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Chronic Daily Opioid Exposure is Associated with Dysphagia, Esophageal Outflow Obstruction and Disordered Peristalsis

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Abstract

Background: Opioid receptors are present in the esophagus, and chronic opioid therapy may be associated with esophageal dysfunction. Given the current opioid epidemic in the US, the potential contribution of opioids to esophageal dysmotility is important from both public health and patient care perspectives.

Aim: To investigate the contribution of opioids to dysphagia and the prevalence of major motor disorders in patients undergoing manometric evaluation.

Method: The anonymized electronic medical records (EMR) of patients linked to their deidentified high-resolution manometry (HRM) studies were reviewed. The patients were grouped based on their opioid exposure history at the time of HRM: opioid naïve and chronic daily users. The oral morphine milligram equivalent daily dose (MMED) of opioids was computed.

Results: 10% of patients referred for esophageal HRM were taking opioid analgesics on a chronic daily basis, and they had a significantly higher prevalence of dysphagia than their opioid naïve counterparts. The chronic daily opioid users displayed a significantly higher prevalence of achalasia type 3 (ACH3) and esophagogastric junction outflow obstruction (EGJOO) motility phenotypes. The MMED of opioids was a significant predictor of esophageal pressure metrics and motility diagnoses ($p < 0.0001$).

Conclusions: Chronic daily opioid intake is associated with impaired deglutitive LES relaxation and disorganized peristaltic sequence. While a minority of patients on chronic daily opioid therapy present with major esophageal motor disorders, they comprise nearly half of ACH3 and a third of EGJOO motility phenotypes.

Abstract

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Arash Babaei had a major role in all aspects of the project including the study concept, data acquisition, data analysis, interpretation of data, statistical analysis, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Aniko Szabo had a major role in statistical analysis of data and contributed to the interpretation of data. Sadaf Shad had a major role in the data acquisition. Benson Massey had a major role in the interpretation of data, drafting and critical revision of the manuscript.

The authors have no conflict of interest to disclose.

Abbreviated abstract: Nearly 10% of patients referred for esophageal motility testing are on chronic daily opioids. Higher opioid doses are associated with impaired deglutitive LES relaxation and disorganized peristaltic sequence

Keywords

narcotics; dysmotility; dysphagia; achalasia; esophageal motor disorders

Introduction

High-resolution manometry (HRM) is the current gold standard technique to identify esophageal motor disorders ¹, and the Chicago Classification of esophageal motility v3.0 (CCv3) defines major motility disorders as achalasia, distal esophageal spasm (DES), esophagogastric junction outflow obstruction (EGJOO), hypercontractile esophagus and absent contractility ¹. The CCv3 classification scheme does not describe the underlying pathophysiology for these different motor patterns and some motor abnormalities may be associated with various etiologies ². For example, the presence of the achalasia motor pattern can also be a manifestation of neoplasia (i.e., pseudoachalasia) ³.

While the effects of opioids on hindgut transit are well known, the literature on the effects of opioids on esophageal motility is sparse. In healthy human volunteers, intravenous administration of morphine resulted in impaired deglutitive LES relaxation and augmented velocity of peristaltic progression ⁴. Naloxone reversed these effects; however, naloxone given alone did not influence peristalsis, suggesting a limited physiologic role for endogenous opioids ⁵. Subsequently, in a seminal observational study, impaired LES relaxation and rapid esophageal contractions were described in patients who were taking opioids chronically ⁶. Recent studies have also suggested that opioid therapy may be associated with major disorders of peristalsis ^{7, 8}.

The National Center for Health Statistics estimates that opioid use has doubled in the U.S. adult population (from 3.4% in 1988 to 6.9% in 2011), and the strength of prescribed opioids has significantly shifted to stronger preparations than morphine (80% of prescriptions) ⁹. Considering the opioid epidemic in the US, the significance of esophageal opioid-induced peristalsis disorder (OPD) is of paramount clinical interest. The main goals of the current study were to: 1) estimate the overall prevalence of prescription opioid use in patients referred for esophageal motility testing; 2) determine if opioid exposure is associated with esophageal symptoms; and 3) investigate the potential contribution of chronic daily opioid use to the development of major esophageal peristaltic disorders.

METHODS:

This study was conducted retrospectively on patients who had esophageal high-resolution manometry (HRM) performed at the Froedtert Hospital and Medical College of Wisconsin (MCW). The investigational review board of the MCW approved the study protocol. Each patient was assigned a unique randomly generated alphanumeric ID to deidentify the HRM file and corresponding de-identified electronic medical records (EMR) ¹⁰. The research

informatics office at the Clinical and Translational Science Institute (CTSI) supervised the de-identification process and conducted secure online data management using the REDCap secure data collection tool.

Study Population:

A total of 2,705 consecutive adult patients from July 1, 2007 until June 30, 2017 were included in the study. The primary indications for the HRM study were recorded. These were categorized as dysphagia, gastroesophageal reflux, supra-esophageal symptoms, non-cardiac chest pain, preoperative assessment (including lung transplant evaluation), nausea/vomiting/abdominal pain, and other.

Clinical Data Extraction:

The relevant de-identified demographic and clinical data of the patients in the EMR (age, sex, race, body mass index, problem list, medication history, medical and surgical history) were extracted through the honest broker data extraction tool of the clinical research data warehouse (CRDW). We used relevant procedure and diagnosis terms, as well as current procedural terminology (CPT) and international classification of diseases (ICD-9 and ICD-10) codes to query the EMR. This included all data available from before the date of HRM until 30 days after the study. Patients with inadequate documentation of history in the EMR and patients with a history of esophageal/gastric surgery or esophageal/gastric cancer were excluded from analysis.

The CRDW database was queried for utilization of prescription opioids in the outpatient setting. Patients were accordingly classified into “opioid-naïve”, “occasional opioid” and “chronic daily opioid” patient groups. Opioids were identified based on documented “opioid analgesic” in the pharmaceutical class of the medication history or presence of opioid formulations as search terms in their medication history. The medication history was queried 180 days before to 30 days after the date of HRM. Patients who were on long-acting and extended-release formulations of the opioids of equal potency or stronger preparations than morphine (Methadone, Fentanyl, Oxycodone, Morphine, Buprenorphine, Butorphanol, Oxymorphone and Hydromorphone) were considered to be chronic daily opioid users. Patients with a history of at least three prescriptions of short-acting opioids of equal potency or stronger preparations than morphine (Oxycodone, Morphine, Hydrocodone, Oxymorphone and Hydromorphone) filled during 90 days before the time of HRM, were also considered to be chronic daily users^{11, 12}. Patients with a history of intermittent opioid use (as needed) of less than 90 days duration, or less potent preparations than morphine (Codeine, Tramadol) were considered occasional users^{11, 12}. The oral morphine milligram equivalent daily dose (MMED) of opioids at the time of HRM was computed for each medication as a product of the prescribed dose, dose frequency, and a drug-specific standard conversion factor. Equi-analgesic conversion factors were adapted from the latest available table published by the Center for Disease Control¹³. We estimated the daily dose of as-needed drugs as half the rate of intake of the prescribed frequency. The total MMED was calculated by a summation of all chronic daily and as needed opioid formulations in each patient. Because we wanted to evaluate the effects of chronic daily opioid use on

manometric findings, patients identified as occasional users were excluded from further analysis.

We re-identified a subset of the cohort to assess duration of opioid exposure and relationship to the onset of their symptoms. This subset of patients (re-identified cohort, N=375) was an enriched sample of chronic daily opioid patients. In the re-identified cohort, all available electronic health record systems used in our institution, outside medical records, and the enhanced prescription drug monitoring program (PDMP) of the state of Wisconsin were reviewed. All relevant consultation and progress notes, medication history, past medical and surgical history, prescription and dispensing data within a year of the date of manometry were reviewed in detail.

HRM Data Analysis:

The Manoview® software generated landmarks and automated analysis were discarded, and each HRM study was manually analyzed to extract the following topographic pressure metrics from available supine wet swallows: 1) integrated relaxation pressure (IRP), 2) distal latency (DL), 3) distal contractile integral (DCI). The median value across the 10 swallows of each patient were used to classify patients into esophageal motility diagnoses according to CCv3¹. Additional pressure metrics of basal lower esophageal sphincter (LES) pressure, contraction front velocity (CFV), and maximum intrabolus pressure (IBP)¹⁴ were also recorded. The four second IRP threshold of 15 mmHg was considered the cut off threshold for the normal range¹. Any study with an elevated IRP associated with a normal IBP (< 17 mmHg)^{14, 15} in supine wet swallows, or with a normal IRP (< 11 mmHg) during the sitting position wet swallows (when available),¹⁶ were considered artefactual. The poor-quality HRM studies and those with artefactually elevated IRP were excluded from the remainder of the analysis.

To ensure unbiased results we implemented the following safeguards: a) a trained research coordinator (SS), blinded to the prior clinical interpretation of HRM, manually analyzed the HRM topographic plots to apply the CCv3 motility diagnostic criteria uniformly; b) the principal investigator (AB) reanalyzed 25% of the HRM studies to confirm accuracy of pressure metrics and the diagnostic interpretation; c) the research coordinator was blinded to the opioid intake status of the cohort; d) the biostatistician (AS) who compiled and organized the anonymized clinical data to determine the opioid exposure status was blinded to the manometric results.

Sample Size Calculation:

Based on a 7% rate of chronic opioid use in the general population, and the preliminary analysis of the enriched sample of the cohort (re-identified cohort), we expected that nearly 10% of patients would be classified into the chronic daily opioid group. With an expected population of more than 2,000 HRM studies, the prevalence of chronic daily opioid use could be estimated with a less than 2% margin of error. When comparing the prevalence of a major motility disorder between the chronic daily opioid use and the opioid-naïve patients, assuming at least 10% prevalence of the major motility disorder in chronic daily opioid use, the study had an expected 80% power at a two-sided 2.5% significance level regardless of

the prevalence of major peristaltic disorder in the opioid naïve patients. With the expected 200 patients with chronic opioid use, we expected to have 80% power overall to detect a correlation between manometric pressure metrics and MMED at a Bonferroni adjusted 5% significance level.

Statistical Analysis:

Continuous variables are shown as median and interquartile range (IQR) and compared using Kruskal-Wallis and Wilcoxon Rank-sum tests across groups and pairwise comparisons respectively. Categorical variables are shown as n (%) and compared using the chi-square test. The relationship between HRM motility diagnosis and opioid use was evaluated using logistical regression analysis with older age (age>65), race, sex, obesity (BMI>30) as covariates. Opioid use, based on MMED quartiles in our cohort, was categorized into low (MMED ≤ 30), medium (45>MMED ≤ 30), high (90>MMED ≤ 45) and very high (MMED > 90) groups. Odds ratio (OR) with 95% confidence limits (95%CL) were then estimated. The relationship between HRM pressure metrics and opioid MMED dose was evaluated using multiple linear regression analysis with age, race, sex, body mass index (BMI) as covariates. Based on scatterplots and a Box-Cox analysis, all variables except DL were logarithmically transformed for multiple linear regression analysis.

RESULTS

2342 patients (1576 Female, 55 ± 16 years) with adequate clinical history and without a history of gastroesophageal surgery/cancer were considered for the analysis. Dysphagia was the most common primary indication for HRM in 1081 patients (46%) followed by GERD in 695 patients (30%). We identified 224 and 228 patients as chronic daily (10%) and occasional opioid (10%) users respectively. The MMED of opioids were 45 mg (IQR 30 – 90 mg) and 20 mg (IQR 10 – 30 mg) for these two groups ($p<0.0001$). Occasional opioid users were excluded from further analysis. Chronic daily opioid users were slightly older and differed in ethnic distribution from opioid naïve patients (Table 1). The primary indication for HRM was significantly different between groups, as chronic daily opioid exposure was associated with a higher prevalence of dysphagia ($p<0.0001$), whereas opioid naïve patients had a higher prevalence of reflux symptoms ($p=0.003$).

Manual EMR review in the re-identified cohort, identified 60 patients (16%) as chronic daily opioid users. The continuous opioid therapy commenced 50 months (IQR 26-84) and the esophageal symptoms began 24 months (IQR 10-60) before the date of the HRM study ($p<0.001$). Chronic back pain, fibromyalgia and rheumatoid arthritis were the most common pain related diagnoses in 14 (23%), 12 (20%) and 8 (13%) patients respectively. We did not identify a pain diagnosis in 20 patients (33%).

In the cohort of patients with interpretable HRM studies (N=1790), the percentage of premature (11% vs 3%) and rapid esophageal contractions (10% vs 2%) were both significantly higher ($p<0.0001$) in chronic daily opioid users. In addition, the IRP, IBP and basal LES pressure values were significantly higher ($p<0.0001$) in the chronic daily opioid users (Table 2). Furthermore, the prevalence of type 3 achalasia (ACH3) and EGJOO motility patterns were both significantly higher ($p<0.0001$) in the patients on chronic daily

opioids. This difference was present independent of the presence of dysphagia as the primary indication for the HRM study. The prevalence of dysphagia as the primary indication for HRM in ACH3 and EGJOO was similar regardless of opioid exposure ($P>0.1$). In the chronic daily opioid exposed patients, the prevalence of dysphagia as the primary indication was significantly ($p=0.01$) higher in ACH3 (88%) and EGJOO (77%) compared to the normal esophageal motility (54%).

Logistic regression analysis confirmed that chronic daily opioid use was a significant predictor ($p<0.0001$) of motility diagnoses (Supplementary Table 1). The low and medium opioid users were not statistically different from opioid naïve patients. On the other hand, high (OR 11.5, 95%CL 6 – 22.1) and very high (OR 65.7, 95%CL 32– 134.8) opioid users showed significantly higher likelihood of displaying ACH3 and EGJOO phenotypes compared to opioid naïve patients. Furthermore, the MMED in ACH3 and EGJOO was significantly higher ($p<0.0001$) than normal esophageal motility (Figure 1).

Some pressure metrics such as DL, CFV and DCI are not quantifiable without an identifiable esophageal contraction in HRM. Therefore, 153 patients who did not have a discernable contractile wave (absent contractility, achalasia type 1 and 2 motility patterns) were excluded from the final analysis. We investigated the relationship between topographic pressure metrics and opioid exposure in the remaining patients (N=1637). Chronic daily opioid exposure was associated with significant differences in all measured pressure metrics compared to opioid naïve patients (Figure 2). Furthermore, among chronic daily opioid users only, all pressure metrics except DCI showed a significant correlation with MMED (Figure 3). In the multiple regression model the MMED remained a significant predictor of IRP, IBP, CFV, DL, LES pressure among the chronic opioid daily users (Supplementary Table 2).

DISCUSSION

In the current study, we report that in a large cohort of patients referred for esophageal motility testing, 10% of patients used opioid analgesics chronically on a daily basis. Patients exposed to prescription opioids reported a significantly higher prevalence of dysphagia as the primary indication for manometry. The pain-related diagnoses were mostly non-cancer non-esophageal pain, and opioid exposure preceded the onset of esophageal symptoms by more than two years. This finding indicated that the esophageal symptoms did not prompt opioid use. Higher doses of opioids were significantly associated with more abnormal pressure metrics of esophageal motility. Consequently, chronic daily opioid exposure was associated with a significantly higher prevalence of ACH3 and EGJOO phenotypes. Indeed, chronic daily opioid users comprised nearly half of ACH3 and a third of EGJOO patients.

The Department of Health and Human Services in October 26, 2017 declared a public health emergency due to the opioid epidemic in the US. Data from a national survey on drug use and health showed that in 2015, 91.5 million US civilian adults (37.8%) had used prescription opioids, 11.5 million (4.7%) misused prescribed opioids, and 1.9 million (0.8%) suffered from opioid use disorder¹⁷. The findings in our study are consistent with these general national trends. The question remains as to how much of the burden of esophageal motor disorders identified during clinical manometry testing in the US results from chronic

opioid use. The majority of our patients resided in the state of Wisconsin (WI), and the rate of opioids dispensed during 2014-2016 in WI were 62.2-71.9 prescriptions/100 persons, which is comparable to the average national rate of 66.5-75.6 prescriptions/100 persons¹⁸. There is a considerable state-to-state variability in the rate of opioid use in the US, from a rate of 32.5 prescriptions /100 persons in the District of Columbia (2016) to 125 prescriptions /100 persons in Alabama (2014). Therefore, while our data are a conservative estimate of opioid use in patients referred for motility testing, we suspect that regional opioid prescription patterns should be carefully considered.

A previous study of opioid patients reported that EGJOO was significantly more prevalent (27%) in patients using opioids within 24 hours of manometry compared to those who did not (7%)⁸. Within our database we were unable to assess the interval between the last opioid intake and the HRM study, as previous studies have addressed⁸, however our study further supports their observations. The prevalence of EGJOO in chronic daily (13%) opioid users was significantly higher than opioid-naïve patients (3%). We also provide evidence that use of chronic daily opioids increases basal LES tone and results in impaired LES relaxation, as evidenced by elevated IRP and IBP. In a robust multiple regression model, the MMED remained a significant predictor of deglutitive relaxation metrics, further supporting our findings.

In another study of achalasia patients, 25% were found to be on opiates, and the ACH3 subtype was over-represented among opiate users⁷. Our study had similar findings: daily opioid users, who usually were on much higher-potency and higher dose of opioids, had a prevalence of ACH3 (13%) that was significantly higher than in opioid-naïve patients (1%). This was not observed for the other two subtypes of achalasia. ACH3 patients are typically considered to require more invasive treatment modalities such as long esophageal myotomy (laparoscopic or POEM)^{19, 20} for adequate palliation of symptoms. Opioid-induced ACH3 however is potentially reversible with modification of the analgesic regimen. While it is important to avoid delay of appropriate palliative therapy in patients who currently have no prospect for recovery of normal motor function in idiopathic cases, it is also important to identify those patients with a potentially reversible motor abnormality (opioid-induced ACH3 or EGJOO), to avoid expensive invasive interventions that carry a risk of adverse events.

Estimates of opioid intake based on medical records may underestimate the prevalence of opioid intake, because 2% of the US population (nearly 4.6 million people) utilize opioids frequently (>30 days/year) for nonmedical purposes²¹. In the majority of nonmedical users (>70%), their source of obtaining opioids (family, friends, or others) cannot be identified by a review of the available medical records or online prescription databases. Therefore, our findings should be considered a conservative estimate of prevalent opioid use in patients referred for esophageal motility testing. It is possible that some of the presumed opiate naïve patients with findings of ACH3 and EGJOO phenotypes might have been patients with unrecognized chronic opioid use. Nevertheless, we still found significant differences between the opioid naïve and chronic daily opiate use groups.

While our retrospective study is not able to establish a causality between opioid use and peristaltic disorder, it confirms a strong association that warrants further investigation. As other investigators have described, and we have experienced, chronic opioid users are unlikely to opt for cessation of their opioid therapy. However, our clinical experience (Figure 4), as well as case reports in the literature ⁶, indicate that cessation or reduction of opioid therapy can improve dysphagia and reverse peristaltic dysfunction, supporting a causal relationship between opioid intake and peristaltic disorder. Future prospective studies with objective measurement of opioid compounds (on and off therapy) are required to independently confirm the causal relationship and verify reversibility of the motor disturbances in opioid-induced peristalsis disorder (OPD).

Our data strengthens the findings from previous studies in several respects. We studied a larger cohort of consecutive patients over a longer period, which provides a more accurate estimate of the OPD problem. Furthermore, we were able to show increased prevalence of dysphagia in this population and quantify the dosage of opioid use in our cohort. Finally, we identified a relationship between the MMED and the patients' motility diagnoses.

In summary, our study shows that higher doses of opioid intake are associated with impaired deglutitive LES relaxation and abnormal peristaltic sequence. The prevalence of ACH3 and EGJO phenotypes are significantly higher in chronic daily opioid users. We propose that chronic opioid therapy should be considered as a possible underlying etiology when diagnosing these major esophageal motor abnormalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY OF ABBREVIATIONS:

(OPD)	Opioid-induced peristaltic disorder
(LES)	Lower Esophageal Sphincter
(EGJ)	EsophagoGastric Junction
(CCv3)	Chicago Classification Version 3.0

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Key Messages:

- Opioid receptors are present in the esophagus, and recent opioid exposure is associated with esophageal dysmotility.
- Nearly 10% of patients referred for esophageal motility testing are on chronic daily opioids, and higher opioid doses are associated with impaired deglutitive LES relaxation and disorganized peristaltic sequence.
- Chronic opioid therapy should be considered as a possible underlying etiology, when diagnosing achalasia type 3 and esophagogastric junction outflow obstruction motility phenotypes.

Figure 1: The oral milligram morphine equivalent daily dose (MMED) of prescription opioid analgesia in chronic daily opioid users by motility diagnosis (N=200).

The MMED across different motility diagnoses (AC: absent contractility [n=7]; ACH 1, 2: achalasia type 1 and 2 [n=6]; ACH3: achalasia type 3 [n=25]; DES: distal esophageal spasm [n=6]; EGJOO: esophagogastric junction outflow obstruction [n=26]; HCE: hypercontractile esophagus [n=6]; IEM: ineffective esophageal motility [n=33]; NL: normal esophageal motility [n=91]) was significantly different (Kruskal-Wallis, $p < 0.0001$). In the pairwise comparison, only ACH3 and EGJOO phenotypes showed significantly higher opioid intake than NL (Wilcoxon Rank-Sum, $p < 0.0001$).

Figure 2: Comparison of esophageal pressure metrics between opioid-naïve and chronic daily users (N=1639).

Patients without a discernable contractile wave (absent contractility, achalasia type 1 and 2) were excluded from the analysis. A) End-expiratory basal lower esophageal sphincter (LES) pressure. B) Integrated relaxation pressure (IRP). C) Intrabolus pressure (IBP). D) Distal latency (DL). E) contraction front velocity (CFV). F) Distal contractile integral (DCI). Data is displayed as box-whisker plots with boxes representing interquartile range. * significantly different from opioid naïve group (Wilcoxon Rank Sum, $p < 0.0001$).

LES Expiratory Pressure (LES)

Integrated Relaxation Pressure (IRP)

Intrabolus Pressure (IBP)

Distal Latency (DL)

Figure 3: The correlation of oral milligram morphine equivalent daily dose (MMED) of opioid with each pressure metric in chronic daily opioid users (N=187). Patients without a discernable contractile wave (absent contractility, achalasia type 1 and 2) were excluded from the analysis. A) End-expiratory basal lower esophageal sphincter (LES)

pressure. B) Integrated relaxation pressure (IRP). C) Intrabolus pressure (IBP). D) Distal latency (DL). E) contraction front velocity (CFV). F) Distal contractile integral (DCI).

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Figure-4. Resolution of EGJOO following reduction in opioid therapy.

A) EPT image shows findings of EGJOO in a patient on high-dose chronic daily opioids (MMED=250 mg) to treat pain associated with sickle cell disease. B) EPT image in the same patient studied 4 years later after opiate therapy had been weaned to as needed dosing (MMED=30 mg). Findings of EGJOO have resolved.

Table 1:
Demographic information and primary indications of esophageal high-resolution manometry (HRM) categorized by opioid exposure (N=2114).

Age is presented as median and interquartile range.

Demographics and Primary HRM Indications	Patients by Opioid Exposure		
	Naive	Chronic Daily	<i>P value</i>
Age	56 (44, 66)	59 (49, 68)	<0.01*
Female (%)	1242 (66%)	159 (71%)	0.1
Race (%)			<0.001*
• Caucasian	1551 (83%)	153 (68%)	
• African-American	198 (11%)	62 (28%)	
• Other	119 (6%)	9 (4%)	
Primary HRM Indication (%)			<0.0001*
• Dysphagia	821 (43%)	139 (62%)	<0.0001*
• GERD	582 (31%)	48 (21%)	0.003*
• Supra-Esophageal Symptoms	141 (8%)	8 (4%)	0.03
• Pre-Operative	144 (8%)	8 (4%)	0.03
• Non-cardiac Chest Pain	109 (6%)	10 (4%)	0.5
• Nausea/Vomiting/Pain	53 (3%)	7 (3%)	0.8
• Other	38 (2%)	4 (2%)	0.8

Table 2:
Frequency of abnormal peristaltic contractile phenotypes and esophageal motility diagnoses based on Chicago Classification of esophageal motor disorders v3.0 categorized by opioid usage (N=1790).

Pressure metric data are presented as median and interquartile range.

Motility Characteristics	Patients by Opioid Exposure		
	Naive	Chronic Daily	<i>P value</i>
Pressure Metrics (mmHg)			
• Integrated Relaxation	8 (5, 12)	11 (7, 17)	<0.0001*
• Intrabolus Maximum	12 (9, 15)	14 (11, 19)	<0.0001*
• Basal Expiratory LES	13 (7, 22)	17 (9, 31)	<0.0001*
Motility Diagnosis (%)			<0.0001*
• Absent Contractility	47 (3%)	7 (3%)	0.7
• Achalasia Type 1	16 (1%)	2 (1%)	1
• Achalasia Type 2	77 (5%)	4 (2%)	0.1
• Achalasia Type 3	22 (1%)	25 (13%)	<0.0001*
• EGJ Outflow Obstruction	42 (3%)	26 (13%)	<0.0001*
• Esophageal Spasm	8 (0.5%)	6 (3%)	<0.01*
• Hyper-contractile Esophagus	56 (4%)	6 (3%)	0.7
• Ineffective Motility	394 (25%)	33 (17%)	0.01
• Normal Peristalsis	928 (58%)	91 (45%)	<0.001*