2017; 30:1–6.
21. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0((c)). Neurogastroenterol Motil 2021;33:e14058.
22. Zhang W, Linghu EQ. Peroral endoscopic myotomy for type III achalasia of Chicago classification: outcomes with a minimum follow-up of 24 months. J Gastrointest Surg 2017;21:785–791.

Received February 20, 2022. Revised April 26, 2022. Accepted April 28, 2022.

Correspondence
Address correspondence to Dhyanesh A. Patel, MD, Center for Esophageal Disorders, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, 1211 Medical Center Drive, Nashville, Tennessee 37232. e-mail: Dan.patel@vumc.org.

CRediT Authorship Contributions
Order of Authors (with Contributor Roles):
Dhyanesh Arvind Patel, MD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).
James Goss, BSc (Data curation: Equal).
Muhammad Hayat, MD (Data curation: Supporting).
Claudio Tombazzi, MD (Data curation: Supporting).
Rishi Naik, MD, MSCI (Data curation: Supporting; Writing – review & editing: Supporting).
James Slaughter, DrPH (Formal analysis: Lead; Methodology: Lead).
Muhammad Aslam, MD (Conceptualization: Supporting).
Shabnam Sarker, MD (Conceptualization: Supporting).
Tina Higginbotham, MPA (Data curation: Supporting; Resources: Supporting).
Michael Vaezi, MD, PhD (Conceptualization: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Writing – review & editing: Lead).

Conflict of Interest
The authors disclose no conflicts.

Funding
None.