Original Article

Opioid Treatment and Excessive Alcohol Consumption Are Associated With Esophagogastric Junction Disorders

Valeria Schindler,[1] Daniel Runggaldier,[1,2] Amanda Bianca,[1] Anton S Becker,[3] Fritz Murray,[1] Edoardo Savarino,[4] and Daniel Pohl[1]*

[1]Division of Gastroenterology and Hepatology, University Hospital Zurich, Switzerland; [2]Department of Otorhinolaryngology, University Hospital of Zurich, Switzerland; [3]Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Switzerland; and [4]Department of Surgery, Oncology and Gastroenterology, University of Padua, Italy

Background/Aims
The influence of external factors such as opioids and alcohol has been extensively investigated for various segments of the gastrointestinal tract. However, the association between their use and the development of esophagogastric junction outflow obstruction disorders (EGJOODs) is unknown. Therefore, the aim of this study is to analyze prevalence and clinical relevance of opioids and alcohol intake in patients with EGJOODs.

Methods
In this single-center, retrospective study, we reviewed clinical and pharmacological data of 375 consecutive patients who had undergone high resolution impedance manometry for EGJOODs. EGJOODs were classified according to the Chicago classification version 3.0 and to recently published normal values for test meals. Demographics, manometric data, and symptoms were compared between different groups using Pearson's chi-squared test, Fisher's exact test, and multivariate analysis. A $P < 0.05$ was considered significant.

Results
EGJOOD was found in 30.7% (115/375) of all analyzed patients. The prevalence of opioids (14.8% vs 4.2%, $P = 0.026$) was significantly higher in patients with EGJOODs compared to patients without EGJOODs. Additionally, excessive alcohol consumption (12.2% vs 3.5%, $P = 0.011$) was associated with EGJOODs. Excessive alcohol consumption was especially frequent in the non-achalasia esophagogastric junction outflow obstruction subgroup (16.2%) and opioid use in the achalasia type III subgroup (20.0%).

Conclusions
We found a significant association between EGJOODs and opioid as well as excessive alcohol consumption. This underlines the importance of detailed history taking regarding medication and ethanol consumption in patients with dysphagia. Further prospective studies on mechanisms undelaying esophagogastric junction dysfunction due to opioids or alcohol are warranted.
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Key Words
Alcohol drinking; Analgesics, Opioids; Esophageal achalasia; Esophagogastric junction; Manometry

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*Correspondence: Daniel Pohl, MD
Division of Gastroenterology and Hepatology, University Hospital Zurich, Raemistr. 100, 8091 Zurich, Switzerland
Tel: +41 44 255 11 11, Fax: +41 44 255 45 91, E-mail: daniel.pohl@usz.ch
Valeria Schindler and Daniel Runggaldier contributed equally to this work.

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Introduction

Esophagogastric junction outflow obstruction disorders (EG-JOODs) are a group of esophageal motility disorders often characterized by an impairment of food intake and symptoms such as dysphagia, odynophagia, regurgitations, and weight loss. Hence, affected individuals often suffer a significantly reduced quality of life.[1] EGJOODs are characterized by an elevated integrated relaxation pressure (IRP) during high-resolution impedance manometry (HRIM) and are further subdivided into achalasia type I-III and esophagogastric junction outflow obstruction (EGJOO) according to Chicago classification (CC; version 3.0). This categorization depends on the level of impairment of peristalsis and the esophageal pressurization pattern upon swallowing (Fig. 1).[2] Current standard testing protocols of esophageal physiology incorporate single low-volume water swallows that frequently fail to detect a significant quantity of esophageal motility disorders and usually do not evoke symptoms. Additional testing such as multiple rapid swallows and, more recently, meal testing offer a more physiologic insight into patient deglutition dynamics and better symptom association (Fig. 1E and 1F).[3] While the diagnostic process and further classification into achalasia type I-III and EGJOO is well established, the underlying etiology and pathophysiological processes are not fully understood. Esophageal peristalsis and lower esophageal sphincter (LES) relaxation are processes primarily controlled by ganglionic cells of the myenteric plexus, which can either induce esophageal smooth muscle cell contraction or relaxation, depending on the neurotransmitter released.[4,5] Hence, neurodegenerative, autoimmune and viral processes causing an imbalance between the excitatory and inhibitory transmission, eg, by the loss of ganglion cells, are thought to be involved in the pathogenesis of EGJOODs.[6-10] The classical EGJOO (CC v3.0), which is characterized by elevated IRP but preserved peristalsis, could also be triggered by other factors such as hiatal hernia, impaired crural relaxation, or a mechanical obstruction, potentially caused by fibrotic stricture.[11] Furthermore, the expression of opioid receptors was shown in the esophageal body and LES, suggesting a potential influence of opioids on esophageal motility and esophagogastric junction (EGJ) relaxation.[12-15] Indeed a higher IRP as well as lower distal latency on esophageal pressure topography have been shown.[12] Moreover, in patients with dysphagia and chronic opioid use an impaired LES relaxation and simultaneous esophageal waves were noticed.[16] However, a deeper knowledge on opioid induced EGJOOD is still scarce.

Not only opioids but also alcohol seems to affect the upper gastrointestinal tract. The most known effect of excessive alcohol consumption is the development of esophageal varices as a consequence of liver damage. While there is accordance with the increased prevalence of gastroesophageal reflux in alcoholics, there are inconsistent data of the impact on the LES. Reduced pressure as well as
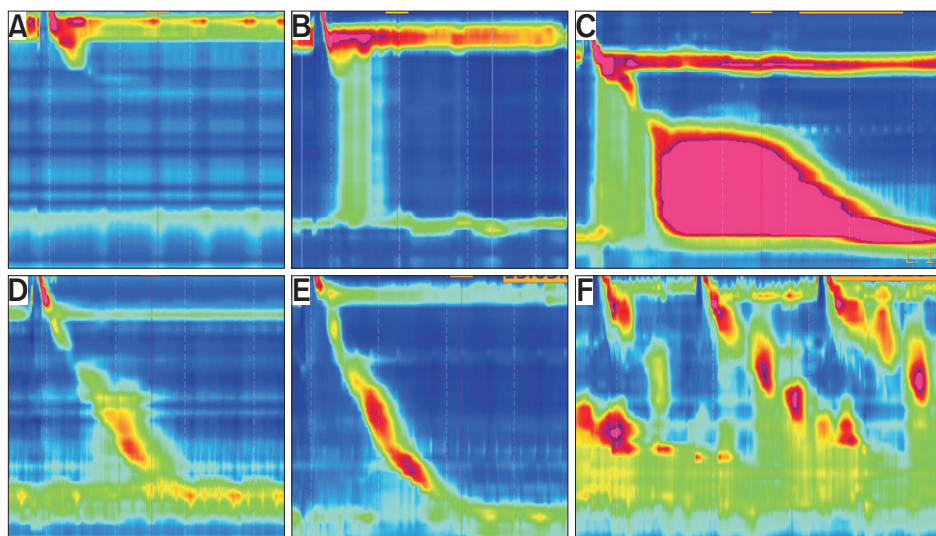

Figure 1. Clouse plots of high-resolution impedance manometry of the different esophagogastric junction outflow obstruction (EGJOO) disorders with achalasia type I (A), type II (B), type III (C), and EGJOO Chicago classification version 3.0 (D). Clouse plot of a single water swallow of a patient with an EGJOO in the standardized test meal (E). Clouse plot of the same patient during a rice test meal (F). The y-axis corresponds to the distance from proximal to distal esophagus, the x-axis constitutes the time. The local pressure at a given time-point is color coded (low pressure = blue, intermediate pressure = green/yellow, and high pressure = red/purple).

a hypertensive LES have been described in conjunction with alcohol.[17-19] Moreover, alcohol has recently been linked with esophageal dysmotility,[20,21] but its role in the development of EGJOODs is still unclear. Therefore, the aim of this study is to analyze the prevalence and clinical relevance in terms of symptomatic esophageal dysfunction of opioids and alcohol intake in patients diagnosed with EGJOODs.

Materials and Methods

We reviewed data of 375 consecutive patients for alcohol consumption (sporadic, regular, and excessive) and opioid use who had undergone HRIM after being referred to our tertiary referral center for symptoms of esophageal dysfunction between 2015 and 2017. All patients underwent endoscopic evaluation including esophageal biopsies to rule out structural etiologies prior to HRIM. Inclusion criteria were age older than 18 years and signed general informed consent. Ethics approval was obtained for the analysis (BASEC-Nr. 2017-00930).

High-resolution Impedance Manometry

HRIM was performed in a standardized protocol.[22] The catheter was inserted nasally in seated position, following local anesthesia with lidocaine gel of the nostrils. Resting pressures of the lower and upper esophageal sphincters were measured after an adaption period of approximately 2 minutes. Then, 10 single swallows, each with 10 mL of water, were performed in semi-upright position. Afterwards, patients were asked to eat a test meal consisting of cooked plain white rice (200 g portion) at liberty, but within a maximum period of 8 minutes, as previously discussed.[3,23] Before and after the test meal, a rapid drink challenge of 200 mL water using a drinking straw was performed.

Esophagogastric Junction Outflow Obstruction Classification

HRIM findings were classified according to CC v3.0 based on 10 single water swallows. EGJOODs were subdivided in achalasia type I-III and EGJOO (Fig. 1).[2] Patients not classifying for EGJOO according to CC v3.0 were reevaluated for EGJOO according to recently published indicative HRIM values[3] during the test meal (Fig. 1D-F).

Opioids and Alcohol

Data on alcohol consumption and opioid use were collected from medical records. Alcohol consumption (sporadic and/or regular) was assessed by patient history. Excessive alcohol consumption was defined as > 2 standard units (24 g alcohol) daily for men and > 1 standard unit (12 g alcohol) for women according the Federal Center for Health, Germany. Opioid use was assessed by patients' medication lists. In all opioid users morphine equivalent doses (MED) were calculated.

Statistical Methods

Statistical analysis was performed with R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Numerical data are presented as mean ± standard deviation (SD) for normally distributed data, and as median and interquartile range (IQR) in not normally distributed data. Normal distribution was assessed visually with normal quantile-quantile plots. For 2-group comparison of categorical data, Pearson's chi-squared test, Fisher's exact test, and odds ratios (OR) were used. The multivariate analysis was based on the type of EGJOOD, opioid, and alcohol consumption as well as demographics. For the analysis of MED in relation to EGJOOD Kruskal Wallis test was used. A P-value < 0.05 was considered statistically significant. All tests were 2-tailed.

Results

Patient Characteristics and Demographics

A total of 375 consecutive patients with no evidence of organic disease at upper endoscopy were considered. The prevalence of EGJOODs among all analyzed patients was 30.7% (115/375). Major motility disorders other than EGJOODs were diagnosed in 20.3% (75/375) of patients and minor motility disorders in 6.6% (25/375) of cases. In the group of EGJOODs the prevalence of achalasia type I was 2.6% (3/115), type II 24.3% (28/115), type III 8.7% (10/115), EGJOO (CC v3.0) 30.4% (35/115), and EGJOO (standardized test meal [STM]) 33.9% (39/115). Demographics of the group with EGJOODs were significantly different compared to the non-EGJOOD group regarding age (64 years vs 53 years, $P < 0.001$), but not regarding gender (46.9% vs 52.7%, $P = 0.362$). Indication for HRIM (multiple symptoms accepted) were dysphagia (45.4%), upper abdominal discomfort (40.3%), acid regurgitation (37.1%), heartburn (33.9%), and regurgitation of liquid and solid foods (18.4%).

Association of Esophagogastric Junction Outflow Obstruction Disorders With Opioids

Indications for opioid consumption were musculoskeletal pain

syndromes in 20/28 patients (71.4%), codeine use for cough in 2 (7.1%), methadone maintenance treatment in 2 (7.1%), loperamide use for chronic diarrhea in 1 (3.6%), and unknown indications in 3 patients (10.7%). All included opioid types are listed in Figure 2.

Opioid consumption was significantly more prevalent in patients with EGJOODs (14.7% [17/115]) as compared to patients without EGJOODs (4.2% [11/260]) (OR, 3.9; 95% CI, 1.8-8.9) (Fig. 3A). Within the group of opioid consumers, patients with EGJOODs consumed significantly higher doses of morphine ($P = 0.023$) (Fig. 4). Prevalence of EGJOODs in patients with

MEDs higher than 100 mg per day was 100.0% (7/7) while it was 47.6% (10/21) in patients consuming less than 100 mg.

Patients with achalasia type III had the highest prevalence of opioid usage (20.0% [2/10]), followed by EGJOO (water swallow, CC v3.0; 17.1%, 6/35), EGJOO (STM 15.4% [6/39]), achalasia type II (10.7% [3/28]), and achalasia type I (0.0% [0/3]) (Fig. 3B). No association of opioid consumption with other major and minor motility disorders was found.
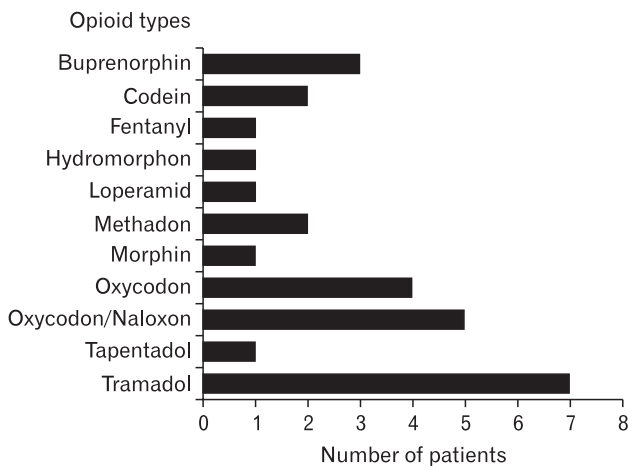

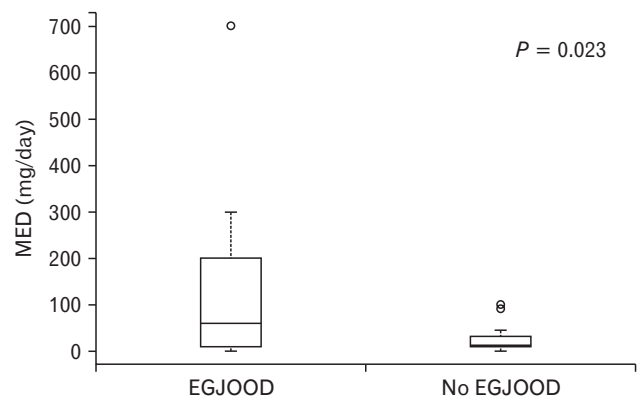**Figure 2.** Number of patients using opioids.

Figure 4. Morphine equivalent doses (MED) in opioid consumers in relation to esophagogastric junction outflow obstruction disorder (EGJOOD). The Kruskal-Wallis test was used for statistical analysis.
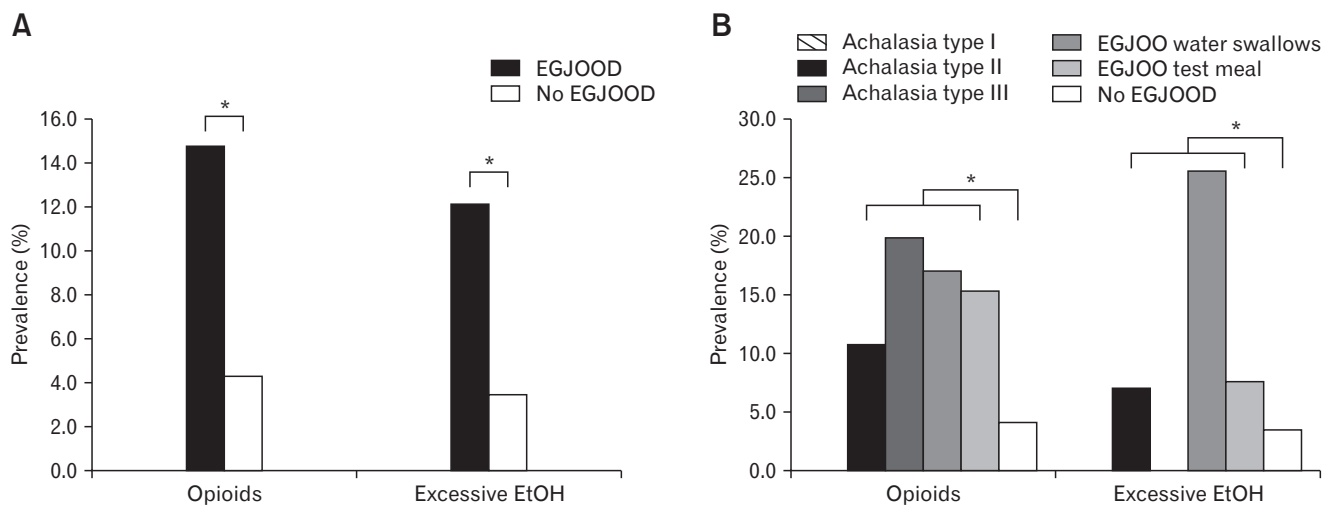

Figure 3. Prevalence of opioid and excessive alcohol consumption in patients according to esophagogastric outflow obstruction disorder (EGJOOD). (A) Prevalence of opioid consumption and excessive alcohol (EtOH) consumption in patients with EGJOOD versus patients without EGJOOD. (B) Prevalence of opioid consumption and excessive EtOH consumption in patients with achalasia type I-III, esophagogastric outflow obstruction (EGJOO) Chicago classification version 3.0, EGJOO in test meals and patients without any EGJOOD. *$P < 0.01$, generalized linear model was used for the multivariate analysis.
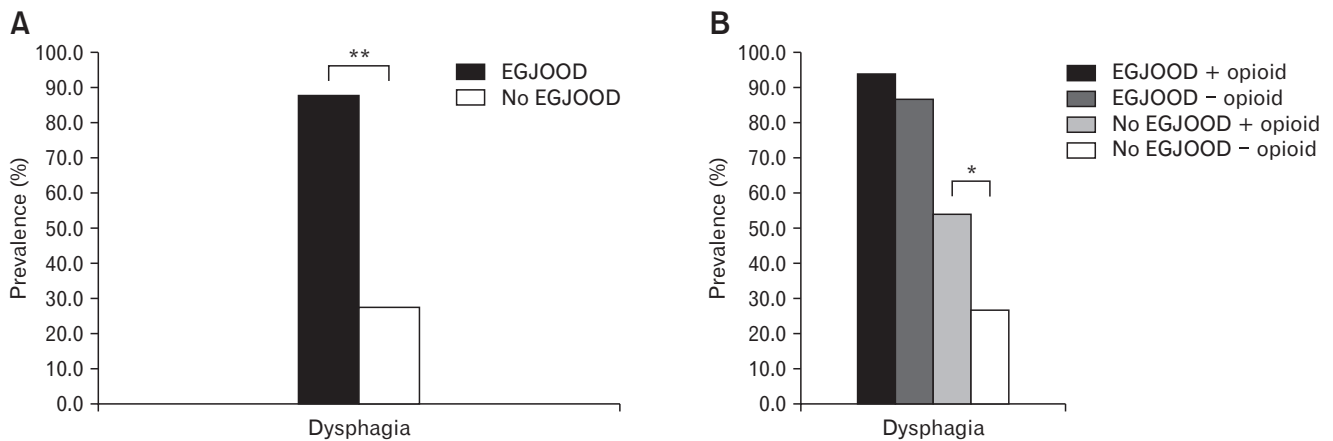
Figure 5. Patients with dysphagia according to esophagogastric outflow obstruction disorder (EGJOOD). (A) Prevalence of dysphagia in patients with EGJOOD vs patients without EGJOOD. (B) Patients with and without EGJOOD and/or opioids reporting dysphagia. *$P < 0.1$, **$P < 0.001$ (Pearson's chi-squared test).

Association of Esophagogastric Junction Outflow Obstruction Disorders With Alcohol Consumption

Of all patients diagnosed with EGJOODs, 12.2% (14/115) were found to excessively consume alcohol versus only 3.5% (9/260) in the group of patients without an EGJOOD (OR, 3.9; 95% CI, 1.6-9.5) (Fig. 3). In a subgroup analysis we also found a significantly different prevalence of EGJOODs according to the amount of alcohol consumption ($P = 0.006$). In excessive alcohol consumer the prevalence of EGJOODs was 60.9% (14/23), in occasional alcohol consumers 25.8% (34/132), in patients with rare alcohol consumption 25.0% (15/60) and in abstinent patients 32.5% (52/160).

In the subgroup analysis of EGJOODs (achalasia type I to III vs non-achalasia EGJOO, according to CC v3.0 and STM), we found excessive alcohol consumption in only 4.8% (2/41) of achalasia patients but 16.2% (12/74) of patients with an EGJOO itself ($P < 0.001$).

Effect of Opioids and Excessive Alcohol Consumption on Upper Gastrointestinal Symptoms

Dysphagia and regurgitation were found significantly more often in patients with EGJOODs (OR, 18.5; 95% CI, 10.2-35.7 and OR, 23.0; 95% CI, 11.8-48.9, respectively) (Fig. 5A). In contrast, other symptoms such as heartburn, upper abdominal discomfort, chronic cough, and cervical globus sensation were predominantly found in patients without EGJOODs. Interestingly, a subgroup analysis showed a trend towards a higher prevalence of dysphagia in the group of non EGJOODs patients if those patients were treated with opioids (Fig. 5B). No other symptoms were influenced by concurrent opioid usage. Excessive alcohol consumption, however, did not influence any of the described symptoms.

Discussion

In this single-center, retrospective study, we reviewed the data of 375 consecutive patients with unremarkable endoscopy who had undergone HRIM for symptoms of esophageal dysfunction. In order to increase the diagnostic sensitivity for EGJOODs, STMs were used additionally to the single water swallows as published recently.[23] In particular, we investigated the association between esophageal abnormalities and alcohol as well as opioids use. Opioid usage has recently become a global epidemic, most pronounced in North America.[24-26] Similarly, the rate of excessive alcohol abuse has increased significantly in many parts of the world.[27-29] Hence, the understanding of adverse effects of opioids and alcohol abuse with potential effects on esophageal motility is of evermore importance. Our analysis revealed several findings: first, we found that the prevalence of opioid usage was significantly higher in patients with EGJ outflow obstruction compared to the group without an EGJOOD. Interestingly we also found in the context that within the group of opioid consumers, patients with EGJOODs consumed significantly higher doses of opioids suggesting a dose dependent opioid effect. It has to be pointed out that all opioids were taken for indications unrelated to EGJOODs. Interestingly, patients diagnosed with achalasia type III had the highest prevalence of opioid consumption, followed by EGJOO. In contrast, we neither found an association of major motility disorders such as hypercontractile esophagus nor minor motility disorders with opioid usage.

Second, our analysis revealed that dysphagia, a cardinal symptom of achalasia, tended to be more frequent in patients without EGJOOD that were treated with opioids. This indicates that in addition to the well-known adverse effects like constipation and nausea, opioids might also cause esophageal symptoms even in the absence of a quantifiable EGJOODs, suggesting either subclinical outlet dysfunction or an influence on the sensory component. In agreement to the above mentioned investigation, a recent study analyzing the prevalence of opioid usage in a group of patients diagnosed with achalasia found that opioid usage was most common in type III achalasia.[13] Furthermore, a study comparing patients on and off opioid medication revealed that opioid usage within 24 hours of HRIM was associated with a higher frequency of EG-JOO as well as type III achalasia.

Third, we identified a significant association between excessive alcohol consumption and EGJOODs, especially in patients diagnosed with non-achalasia EGJOO. After the exclusion of external compression of the EGJ, the underlying etiology and pathophysiology of the EGJOO is poorly understood: a recent study identified a decreased immune-reactivity of endothelial nitric oxide synthase in the esophageal myenteric plexus, additionally to a significantly decreased serotonin-induced relaxation of the LES in ethanol-fed rats.[20] In line with the limited animal data, we speculate that excessive alcohol consumption might lead to EGJOO by interfering with the nitric oxide mediated relaxation of the LES. A possible other mechanism might be mediated via an increased rate of gastroesophageal reflux, which in turn leads to inflammation and consecutive stiffening of the EGJ. The latter hypothesis would also explain why alcohol abuse is only associated with the EGJOO itself, but with no other motility disorders of the esophageal body such as achalasia. Other alcohol induced causes might be neuropathy or impairment of contractile proteins, as previously hypothesized for bowel motility disorders.[20]

We recognize that our study does have certain limitations. The retrospective nature of the study is connected to a risk of confounding factors despite the usage of a multivariate modelling to mitigate this problem. Even though the study was conducted at a university hospital with patients from a wide geographical area, it was a single center study in a tertiary center which further limits the generalizability. Moreover, we do not have any HRIM data after cessation of opioid treatment or excessive alcohol consumption which hinders us to directly compare patients "on" and "off" opioids/excessive alcohol. Hence, to reveal the exact pathophysiologic mechanisms of opioid and ethanol induced EGJOODs, more basic and clinical research, including multicenter studies, are needed.

In summary, our data support the hypothesis of heterogeneous pathophysiologic processes and etiology of EGJOODs, which might not only be triggered by autoimmune disease as proposed for achalasia type I and II.[4,9,30] In accordance to the presented data, we suggest an important role and dose dependent effect of opioids and alcohol in the development of EGJOODs. Especially the high prevalence of opioid treatment and excessive ethanol consumption in patients diagnosed with achalasia type III and EGJOO may be the result of ganglionic dysfunction or imbalance of the proposed excitatory and inhibitory neurotransmission of the LES region. Since some of these proposed effects are potentially reversible, further studies are warranted investigating the replacement or stoppage of the identified triggers as a feasible treatment option in patients with type III achalasia or classical outflow obstruction. In addition, our results emphasize the importance of a detailed history taking regarding medication and alcohol consumption in patients presenting with suspected esophageal dysfunction and dysphagia.

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