ORIGINAL ARTICLE

Observational Study

Chronic opioids in gastroparesis: Relationship with gastrointestinal symptoms, healthcare utilization and employment

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Abstract

AIM

To examine the relationship of chronic scheduled opioid use on symptoms, healthcare utilization and employment in gastroparesis (Gp) patients.

METHODS

Patients referred to our tertiary care academic center from May 2016 to July 2017, with established diagnosis or symptoms suggestive of Gp filled out the Patient Assessment of Upper GI Symptoms, abdominal pain and demographics questionnaires, and underwent gastric emptying and blood tests. They were asked about taking pain medicines and the types, doses, and duration. We used Mann Whitney U test, Analysis of Variance, Student's t test and χ^2 tests where appropriate for data analyses.

RESULTS

Of 223 patients with delayed gastric emptying, 158 (70.9%) patients were not taking opioids (GpNO), 22 (9.9%) were taking opioids only as needed, while 43 (19.3%) were on chronic (> 1 mo) scheduled opioids (GpCO), of which 18 were taking opioids for

reasons that included gastroparesis and/or stomach pain. Median morphine equivalent use was 60 mg per day. GpCO reported higher severities of many gastrointestinal symptoms compared to GpNO including nausea (mean ± SE of mean of 4.09 ± 0.12 *vs* 3.41 ± 0.12, *P* = 0.011), retching (2.86 ± 0.25 *vs* 1.98 ± 0.14, *P* = 0.003), vomiting (2.93 ± 0.24 *vs* 2.07 ± 0.15, *P* = 0.011), early satiety (4.17 ± 0.19 *vs* 3.57 ± 0.12, *P* = 0.004), post-prandial fullness (4.14 ± 0.18 *vs* 3.63 ± 0.11, *P* = 0.022), loss of appetite (3.64 ± 0.21 *vs* 3.04 ± 0.13, *P* = 0.039), upper abdominal pain (3.86 ± 0.20 *vs* 2.93 ± 0.13, *P* = 0.001), upper abdominal discomfort (3.74 ± 0.19 *vs* 3.09 ± 0.13, *P* = 0.031), heartburn during day (2.55 ± 0.27 *vs* 1.89 ± 0.13, *P* = 0.032), heartburn on lying down (2.76 ± 0.28 *vs* 1.94 ± 0.14, *P* = 0.008), chest discomfort during day (2.42 ± 0.20 *vs* 1.83 ± 0.12, *P* = 0.018), chest discomfort at night (2.40 ± 0.23 *vs* 1.61 ± 0.13, *P* = 0.003), regurgitation/reflux during day (2.77 ± 0.25 *vs* 2.18 ± 0.13, *P* = 0.040) and bitter/acid/sour taste in the mouth (2.79 ± 0.27 *vs* 2.11 ± 0.14, *P* = 0.028). GpCO had a longer duration of nausea per day (median of 7 h *vs* 4 h for GpNO, *P* = 0.037), and a higher number of vomiting episodes per day (median of 3 *vs* 2 for GpNO, *P* = 0.002). Their abdominal pain more frequently woke them up at night (78.1% *vs* 57.3%, *P* = 0.031). They had a lower employment rate (33.3% *vs* 54.2%, *P* = 0.016) and amongst those who were employed less number of working hours per week (median of 23 *vs* 40, *P* = 0.005). They reported higher number of hospitalizations in the last 1 year (mean ± SE of mean of 2.90 ± 0.77 *vs* 1.26 ± 0.23, *P* = 0.047).

CONCLUSION
GpCO had a higher severity of many gastrointestinal symptoms, compared to GpNO. Hospitalization rates were more than 2-fold higher in GpCO than GpNO. GpCO also had lower employment rate and working hours, when compared to GpNO.

Key words: Opioid; Gastroparesis; Symptoms; Hospitalizations; Employment

Core tip: Chronic opioid use can cause gastrointestinal side effects and negatively influence the quality of life. The impact of chronic opioid use on symptoms, healthcare utilization, and employment of gastroparesis patients is not well studied. In our study, gastroparesis patients on chronic scheduled opioids had more severe gastrointestinal symptoms, less work productivity and more frequent hospitalizations compared to gastroparesis patients without opioid use. Whether opioid use is to treat a higher symptom severity from gastroparesis, or the opioid use worsens symptoms requires further study.

INTRODUCTION

Opioid use has become a healthcare epidemic in United States with increasing prescription rates in the recent years, and over 3% of the adults are now chronically using opioids[1-3]. In 2013, the overall cost burden from opioids in United States was estimated to be $78.5 billion[4]. A recent systematic review identified mean costs to the payer (commercial or private insurance) of $23000-$25000 per year for the opioid misusers, approximately $15000 more than the non-opioid users[5].

Patients on chronic opioids are more likely to have bowel related issues[2]. The wide array of gastrointestinal symptoms that the patients on chronic opioids may experience, including constipation (38%-63%), gastroesophageal reflux disease (33%), nausea (20%-90%), vomiting (9%-84%), bloating (24%-75%) and delayed gastric emptying are known as opioid induced bowel dysfunction[2,6-13]. The actual incidence of some of these side effects may even be higher as many patients tend to underreport their symptoms, and may self-adjust their regimen to avoid side effects[12]. Approximately 6% of the chronic opioid patients develop worsening chronic or intermittent abdominal pain (AP) even with continuous or increasing doses of opioids, a condition termed narcotic bowel syndrome[8]. The opioid-induced gastrointestinal side effects are often not anticipated while prescribing these medications, and may lead to increase healthcare utilization[9].

Despite the known gastrointestinal side effects of opioids, they are used in some patients with gastroparesis (Gp). Previous studies reported that 30%-46% of the Gp patients regularly use opioids[10,14,15]. In addition to opioids causing constipation, opioids slow gastric emptying and also can cause nausea and vomiting by activating the chemoreceptor trigger zone in the area postrema at the floor of the fourth ventricle[9,16]. Moreover, it has been shown that Gp patients on opioids may have worse outcomes with medical treatment with prokinetics agents and after gastric pacemaker placement[14].

The aim of this study was to examine the relationship of chronic opioid use on symptoms, healthcare utilization and employment in patients referred for Gp. We studied gastroparesis patients; comparing those on chronic scheduled opiates (GpCO) to gastroparesis patients

not taking opiates (GpNO).

MATERIALS AND METHODS

Patients referred to our tertiary care academic center gastroenterology motility clinic at Temple University Hospital (TUH) with established diagnosis of gastroparesis, or patients who presented with symptoms suggestive of gastroparesis from May 2016 to July 2017 (*n* = 303) were studied. This observational study was reviewed and approved by the TUH Intuitional Review Board. Patients are often referred to our motility clinic for persistent or refractory symptoms of gastroparesis. Subjects were recruited at the end of their regularly scheduled appointments after obtaining informed consent. Inclusion criteria were the following: (1) adults aged 18 to 80 years old; (2) symptoms suggestive of gastroparesis; and (3) delayed gastric emptying on scintigraphy.

On their initial evaluation, patients were asked to fill out a questionnaire about their clinical condition. This questionnaire contained the following: Patient Assessment of Upper Gastrointestinal Symptom (PAGI-SYM), Abdominal Pain Questionnaire, and demographic questionnaire. Patients underwent 4-h gastric emptying scintigraphy (GES)[17] if had not already recently been performed. Blood tests were obtained (see below). A retrospective review of the questionnaires, gastric emptying scintigraphy and blood tests was subsequently performed.

Questionnaires

PAGI-SYM: This validated questionnaire for upper gastrointestinal symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease asked patients to rate the severity of 20 common gastrointestinal symptoms over the past two weeks[18]. Patients were asked to rate symptoms over the prior two weeks as none (0), very mild (1), mild (2), moderate (3), severe (4), and very severe (5). They were also asked to rate symptoms of diarrhea and constipation on the same scale. In addition, they were asked about the duration of nausea per day in the past week, number of episodes of vomiting and bowel movements in the past week. We also asked the patients about the frequency of some of their gastrointestinal symptoms over the preceding 3 mo using the Rome IV questionnaires[19].

Abdominal pain questionnaire: This questionnaire was modified from previous studies assessing the presence and severity of abdominal pain in chronic pancreatitis[20,21]. If abdominal pain was present, patients filled out the remaining portion of the questionnaire asking about the duration, location of the most severe pain, relationship of pain to meals and nocturnal awakenings as a result of the pain.

Demographics questionnaire: This questionnaire asked patients to report information such as age, gender, race/ethnicity, height, weight, smoking history, alcohol usage, employment and working hours per week if employed. It also asked about the length of diagnosis with Gp, history of diabetes, and prior abdominal surgeries. Patients were asked about taking pain medicines and the types, doses, frequency, clinical indication and total duration of pain medicine use.

Laboratory analysis

Patients underwent blood drawing including hemoglobin A1c and thyroid stimulating hormone, as hyperglycemia and hypothyroidism are risk factors for delayed gastric emptying[22,23]. We also checked serum trypsinogen level as symptoms of Gp can resemble those of chronic pancreatitis (CP)[24]. Lastly, we ordered random serum cortisol levels as opioid-induced adrenal insufficiency has been reported in the literature[25-27].

Gastric emptying scintigraphy

Gastric emptying scintigraphy was performed using a low-fat, egg white meal with imaging at 0, 1, 2, 4 h after meal ingestion[17]. Patients were instructed to stop medications that could affect gastrointestinal motility (including prokinetics) for 48 h prior to the study and to come to the Nuclear Medicine Section in the morning after fasting overnight, that is, an 8 h fast. The patients on chronic opioids were advised to gradually taper off their opioids as tolerated prior to their scheduled GES to prevent opioid withdrawal. Diabetics have their glucose checked at the beginning of the study, with appropriate treatment measures being taken if low blood sugar (hypoglycemia) or high blood sugar (hyperglycemia > 250 mg/dL) is detected. Gastric emptying scintigraphy is performed using a standard low-fat, Eggbeaters® meal to measure solid emptying. The meal consists of the equivalent of two large eggs radiolabeled with 0.5-1 mCi Tc-99m sulfur colloid served with two pieces of white bread and jelly. Patients are given 120 mL water. Following ingestion of the meal, imaging is performed at 0, 1, 2 and 4 h with the patient standing upright for measuring gastric emptying of Tc-labeled solids. Gastric emptying is analyzed as percent of radioactivity retained in the stomach over time using the geometric center of the decay-corrected anterior and posterior counts for each time point. Gastric retention of Tc-99m > 60% at 2 h. and/or > 10% at 4 h is considered delayed gastric emptying of solids.

Statistical analysis

We used Kolmogorov-Smirnov test to determine the normal distribution of continuous variables; Student's *t*-test was used for variables with normal distribution, while Mann Whitney *U* Test was used for variables with skewed distribution and symptoms assessed on ordinal scale. These results are expressed as mean ± SE of mean, or median with interquartile range as

appropriate. χ^2 test was used for categorical data, with results expressed as percentages[28]. A two-tailed *P* value less than 0.05 was considered as statistically significant while comparing chronic opioid using Gp patients to non-opioid users; no adjustment for multiple comparisons was made. Analysis of Variance (ANOVA) was used for comparison of multiple groups, followed by Students; *t*-test with *p* value adjusted with Bonferroni correction for multiple comparisons. Unanswered questions were excluded from the analyses. Gp patients who were using opioids as needed (*n* = 22) were not included in the analyses. Statistical review of the study was performed by an epidemiologist/statistician of our department.

RESULTS

Patients
Of 303 patients referred for symptoms suggestive of gastroparesis in 15 mo, 80 patients had normal gastric emptying tests and were excluded from the analyses. Of the remaining 223 patients, the majority (*n* = 196, 87.9%) had previously been diagnosed with Gp. More than half (52%) of the Gp patients came from outside the catchment area of TUH that we defined as more than 50 miles from our center. The most frequent type of Gp was idiopathic Gp (*n* = 122; 54.7%), followed by diabetic Gp (*n* = 62, 27.8%), post-surgical Gp (*n* = 20; 9.0%), and atypical Gp (*n* = 19; 8.5%) (Table 1). The median age of these patients was 44 years (interquartile range of 32 to 56 years), and 80.7% were females. Amongst 210 patients who reported their race, the most common races were Whites (79.4), African Americans (7.6%) and Hispanics (6.7%). Over two third of patients with Gp (*n* = 158, 70.9%) were not taking opioids, 22 (9.9%) were taking opioids only as needed, while 43 (19.3%) were on chronic scheduled opioids (Table 1).

Gastroparesis patients on chronic scheduled opioids
Amongst the 43 patients on chronic scheduled opioids, 6 (14%) were taking opioids exclusively for Gp and/or stomach pain, while another 12 (27.9%) were taking opioids for reasons that included Gp and/or stomach pain. Other frequent causes of opioid use included back pain (*n* = 27, 62.8%), leg pain (*n* = 10), arthritis (5), fibromyalgia (4), Reflux Sympathetic Dystrophy (3), and neuropathy (2). Nearly one fourth of these patients (*n* =10, 23.3%) were taking more than 1 opioid. The opioids used chronically included oxycodone (18 patients), fentanyl (9), methadone (5), morphine (5), tramadol (5), hydromorphone (4), hydrocodone (3), and oxymorphone (2). Median duration of narcotic use was 2 years (interquartile range of 0.6-6.5 years). Median oral morphine equivalent dose for GpCO was 60 mg/d, with interquartile range of 22.5 mg to 112.5 mg per day.

Patients with diabetic gastroparesis were more likely to be on chronic scheduled opioids (24.2 % *vs* 18.9%), or as needed opioids (14.5% *vs* 4.9%), when compared to the patients with idiopathic gastroparesis who were more likely to be non-opioid users (76.2% *vs* 61.3%), *P* = 0.039. Thirty-three Gp patients on chronic opioids were able to recall the duration of their Gp symptoms as well as chronic opioid use. Out of these, about 1 in every 4 GpCO (27.3%) stated that they started using opioids chronically before their symptoms of Gp started. For another 21.2% of GpCO, the duration of opioid use was the same as the duration of their Gp symptoms. For 51.5% of GpCO, the Gp symptoms started before the use of chronic opioids. Of note however, we had to rely on patients' recall for the duration of their opioids use, and patients reported drug ingestion histories can often be inaccurate[29].

GpCO and GpNO did not have any statistically significant difference in their age, duration of symptoms, gender, body mass index, racial distribution, history of diabetes, and past surgeries on esophagus and stomach (Table 2). GpCO were more likely to be active smokers (31.7% *vs* 13.0%, *P* = 0.004). There was a trend towards higher prior and/or current alcohol use in GpNO compared to GpCO (37.4 % *vs* 23.8% respectively, *P* = 0.100), as well as current alcohol use (20.0% *vs* 7.3% respectively; *P* = 0.057).

Laboratory studies
GpCO were also more likely to have low trypsinogen levels compared to GpNO (23.1% *vs* 4.2% respectively, *P* = 0.004). However, only about half of these patients had their trypsinogen levels drawn (Table 2). Among GpCO, 16.2% had low random serum cortisol levels, *vs* 10.4% among GpNO, *P* = 0.345 (Table 2). We did not confirm the diagnosis of adrenal insufficiency by checking adrenocorticotrophic hormone or by performing stimulation test; this requires further study to determine the actual incidence of adrenal insufficiency in chronic opioid using Gp patients. There was no statistically significant difference in the other laboratory tests, including hemoglobin A1c, thyroid stimulating hormone.

Gastric emptying scintigraphy
On gastric emptying tests, there was no difference between GpCO and GpNO at 2 h (median of 62% *vs* 66%, normal ≤ 60%) and 4 h (median of 22% *vs* 24%, normal ≤ 10%) (*P* > 0.05) (Table 2). Amongst GpCO 11 patients (25.6%) had severe delays in gastric emptying (> 35% retention at 4 h), compared to 30 patients (19%) in GpNO (*P* = 0.341).

Opioids did not seem to have a dose-related effect on the delay in gastric emptying, as we did not find any difference in the four quartiles of GpCO based on morphine equivalents per day by comparing the gastric emptying results of these groups using ANOVA (Table 3). We also calculated Pearson correlation coefficient

Table 1 Patients with gastroparesis referred to a tertiary care center between May 2016 and July 2017

Classification	Total	Chronic scheduled opioids	PRN opioids	No opioids
Idiopathic	122	23	6	93
Diabetic	62	15	9	38
Post-surgical[1]	20	2	5	13
Atypical[2]	19	3	2	14
Total	223	43	22	158

[1]Post-surgical gastroparesis consisted of patients with history of duodenal-jejunostomy, esophagectomy, fundoplication, gastric sleeve, gastric banding, gastric bypass, hiatal hernia repair, and vagotomy with pyloroplasty. [2]Atypical gastroparesis consisted of gastroparesis patients with history of Bulimia, Complex Regional Pain Syndrome, Ehlers Danlos Syndrome, Lupus, Parkinson's Disease, Reflux Sympathetic Dystrophy, Scleroderma and Sjogren's Syndrome.

between opioid dose and delay in gastric emptying, and there was no significant correlation between morphine equivalents per day and gastric retention at 2 h ($r < 0.01$, $P = 0.988$) or 4 h ($r = 0.19$, $P = 0.356$).

Of note, 14 patients on chronic scheduled opioids were still taking opioids at the time of their GES, which may have resulted in the delay in their gastric emptying. However, when we compared these patients to GpCO who were able to taper off the opioids prior to the study, there was no difference in gastric retention at 2 h (median of 60% *vs* 70% respectively, $P = 0.461$) and 4 h (16% *vs* 20%, $P = 0.718$).

GI Symptoms
GpCO had higher symptom severities of many GI symptoms including nausea, retching, vomiting, early satiety, post-prandial fullness, loss of appetite, upper abdominal pain, upper abdominal discomfort, heartburn during day, heartburn on lying down, chest discomfort during day, chest discomfort at night, regurgitation/reflux during day, and bitter/acid/sour taste in the mouth compared to GpNO ($P < 0.05$) (Table 4). The severity of constipation was not statistically different between the two groups (2.92 ± 0.30 in GpCO, compared to 2.63 ± 0.14 in GpNO, $P = 0.296$). On PAGI-SYM questionnaire, the total symptom severity score in GpCO was also higher than GpNO (Table 4).

As stated previously the median morphine equivalent use in GpCO was 60 mg per day. When we compared GpCO taking more than 60 mg morphine equivalents per day to GpCO taking 60 mg per day or less, the patients taking more than 60 mg per day reported more severe heartburn during the day (3.30 ± 0.45 *vs* 2.0 ± 0.21, $P = 0.023$). There was also a trend towards more severe heartburn in recumbent position (3.30 ± 0.46 *vs* 2.30 ± 0.38, $P = 0.116$), and bitter, acid or sour taste in the mouth (3.50 ± 0.44 *vs* 2.30 ± 0.36, $P = 0.058$) amongst GpCO taking more than 60 mg morphine equivalents per day (results not

shown).

When we compared GpCO with severe delay in gastric emptying (> 35% at 4 h) with GpCO with mild to moderate delay in gastric emptying, there was no difference in symptom severity on PAGI-SYM questionnaire, and we did not notice any differences in the impact of gastroparesis on their employment and healthcare utilization (results not shown).

GpCO had a longer duration of nausea per day in the past week (median of 7 h *vs* 4 h in GpNO, $P = 0.037$), as well as higher number of vomiting episodes per day (median of 3 *vs* 1 in GpNO, $P = 0.002$) but there was no statistically significant difference in the number bowel movements in the past week (Table 5).

AP was frequently present in GpCO and GpNO (84.1% and 85.2% respectively, $P = 0.861$). Epigastrium was the most common location of the most severe AP in GpNO (44.2%); while GpCO most commonly had their most severe AP in periumbilical area (41.7%) followed by epigastric area (38.9%), $P = 0.863$. AP got worse with meal intake in majority of patients (76.5% in GpCO *vs* 80.0% in GpNO, $P = 0.508$). There was no difference in the overall duration of AP (median of 2 years in GpCO *vs* 1.5 years in GpNO, $P = 0.526$). AP more frequently woke up GpCO at night compared to GpNO (78.1% *vs* 57.3%, $P = 0.031$).

Nausea and vomiting were more frequent in GpCO in the past 3 mo (Table 6); 92.5% of GpCO had nausea interfering with their activities at least once a week or more frequently *vs* 76% amongst GpNO ($P = 0.021$).

Employment
The employment rate was lower in GpCO compared to GpNO (33.3% *vs* 54.2%, $P = 0.016$). The average number of working hours per week in GpCO (who were employed) was also lower than GpNO (median of 23 h *vs* 40 h respectively, $P = 0.005$).

It is plausible that a higher severity of abdominal pain in GpCO compared to GpNO was affecting employment. However, when we studied only those patients who had moderate to very severe abdominal pain as one of the symptoms from gastroparesis, GpCO still had a lower rate of employment (35.9% *vs* 54.5%, $P = 0.037$), and lower number of working hours per week (median of 20 h *vs* 40 h, $P = 0.003$), compared to GpNO. In GpCO on more than 60 mg morphine equivalents per day, there was a trend towards less working hours per week compared to GpCO on 60 mg or less morphine equivalents per day (median of 17.5 h *vs* 26 h, $P = 0.071$).

Health care utilization
There were higher number of hospital admissions for GpCO in the past year compared to GpNO (2.90 ± 0.77 *vs* 1.26 ± 0.23, $P = 0.047$) (Table 7). There was a trend towards a higher number of emergency room

Table 2 Gastroparesis patients: Demographics, employment, social history, laboratory tests and gastric emptying test in chronic opioid using gastroparesis patients, and patients with no opioid use

	Chronic scheduled opioids	No opioids	P value
Age (median in years with IQR)	49.0 (34.0-56.0)	[4]41.0 (30.0-55.0)	0.091
Age symptoms started (median in years with IQR)	40.0 (24.3-52.0)	[4]33 (22.8-47.3)	0.281
Average duration of symptoms (median in years)	[4]3.0 (1.0-15.5)	[4]4.0 (1.0-10.0)	0.937
Previously established diagnosis of Gp (%)	90.7% (39/43)	86.7% (137/158)	0.482
Female (%)	74.4% (32/43)	81.0% (128/158)	0.341
Body mass Index (median in kg/m^2 with IQR)	[4]24..3 (22.1-29.3)	[4]24.7 (20.3-30.8)	0.983
Race (% White)	83.3% (35/42)	83.9% (125/149)	0.917
Residing outside catchment area (50 miles)	53.5% (23/43)	51.6% (80/155)	0.828
Diabetes (%)	35.7% (15/42)	25.9% (41/158)	0.055
Surgery on stomach/esophagus (%)	28.6% (12/42)	19.1% (28/147)	0.136
Employed (%)	33.3% (14/42)	54.2% (84/155)	0.016
Working hours per week (median with IQR)	23.0 (10.5-35.0)	[4]40 (24.5-40.0)	0.005
Smoking history, current or past (%)	46.3% (19/41)	31.2% (48/154)	0.069
Current smoker (%)	31.7% (13/41)	13.0% (20/154)	0.004
Alcohol history, current or past (%)	23.8% (10/42)	37.4% (58/155)	0.100
Current alcohol use (%)	7.3% (3/41)	20.0% (30/150)	0.057
Random cortisol (% with low cortisol[1])	16.2% (6/37)	10.4% (11/106)	0.345
Hemoglobin A1c (median with IQR)	[4]5.9% (5.3%-7.7%)	[4]5.7% (5.4%-6.4%)	0.377
Thyroid stimulating hormone (% with high TSH[2])	4.9% (2/41)	1.7% (2/116)	0.271
Trypsinogen (% with low trypsinogen[3])	23.1% (6/26)	4.2% (3/72)	0.004
History of chronic pancreatitis	7.0% (3/43)	1.3% (2/158)	0.033
Gastric emptying scintigraphy: Retention at 2 h (median with IQR)	62% (50%-80%)	[4]66% (50%-72%)	0.359
Gastric emptying scintigraphy: Retention at 4 h (median with IQR)	[4]22% (14%-42%)	[4]24% (15%-35%)	0.522

[1]Low cortisol: AM less than 6.2 μg/dL (171 nmol/L), PM less than 2.3 μg/dL (63.4 μg/dL); [2]High TSH: Greater than 4.50 μIU/mL; [3]Low trypsinogen: Less than 19 ng/mL. [4]Results with non-normal distribution. Results expressed as median ± interquartile range, or percentage as appropriate. Gp: Gastroparesis; IQR: Interquartile range; TSH: Thyroid stimulating hormone.

Table 3 Comparison of gastric emptying scintigraphy results at different morphine equivalents per day in gastroparesis patients on chronic opioids using analysis of variance

Gastric emptying scintigraphy	1st quartile ($\leqslant$ 22.5 mg of morphine equivalents per day)	2nd quartile (> 22.5 mg/d, and $\leqslant$ 60 mg/d)	3rd quartile (> 60 mg/d, and $\leqslant$ 112.5 mg/d)	4th quartile (> 112.5 mg/d)	P value
Retention at 2 h (mean ± SEM)	68% ± 6%	54% ± 8%	84% ± 5%	60% ± 9%	0.157
Retention at 4 h (mean ± SEM)	31% ± 7%	21% ± 8%	37% ± 10%	36% ± 19%	0.678

SEM: Standard error of mean.

visits in the past year in GpCO compared to GpNO (5.13 ± 1.46 *vs* 3.74 ± 0.65) but this did not reach statistical significance (P = 0.468).

DISCUSSION

Our study shows that chronic opioid use is present in nearly one fifth of the gastroparesis patients referred for evaluation and treatment of their gastroparesis. Use of chronic opioids in these gastroparesis patients was associated with a higher severity of many gastrointestinal symptoms, especially the symptoms often attributable to gastroparesis. In addition, patients on chronic opioids had decreased work productivity, and more frequent hospitalizations.

The prevalence of chronic scheduled opioid use in our study (19.2%) is less than 30%-46% reported in other studies[10,14,15]. It is plausible that many of our patients on opioids as needed were also taking opioids at least once a day, and including these patients gives

a much higher prevalence of opioid use (29.1%). A significantly higher proportion of the Gp patients use opioids compared to the general adult population, which is estimated to be 3%[30].

Our study shows that Gp patients on chronic scheduled opioids have a higher severity of many upper gastrointestinal symptoms especially in those symptoms often attributable to gastroparesis. A higher frequency of upper gastrointestinal symptoms in patients taking opioids for chronic non-cancer pain (CNCP) has previously been reported[2]. Females have been shown to have a 60% greater chance of experiencing nausea and vomiting after receiving opioid therapy, which is noteworthy as majority of patients who suffer from Gp are females[12]. The female preponderance in our study is consistent with the previous literature that shows a higher prevalence of Gp and other functional gastrointestinal disorders in females[31]. The most common types of Gp in our population (idiopathic and diabetic) were also similar

Table 4 Symptom Severity as assessed with Patient Assessment of Upper Gastrointestinal Symptoms questionnaire; comparison between gastroparesis patients on chronic opioids and patients with no opioid use

GI symptom	GpCO (n = 43)	GpNO (n = 158)	P value
Nausea	4.09 ± 0.12	3.41 ± 0.12	0.011
Retching	2.86 ± 0.25	1.98 ± 0.14	0.003
Vomiting	2.93 ± 0.24	2.07 ± 0.15	0.011
Stomach fullness	3.84 ± 0.18	3.59 ± 0.11	0.254
Early satiety	4.17 ± 0.19	3.57 ± 0.12	0.004
Post prandial fullness	4.14 ± 0.18	3.63 ± 0.11	0.022
Loss of appetite	3.64 ± 0.21	3.04 ± 0.13	0.039
Bloating	3.67 ± 0.19	3.36 ± 0.13	0.396
Abdominal distension	2.95 ± 0.25	3.01 ± 0.14	0.753
Upper AP	3.86 ± 0.20	2.93 ± 0.13	0.001
Upper abdominal discomfort	3.74 ± 0.19	3.09 ± 0.13	0.031
Lower AP	2.67 ± 0.27	2.38 ± 0.13	0.315
Lower abdominal discomfort	2.79 ± 0.25	2.38 ± 0.13	0.130
Heartburn during day	2.55 ± 0.27	1.89 ± 0.13	0.032
Heartburn on lying down	2.76 ± 0.28	1.94 ± 0.14	0.008
Chest discomfort during day	2.42 ± 0.20	1.83 ± 0.12	0.018
Chest discomfort at night	2.40 ± 0.23	1.61 ± 0.13	0.003
Regurgitation or reflux during day	2.77 ± 0.25	2.18 ± 0.13	0.040
Regurgitation or reflux on lying down	2.64 ± 0.28	2.21 ± 0.14	0.120
Bitter/acid/sour taste	2.79 ± 0.27	2.11 ± 0.14	0.028
Constipation	2.92 ± 0.30	2.63 ± 0.14	0.296
Diarrhea	1.80 ± 0.30	1.79 ± 0.14	0.891
Total Symptom Severity Score	68.40 ± 2.82	56.63 ± 1.77	0.001

[1]Results with non-normal distribution. Results expressed as median with interquartile range, and percentage as appropriate. AP: Abdominal pain; BMs: Bowel movements; GpCO: Gastroparesis patients on chronic opioids; GpNO: Gastroparesis patients not on opioids.

Table 5 Comparison of gastrointestinal symptoms between gastroparesis patients on chronic opioids and patients with no opioid use trial[10,11,27]

	GpCO	GpNO	P value
Episodes of vomiting in last 1 wk	13.0 (1.0-7.0)	11.0 (0.0-3.0)	0.002
Hours of nausea/day in last 1 wk	17.0 (3.0-18.0)	14 (1.5-12.0)	0.037
Total number of BMs in last 1 wk	14.0 (2.0-7.0)	4.0 (2.0-7.0)	0.714
AP one of the symptoms (%)	84.1% (37/43)	85.2% (132/155)	0.861
Duration of AP (yr)	12.0 (0.5-4.0)	[1]1.5 (0.7-4.5)	0.526
Location of most severe AP	Umbilical 41.7% (15/36)	Epigastric 44.2% (57/129)	0.863
AP wakes up at night (%)	78.1% (7/32)	57.3% (71/124)	0.031
AP worse with meals (%)	76.5% (26/34)	80.0% (100/125)	0.508

[1]Results with non-normal distribution. Results expressed as median with interquartile range, and percentage as appropriate. AP: Abdominal pain; BMs: Bowel movements; GpCO: Gastroparesis patients on chronic opioids; GpNO: Gastroparesis patients not on opioids.

to previous studies on Gp[10,31].

In our study, the higher prevalence of opioid use in patients with diabetic gastroparesis compared to patients with idiopathic gastroparesis is possibly related to other co-morbidities, as both diabetic and idiopathic gastroparesis patients were equally likely to have abdominal pain as one of their symptoms of Gp, and there was no statistically significant difference in the severity of their abdominal pain or discomfort on PAGI-SYM questionnaire (results not shown). GpCO with diabetes more frequently reported using opioids for leg pain and/or neuropathy (33.3%) *vs* GpCO with idiopathic gastroparesis (21.7%), though the difference was not significant (P > 0.05).

The prevalence of abdominal pain in our study groups (> 80%) is towards the higher end of the reported prevalence of abdominal pain in Gp (42%-89%)[15]. Epigastrium was the most common location of the most severe AP, and majority of the patients with AP experienced post-prandial worsening of pain, similar to a previous study performed at our center on a different cohort of Gp patients[32]. Every 3 in 4 GpCO in our study woke up at night from AP, higher than about 1 in 2 of our GpNO patients and significantly higher than the reported 1 in 4 patients on opioids for CNCP reported by Tuteja *et al*[2]. It is possible that the abdominal pain may be the reason these patients were taking opioids. Alternatively, there could be enhanced pain perception in disabling narcotic bowel syndrome.

In this cohort, GpCO did not have increased severity of constipation, which is historically one of

Table 6 Frequency of symptoms in the past 3 mo using Rome IV questionnaire: comparison between gastroparesis patients with chronic scheduled opioid use and patients with no opioid use (percentage of patients with symptoms once a week or more often)

Symptom	GpCO	GpNO	*P* value
Post-prandial fullness interfering with activities	81.6% (31/38)	78.7% (118/150)	0.692
Unable to finish regular sized meal due to fullness	84.6% (33/39)	79.1% (117/148)	0.438
Epigastric pain/burning interfering with activities	75.0% (30/40)	66.9% (103/154)	0.324
Nausea interfering with activities	92.5% (37/40)	76.0% (117/154)	0.021
Vomiting	70.7% (29/41)	50.6% (78/154)	0.022
Bloating or stomach distension	72.5% (29/40)	68.8% (106/154)	0.653
Belching interfering with activities	62.5% (25/40)	51.3% (79/154)	0.206

GpCO: Gastroparesis patients on chronic opioids; GpNO: Gastroparesis patients not on opioids.

the most commonly reported symptoms of opioid induced bowel dysfunction[2]. Fentanyl was the second most commonly used opioid in GpCO, and a randomized cross over trial showed a lower prevalence of constipation in patients taking transdermal fentanyl compared to sustained release oral morphine[7]. Even though our questionnaire did not ask specifically about usage of stool softeners or laxatives, some of these patients had stool softeners (*n* = 4), stimulant laxatives (2) and osmotic laxative (1) listed on their medication list, and it is plausible that many other patients were on these over-the-counter medications as well, as these medications are often taken prophylactically in patients on chronic opioids[6,33]. Future studies can look into the prevalence of laxative use in opioid using gastroparesis patients. Our finding of higher severity of many gastrointestinal symptoms in GpCO compared to opioid-naïve Gp patients, despite no statistically significant difference in the 2 and 4 h retention in gastric emptying tests between the two groups is not novel, as Karamanolis et al showed that the symptom pattern in Gp is not determined by the severity of delay in gastric emptying[34].

Patients with Gp may have symptoms that mimic clinical manifestations of CP. In fact, Chowdhury *et al*[24] reported that 44% of small duct CP patients may have concomitant Gp. While the prevalence of CP in the general population is only 41.76 per 100000[35], the prevalence of CP in patients with Gp is not known. In our study, GpCO (7%) were more likely to have a history of CP compared to GpNO (1.3%). In addition, nearly one fourth (23.1%) of GpCO who had their trypsinogen levels checked had low levels, compared to < 5% in GpNO, suggesting some of our Gp patients using opioids chronically possibly had severe calcific CP with associated Gp, which might have been causing them abdominal pain. While the sensitivity of serum trypsinogen level in diagnosing CP was only 28%, the specificity was 100% in a study by Pezzilli *et al*[36].

Gp patients have been reported to have the longest length of hospital stay (5 d) amongst the functional gastrointestinal disorders[31]. Recent studies suggest increasing hospitalization due to Gp over the past 20 years[37-39]. A Nationwide Inpatient Sample Study reported 17220 admissions from Gp in 2012, a more than 400% increase compared to 1997[39]. Some authors suggest that the increasing hospitalization due to Gp comes from better recognition of this disorder[40]. Our study suggests a higher number of hospitalizations in GpCO than in Gp patients not taking opiates.

Our finding that GpCO are more likely to be unemployed and work less is consistent with the multinational questionnaire based study showing that the chronic use of opiates negatively influences the quality of life[41]. We found a higher prevalence of current smoking in GpCO, and a study by Young-Wolff *et al*[42] suggested a higher likelihood of opioid use disorder in current smokers *vs* non-smokers.

Our study has some limitations. Whether opioid use is to manage a higher severity of Gp symptoms, or is responsible for the higher severity of symptoms is unclear as we do not have symptoms of patients prior to starting opioids. Increased opioid use in Gp patients with moderate to severe abdominal pain has previously been reported[15], however nausea, vomiting and retching are frequently reported side effects of opioids and it is plausible that the opioid use itself explains the higher severity of these symptoms amongst GpCO in our study. Secondly, these patients were generally referred from community settings and over half of these patients were referred from outside the catchment area of our tertiary care center, with GpCO and GpNO equally likely to be referred from outside the catchment area. This was a questionnaire based study. Some of the questions were not answered by all the patients, and some patients did not go for the laboratory tests that we requested. These missed questions and laboratory tests were excluded from analyses, however their number were relatively small in most cases, and likely did not to affect the results. Lastly, since this is a questionnaire based study, there is a potential of recall bias as well. This would likely apply both to patients taking and those not taking opioid analgesics.

In conclusion, chronic regular opioid use is present in a significant number (19.3%) of gastroparesis patients. These patients have a higher severity of many gastrointestinal symptoms including those of Gp. They have decreased work productivity compared to non-opioid using Gp patients. Whether opioid use is to

Table 7 Comparison of healthcare utilization between chronic opioid using gastroparesis patients and patients with no opioid use

	GpCO (*n* = 43)	GpNO (*n* = 158)	*P* value
ER visits in last 1 yr from Gp	5.13 ± 1.46	3.74 ± 0.65	0.468
Hospital admissions in last 1 yr from Gp	2.90 ± 0.77	1.26 ± 0.23	0.047

Results expressed as mean ± SE of mean. ER: Emergency room; GpCO: Gastroparesis patients on chronic opioids; GpNO: Gastroparesis patients not on opioids.

treat a higher symptom severity from Gp, or opioid use itself worsens symptoms in patients with Gp requires further study.

ARTICLE HIGHLIGHTS

Research frontiers
Despite the gastrointestinal side effects associated with opioid use, they are used in some patients with gastroparesis. The relationship of opioid use to the gastrointestinal symptoms, healthcare utilization and employment is not known.

Research motivation
As opioid use had become a healthcare epidemic in United States, studies on opioid use in gastroparesis would be useful for clinicians and researchers.

Research objectives
This objective was to study the relationship of chronic scheduled opioid use to gastrointestinal symptoms, healthcare utilization and employment in gastroparesis patients.

Research methods
The authors used Mann Whitney *U* Test, Student's *t*-test, Analysis of Variance, and χ^2 test as appropriate for data analysis.

Research results
This study shows higher severity of many gastrointestinal symptoms, and more frequent hospitalizations in gastroparesis patients on chronic scheduled opioids, compared to gastroparesis patients not using opioids. Chronic opioid using patients also reported their work being effected more frequently by their gastrointestinal symptoms. The prevalence of chronic pancreatitis is also higher in opioid using gastroparesis patients.

Research conclusions
This study confirmed the hypothesis that chronic opioid use in gastroparesis is related with more severe gastrointestinal symptoms, and hospitalizations. Whether opioid use is to manage a higher severity of gastroparesis symptoms, or is responsible for the higher severity of symptoms is not clear as we did not have symptoms of patients prior to starting opioids. In clinical practice, this study implicates that the opioids may need to be used with caution in gastroparesis patients.

Research perspectives
Opioid use is quite prevalent in patients with gastroparesis. Opioid-using gastroparesis patients have more severe gastrointestinal symptoms. These opioid-using patients are more frequently hospitalized, compared to the patients without opioid use. They also more commonly report their employment being affected due to their gastrointestinal symptoms. Patients with gastroparesis may have chronic pancreatitis, possibly contributing to their gastrointestinal symptoms.

Future studies can look into the trends of laxative-use in opioid-using gastroparesis patients. The noticeable prevalence of chronic pancreatitis in gastroparesis patients in this study can be further confirmed in studies with larger sample size. This study found more frequent hospitalizations in gastroparesis patients; future studies to evaluate opioid use during hospitalizations in gastroparesis patients will add useful information to the current literature on gastroparesis.

Future research can look into opioid use in gastroparesis through different perspectives, this could be not only in the tertiary care centers, but also in smaller community settings so that the results more accurately reflect the generalized population. Moreover, bigger databases using diagnosis codes and medication-lists can be used to get a larger sample size.

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