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GLP-1 Receptor Agonist Use Does Not Increase the Risk of Respiratory Complications Post-Endoscopy

Jena Velji-Ibrahim, Piyush Nathani, Harsh K Patel, Prateek Sharma.

Affiliations below.

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Abstract:
Background and study aims: Data on respiratory complications associated with GLP-1 receptor agonist (GLP-1 RA) use before endoscopic procedures is limited.
Methods: We conducted a retrospective cohort study using TriNetX in adults with diabetes or obesity on GLP-1 RAs within three months of endoscopy, comparing them to non-GLP-1 RA users. Propensity score matching and Cox proportional hazards models assessed outcomes.
Results: Among 46,948 patients, no significant differences in post-endoscopy aspiration pneumonitis (HR 0.92, 95% CI: 0.54-1.56) or pneumonia (HR 1.01, 95% CI: 0.83-1.24) were found between groups.
Conclusion: GLP-1 RA use before endoscopy does not increase respiratory complications, supporting continued preoperative medication use.

Corresponding Author:
Dr. Jena Velji-Ibrahim, Prisma Health Upstate, Internal Medicine, 701 Grove Road, 29605 Greenville, United States, jenavelji@gmail.com

Affiliations:
Jena Velji-Ibrahim, Prisma Health Upstate, Internal Medicine, Greenville, United States
Jena Velji-Ibrahim, University of South Carolina School of Medicine Greenville Campus, Internal Medicine, Greenville, United States
Piyush Nathani, The University of Kansas Medical Center, Gastroenterology, Kansas City, United States
[...]
Prateek Sharma, The University of Kansas Medical Center, Gastroenterology, Kansas City, United States

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INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved for diabetes treatment and recently, for weight loss, potentially addressing the global obesity epidemic, metabolic syndrome, and cardiovascular risk [1]. GLP-1 RAs are incretin mimics that prompt glucose-dependent insulin release from the pancreatic islets, reducing glucagon secretion, increasing satiety, and delaying gastric emptying [2].

In September 2023, the American Gastroenterological Association (AGA) addressed the management of patients taking GLP-1 RAs, finding no evidence to support all patients stopping GLP-1 RAs before elective endoscopy procedures [3]. This was in response to the American Society of Anesthesiologists' recommendation to discontinue GLP-1 RAs before elective procedures [4] due to reports suggesting an increased risk of aspiration and respiratory complications in patients who present for procedures requiring sedation [5, 6]. While preoperative medication guidelines can prevent complications, withholding medications can result in adverse effects and significant logistical burdens, including procedure cancellations, care delays, and financial losses [7, 8]. These issues are particularly significant for GLP-1 RAs, which require withholding periods of up to a week. Consequently, the ASA's preoperative suggestions may necessitate enhanced nursing resources, exacerbating barriers, and care delays for patients requiring endoscopic procedures [3]. Furthermore, it may not be appropriate to withhold these medications given the clear benefit of GLP-1 RAs in cardiovascular health and

glycemic control in diabetic patients, and it is unclear if withholding a single dose is sufficient for gastric motility to return to normal. We conducted a real-world analysis to determine the risk of respiratory complications in patients prescribed GLP-1 RAs within three months of an endoscopic procedure.

METHODS

We conducted a population-based retrospective cohort study using TriNetX, a global federated health research network with anonymized electronic medical records from 83 large healthcare organizations. We included all patients aged 18-70 years with type 2 diabetes mellitus or overweight/ obesity with active GLP-1 RA prescriptions within three months before undergoing endoscopic procedures defined by current procedural terminology codes. The age cutoff was set at 70 years to minimize confounding from age-related comorbidities and the higher baseline risk of pneumonia in older adults. The study period ranged from January 1, 2018, to December 31, 2022. For the GLP-1 procedure cohort, we selected patients who underwent endoscopic procedures during the study period and had an active GLP-1 RA prescription within 3 months before the procedure. For the control group, we selected patients who had endoscopic procedures between January 01, 2018, and June 30, 2022, and have never received a GLP-1 prescription in their entire lifetime. The control group enrollment period was shortened by 6 months to ensure that the sample size remained within the TriNetX processing capacity. Patients with a history of surgery, anesthesia, or mechanical ventilation within three months before the procedure were excluded.

The primary outcome was aspiration pneumonitis or pneumonia within 30 days of endoscopic procedures in patients taking preoperative GLP-1 RAs. Secondary outcomes included risk association of other outcomes, per procedure, and individual GLP-1 RA. The study was deemed exempt by the institutional review board and is reported in accordance with the STROBE guidelines [9].

We performed 1:1 propensity score matching using patient demographics, Charlson comorbidity index, aspiration risk factors, and frailty risk (**Supplemental Table 1**). We used Kaplan-Meier analysis and log-rank tests on the TriNetX platform to compare the time to event for all outcomes between cohorts. GLP-1RA users were 1:1 matched to non-users using the Greedy algorithm. A standardized mean difference below 0.1 between characteristics after matching was deemed appropriate. We calculated the association of aspiration using risk ratio (RR) and hazard ratio (HR), with 95% confidence intervals (CI) from a univariate Cox proportional hazards model. The proportionality of hazards was checked with scaled Schoenfeld residuals. For outcomes not meeting the proportional hazards assumption, we conducted a landmark analysis at three months. To explore potential unknown confounders, we performed an E-value sensitivity analysis for HR and CI using an online tool. Statistical significance was set at 0.05.

RESULTS

Of the 1,018,770 patients undergoing endoscopy, 29,094 were prescribed GLP-1 RAs and 989,676 were not. Of these, 46,948 patients met inclusion criteria, 23,474 in the GLP-1 RA cohort and 23,474 in the comparison group with baseline demographics shown in **Table 1**. As shown in **Figure 1A**, the overall incidence of post-endoscopy aspiration pneumonitis was 0.11%

for those with GLP-1 RA prescriptions and 0.12% for those without (hazard ratio [HR] 0.92; 95% CI: 0.54-1.56; p=0.752). Similarly, the incidence of pneumonia was not significantly different between those with GLP-1 RA prescription (0.81%) and those without (0.79%) (hazard ratio [HR] 1.01; 95% CI: 0.83-1.24; p=0.877). The risk of other adverse events post-endoscopy was also not significantly different between these two groups. On subgroup analysis, there was no significant difference between the incidence of aspiration pneumonitis or pneumonia for the type of endoscopic procedure or specific GLP-1 RA (**Figure 1B, 1C**; **Table 1**). Confidence intervals were wide for aspiration pneumonitis but narrow for pneumonia and subgroup analysis. There was no significant difference in the Charlson comorbidity index, risk factors for aspiration, and frailty between the groups.

DISCUSSION

GLP-1 RA use before endoscopy was not associated with a higher risk of post-procedure respiratory complications compared with patients not prescribed GLP-1 RAs. In our subgroup analysis by procedure, gender, and GLP-1 RA medication, this was also the case. Previous studies have indicated that the use of GLP-1 RAs is associated with retained gastric contents, which is a direct consequence of delayed gastric emptying [5]. The clinical impact of solid and liquid gastric emptying is different. Retained contents in the stomach may not pose a significant issue for patients undergoing combined EGD and colonoscopy, as they typically fast and consume only a liquid diet the day before the procedures and do not consume solids in that time. Given that our study included more participants undergoing colonoscopy than EGD, the duration of fasting may have contributed to our findings of no increased risk of respiratory complications.

While the nationwide rate of aspiration is reported to be around 1%, our findings indicated a lower rate. This may be due to the participants undergoing colonoscopy. The lower aspiration rate may also be attributed to differences in patient management practices across multiple hospitals and the lack of standardized protocols that exists in our population-based study that includes data from numerous healthcare organizations. Additionally, it is possible that not all aspirations may have been reported, as they may not have been clinically significant or accurately documented. This could lead to an underestimation of the true incidence of respiratory complications.

Our study has certain limitations. We were unable to measure the preoperative duration of GLP-1 RA therapy, duration of fasting, medication adherence, or cessation of medication before endoscopic procedures. Our selection of the 2018-2022 cohort was made before concerns arose regarding the risk of aspiration associated with GLP-1 RAs. Our study did not measure gastric contents, however, previous studies have addressed the association between GLP-1 RA use and retained gastric contents [5]. This retrospective study relies on accurate documentation of symptoms, disease, and treatments, rendering it susceptible to biases in charting, coding, and recall. Our study has wide confidence intervals which may be due to the low incidence of these events and a larger series is needed to further address the incidence and impact of GLP-1 RAs in this setting.

Our results align with those of Dixit et al., (2024) who found that the use of GLP-1 RAs before emergency surgery did not elevate the risk of respiratory complications [10]. However, Yeo et al. (2024) reported an increased risk of aspiration pneumonia associated with GLP-1 RAs following

endoscopy [6]. The discrepancy in results might stem from differences in the robustness of matching, as some covariates in their study exhibited residual imbalances.

Our study suggests a low incidence of respiratory complications including aspiration post-endoscopy in individuals prescribed a GLP-1 RA. Future large studies are needed to assess respiratory complications post-endoscopy including more complex procedures that require deep sedation such as endoscopic retrograde cholangiopancreatography or endoscopic ultrasound in which the risk of aspiration could be higher. An individualized approach based on GLP-1 RA indication and symptoms of nausea, vomiting, dyspepsia, or abdominal distention may be the best determination of those who can safely undergo upper and/or lower endoscopy procedures.

Figure 1. Incidence of aspiration pneumonitis and pneumonia among GLP-1 RA users and non-users post-endoscopy. 1A demonstrates the incidence of respiratory complications and other adverse events post-upper and/or lower endoscopy. 1B shows the results of subgroup analysis of the incidence of aspiration pneumonitis stratified by endoscopy type, sex, and GLP-1 RA. 1C illustrates subgroup analysis of the incidence of pneumonia stratified by endoscopy type, sex, and GLP-1 RA.

Table 1. Baseline characteristics and risk adverse events post-endoscopy in GLP-1 RA users and non-users. Subgroup analysis of aspiration pneumonitis and pneumonia risk by procedure type, sex, and GLP-1 RA.

Outcomes	GLP-1 Cohort	Control Cohort	Hazard Ratio [95% CI]	P-value
Sample Size Before Match	29,094	989,676	NA	NA
Sample Size After Match	23,474	23,474	NA	NA
Age	53.8 ± 9.3 years	54.2 ± 10.0 years	NA	NA
Females	58.7%	59.2%	NA	NA
Males	36.1%	35.5%	NA	NA
White	60.1%	59.3%	NA	NA
African American	19.3%	20.4%	NA	NA
Hispanic	10.6%	10.7%	NA	NA
Diabetes Mellitus	76.1%	78.7%	NA	NA
Overweight BMI and obesity	67.9%	72.3%	NA	NA
Hemoglobin A1c	7.3 ± 2.0	7.1 ± 2.0	NA	NA
BMI	36.1 ± 8.5	35.6 ± 8.9	NA	NA
Post-Endoscopy Adverse Events				
Aspiration Pneumonitis	0.11%	0.12%	0.92 [0.54, 1.57]	0.752
Pneumonia	0.81%	0.79%	1.01 [0.83, 1.24]	0.877
Cardiac adverse events	0.28%	0.28%	1.01 [0.71, 1.46]	0.941
Infectious adverse events	0.86%	0.76%	1.11 [0.91, 1.36]	0.313
Thoracic adverse events	0.14%	0.08%	1.65 [0.92, 0.96]	0.090
Genitourinary adverse events	1.44%	1.10%	1.30 [1.11, 1.53]	0.002
Other adverse events	0.19%	0.18%	1.05 [0.68, 1.64]	0.819
Deaths	0.20%	0.28%	0.71 [0.49, 1.04]	0.076
Subgroup Analysis of Aspiration Pneumonitis				
By Procedures				
EGD (n=11,477)	0.17%	0.19%	0.90 [0.49, 1.65]	0.732
Colonoscopy (n=15,910)	≤0.06%	≤0.06%	1.65 [0.60, 4.53]	0.328
By Sex				
Female (n=13,327)	0.13%	≤0.08%	2.10 [0.91, 4.87]	0.076
Male (n=7,893)	≤0.13%	0.20%	0.43 [0.18, 1.05]	0.056
By GLP Medication				
Semaglutide (n=10,717)	≤0.09%	0.11%	0.82 [0.36, 1.91]	0.650
Dulaglutide (n=9,366)	0.14%	0.14%	0.99 [0.46, 2.13]	0.976
Liraglutide (n=6,928)	0.16%	≤ 0.14%	1.82 [0.67, 4.92]	0.232
Subgroup Analysis of Pneumonia				
By Procedures				
EGD (n=11,477)	1.09%	1.04%	1.04 [0.81, 1.34]	0.757

Colonoscopy (n= 15,910)	0.78%	0.61%	1.27 [0.97, 1.65]	0.081
By Sex				
Female (13,327)	0.94%	0.71%	1.32 [1.00, 1.72]	0.050
Male (7,893)	0.79%	0.71%	1.09 [0.76, 1.57]	0.625
By GLP-1 Medication				
Semaglutide (10,717)	0.88%	0.77%	1.12 [0.83, 1.50]	0.452
Dulaglutide (n=9,366)	0.89%	1.01%	0.86 [0.64, 1.16]	0.323
Liraglutide (n=6,928)	0.97%	1.03%	0.94 [0.97, 1.31]	0.697

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Supplemental Table 1: Demographic and clinical characteristics of GLP-1 RA users and non-users before and after propensity matching results. Propensity matching was done for the 59 characteristics.

	Cohort patient count before and after propensity score matching		
Cohort		Patient count before matching	Patient count after matching
Cohort 1: GLP-1 procedures		29,094	23,474
Cohort 2: Control procedures		989,676	23,474

Propensity score density function - Before and after matching (GLP1 - purple, control - green)	
PLEASE INSERT SUPPL FIG 1 HERE	PLEASE INSERT SUPPL FIG 2 HERE

GLP 1 (N = 23,474) and control (N = 23,474) characteristics before and after propensity score matching

Age

				Before Matching			After Matching		
Cohort		Code	Characteristic	Patients	Mean ± SD	Std diff	Patients	Mean ± SD	Std diff.
	1	AI	Age at Index	29,094	54.1 +/- 9.1	0.381	23,474	53.8 +/- 9.3	0.040
	2			989,676	49.8 +/- 13.0		23,474	54.2 +/- 10.0	

Demographics

				Before Matching			After Matching		
Cohort		Code	Characteristic	Patients	% of Cohort	Std diff	Patients	% of Cohort	Std diff.
	1	2106-3	White	17,665	60.7%	0.074	14,112	60.1%	0.017
	2			636,551	64.3%		13,912	59.3%	
	1	UNK	Unknown Race	3,765	12.9%	0.074	3,071	13.1%	0.004
	2			153,737	15.5%		3,042	13.0%	
	1	F	Female	17,383	59.7%	0.172	13,786	58.7%	0.010
	2			507,003	51.2%		13,905	59.2%	
	1	2135-2	Hispanic or Latino	3,095	10.6%	0.048	2,486	10.6%	0.003
	2			91,088	9.2%		2,508	10.7%	
	1	2186-5	Not Hispanic or Latino	20,983	72.1%	0.109	16,795	71.5%	0.002
	2			664,244	67.1%		16,821	71.7%	
	1	2054-5	Black or African American	5,596	19.2%	0.211	4,534	19.3%	0.028
	2			115,406	11.7%		4,797	20.4%	
	1	M	Male	10,266	35.3%	0.138	8,481	36.1%	0.012
	2			415,677	42.0%		8,344	35.5%	
	1	2131-1	Other Race	1,133	3.9%	0.012	939	4.0%	0.008
	2			36,325	3.7%		904	3.9%	

Diagnosis

				Before Matching			After Matching		
Cohort		Code	Characteristic	Patients	% of Cohort	Std diff.	Patients	% of Cohort	Std diff.
	1	E08-E13	Diabetes mellitus	23,477	80.7%	1.999	17,865	76.1%	0.062
	2			101,789	10.3%		18,476	78.7%	
	1	E65-E68	Overweight, obesity and other hyperalimentation	21,131	72.6%	1.303	15,929	67.9%	0.096
	2			180,910	18.3%		16,964	72.3%	
	1	K21	Gastro-esophageal reflux disease	15,468	53.2%	0.556	11,686	49.8%	0.016
	2			266,456	26.9%		11,870	50.6%	
	1	K25	Gastric ulcer	1,054	3.6%	0.160	717	3.1%	<0.001
	2			11,694	1.2%		717	3.1%	
	1	K26	Duodenal ulcer	358	1.2%	0.072	259	1.1%	0.002
	2			5,510	0.6%		253	1.1%	
	1	K44	Diaphragmatic hernia	3,180	10.9%	0.245	2,319	9.9%	0.010
	2			43,977	4.4%		2,391	10.2%	

	1 2	K74	Fibrosis and cirrhosis of liver	2,135 18,816	7.3% 1.9%	0.261	1,490 1,507	6.3% 6.4%	0.003
	1 2	K22.4	Dyskinesia of esophagus	538 7,189	1.8% 0.7%	0.100	381 393	1.6% 1.7%	0.004
	1 2	R13	Aphagia and dysphagia	5,566 90,472	19.1% 9.1%	0.290	3,964 3,934	16.9% 16.8%	0.003
	1 2	I20-I25	Ischemic heart diseases	7,299 64,127	25.1% 6.5%	0.528	5,224 5,238	22.3% 22.3%	0.001
	1 2	I60-I69	Cerebrovascular diseases	4,122 39,685	14.2% 4.0%	0.359	2,914 2,954	12.4% 12.6%	0.005
	1 2	I50	Heart failure	3,738 23,381	12.8% 2.4%	0.404	2,607 2,655	11.1% 11.3%	0.006
	1 2	I73	Other peripheral vascular diseases	2,886 23,577	9.9% 2.4%	0.318	1,929 1,906	8.2% 8.1%	0.004
	1 2	M30-M36	Systemic connective tissue disorders	2,042 23,424	7.0% 2.4%	0.221	1,379 1,382	5.9% 5.9%	0.001
	1 2	J45	Asthma	7,530 96,899	25.9% 9.8%	0.430	5,411 5,488	23.1% 23.4%	0.008
	1 2	J44	Other chronic obstructive pulmonary disease	3,281 32,908	11.3% 3.3%	0.309	2,355 2,370	10.0% 10.1%	0.002
	1 2	J43	Emphysema	823 12,002	2.8% 1.2%	0.115	613 619	2.6% 2.6%	0.002
	1 2	C00-D49	Neoplasms	14,548 283,249	50.0% 28.6%	0.449	10,900 10,931	46.4% 46.6%	0.003
	1 2	B20-B20	Human immunodeficiency virus [HIV] disease (B20)	723 8,497	2.5% 0.9%	0.127	486 465	2.1% 2.0%	0.006
	1 2	F17	Nicotine dependence	6,474 115,939	22.3% 11.7%	0.283	4,896 4,874	20.9% 20.8%	0.002
	1 2	F10	Alcohol related disorders	2,382 44,766	8.2% 4.5%	0.151	1,793 1,756	7.6% 7.5%	0.006
	1 2	F11	Opioid related disorders	780 11,132	2.7% 1.1%	0.114	569 550	2.4% 2.3%	0.005
	1 2	G30-G32	Other degenerative diseases of the nervous system	449 4,819	1.5% 0.5%	0.106	308 309	1.3% 1.3%	<0.001
	1 2	G47.3	Sleep apnea	12,483 90,199	42.9% 9.1%	0.835	8,962 9,121	38.2% 38.9%	0.014
	1 2	I38	Endocarditis, valve unspecified	319 2,778	1.1% 0.3%	0.099	221 210	0.9% 0.9%	0.005
	1 2	I35	Nonrheumatic aortic valve disorders	1,093 10,153	3.8% 1.0%	0.179	765 734	3.3% 3.1%	0.008
	1 2	I34	Nonrheumatic mitral valve disorders	1,902 23,292	6.5% 2.4%	0.204	1,368 1,390	5.8% 5.9%	0.004
	1 2	I48	Atrial fibrillation and flutter	1,878 20,795	6.5% 2.1%	0.216	1,400 1,456	6.0% 6.2%	0.010
	1 2	I21	Acute myocardial infarction	1,994 15,997	6.9% 1.6%	0.262	1,391 1,420	5.9% 6.0%	0.005
	1 2	I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	12 170	0.0% 0.0%	0.014	10 16	0.0% 0.1%	0.011
	1 2	I46	Cardiac arrest	189 1,687	0.6% 0.2%	0.075	129 126	0.5% 0.5%	0.002
	1 2	E78	Disorders of lipoprotein metabolism and other lipidemias	22,096 266,185	75.9% 26.9%	1.126	16,798 17,113	71.6% 72.9%	0.030
	1 2	N17	Acute kidney failure	3,501 25,484	12.0% 2.6%	0.370	2,552 2,560	10.9% 10.9%	0.001
	1 2	I05-I09	Chronic rheumatic heart diseases	1,172 12,384	4.0% 1.3%	0.174	848 817	3.6% 3.5%	0.007
	1	N18	Chronic kidney disease	4,996	17.2%	0.434	3,609	15.4%	0.003

	2		(CKD)	40,618	4.1%		3,631	15.5%	
	1 2	N28	Other disorders of kidney and ureter, not elsewhere classified	4,208 41,028	14.5% 4.1%	0.361	2,946 2,896	12.6% 12.3%	0.006
	1 2	N20-N23	Urolithiasis	3,455 44,061	11.9% 4.5%	0.274	2,502 2,438	10.7% 10.4%	0.009
	1 2	N10-N16	Renal tubulo-interstitial diseases	2,778 29,752	9.5% 3.0%	0.272	1,949 1,851	8.3% 7.9%	0.015
	1 2	F01	Vascular dementia	42 467	0.1% 0.0%	0.031	34 35	0.1% 0.1%	0.001
	1 2	F02	Dementia in other diseases classified elsewhere	44 737	0.2% 0.1%	0.023	39 38	0.2% 0.2%	0.001
	1 2	F03	Unspecified dementia	183 1,812	0.6% 0.2%	0.070	142 133	0.6% 0.6%	0.005
	1 2	F04	Amnestic disorder due to known physiological condition	16 126	0.1% 0.0%	0.023	13 10	0.1% 0.0%	0.006
	1 2	M62.84	Sarcopenia	12 155	0.0% 0.0%	0.015	10 10	0.0% 0.0%	<0.001
	1 2	R54	Age-related physical debility	46 411	0.2% 0.0%	0.037	32 35	0.1% 0.1%	0.003
		Procedure							
Cohort	Code	Characteristic		Patients	% of Cohort	Std diff.	Patients	% of Cohort	Std diff.
	1 2	1006964	Surgical Procedures on the Digestive System	11,679 181,446	40.1% 18.3%	0.494	8,523 8,513	36.3% 36.3%	0.001
		Medication							
Cohort	Code	Characteristic		Patients	% of Cohort	Std diff.	Patients	% of Cohort	Std diff.
	1 2	CN101	OPIOID ANALGESICS	21,314 388,931	73.3% 39.3%	0.729	16,403 16,894	69.9% 72.0%	0.046
	1 2	M05BA	Bisphosphonates	507 9,846	1.7% 1.0%	0.064	370 393	1.6% 1.7%	0.008
	1 2	24947	ferrous sulfate	4,130 41,105	14.2% 4.2%	0.353	2,963 3,052	12.6% 13.0%	0.011
	1 2	3640	doxycycline	7,265 77,020	25.0% 7.8%	0.478	5,021 5,018	21.4% 21.4%	<0.001
	1 2	CN104	NON-STEROIDAL ANTI-INFLAMMATORY ANALGESICS	11,960 189,372	41.1% 19.1%	0.493	8,853 8,859	37.7% 37.7%	0.001
	1 2	DX100	RADIOLOGICAL/ CONTRAST MEDIA	293 4,566	1.0% 0.5%	0.064	198 178	0.8% 0.8%	0.010
	1 2	CV800	ACE INHIBITORS	13,970 106,052	48.0% 10.7%	0.898	10,247 10,377	43.7% 44.2%	0.011
	1 2	6809	metformin	21,164 48,297	72.7% 4.9%	1.940	15,643 15,714	66.6% 66.9%	0.006
	1 2	26225	ondansetron	17,132 291,814	58.9% 29.5%	0.620	12,996 13,403	55.4% 57.1%	0.035
	1 2	CN302	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS	16,649 284,175	57.2% 28.7%	0.601	12,595 12,897	53.7% 54.9%	0.026
	1 2	N05CD	Benzodiazepine derivatives	12,745 194,651	43.8% 19.7%	0.537	9,451 9,564	40.3% 40.7%	0.010
	1 2	4821	glipizide	5,528 7,976	19.0% 0.8%	0.639	3,544 3,400	15.1% 14.5%	0.017
	1 2	3498	diphenhydramine	9,243 131,994	31.8% 13.3%	0.452	6,829 6,968	29.1% 29.7%	0.013
	1 2	8745	promethazine	8,028 113,210	27.6% 11.4%	0.416	5,958 6,137	25.4% 26.1%	0.017
	1 2	3444	dimenhydrinate	516 5,386	1.8% 0.5%	0.115	362 366	1.5% 1.6%	0.001

	1 2	A10BB	Sulfonylureas	9,314 13,493	32.0% 1.4%	0.902	6,004 5,606	25.6% 23.9%	0.039
	1 2	A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	8,017 5,142	27.6% 0.5%	0.845	4,106 3,337	17.5% 14.2%	0.090
	1 2	6676	meclizine	2,616 26,812	9.0% 2.7%	0.270	1,817 1,780	7.7% 7.6%	0.006
	1 2	CN601	TRICYCLIC ANTIDEPRESSANTS	4,062 41,599	14.0% 4.2%	0.345	2,811 2,792	12.0% 11.9%	0.002
	1 2	9601	scopolamine	2,273 27,322	7.8% 2.8%	0.227	1,628 1,755	6.9% 7.5%	0.021
	1 2	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	5,970 7,984	20.5% 0.8%	0.674	3,750 3,448	16.0% 14.7%	0.036
	1 2	8704	prochlorperazine	3,421 38,556	11.8% 3.9%	0.296	2,431 2,447	10.4% 10.4%	0.002
	1 2	A10BG	Thiazolidinediones	2,569 2,608	8.8% 0.3%	0.420	1,444 1,264	6.2% 5.4%	0.033
	1 2	HS501	INSULIN	16,090 49,516	55.3% 5.0%	1.310	11,223 11,076	47.8% 47.2%	0.013
	1 2	A10A	INSULINS AND ANALOGUES	15,995 48,821	55.0% 4.9%	1.304	11,146 11,001	47.5% 46.9%	0.012
	1 2	8782	propofol	11,774 161,924	40.5% 16.4%	0.555	8,520 8,619	36.3% 36.7%	0.009
	1 2	6915	metoclopramide	5,105 61,338	17.5% 6.2%	0.356	3,693 3,754	15.7% 16.0%	0.007
	1 2	N05A	ANTIPSYCHOTICS	6,684 88,147	23.0% 8.9%	0.392	4,942 5,036	21.1% 21.5%	0.010
	1 2	A10BF	Alpha glucosidase inhibitors	158 259	0.5% 0.0%	0.097	84 78	0.4% 0.3%	0.004
	1 2	A04AA	Serotonin (5HT3) antagonists	17,144 292,071	58.9% 29.5%	0.620	13,007 13,409	55.4% 57.1%	0.035
	1 2	2403	chlorpromazine	115 1,578	0.4% 0.2%	0.045	88 90	0.4% 0.4%	0.001
	1 2	2356	chlordiazepoxide	144 4,123	0.5% 0.4%	0.012	117 121	0.5% 0.5%	0.002
	1 2	1731071	fosaprepitant	141 1,806	0.5% 0.2%	0.052	107 98	0.5% 0.4%	0.006
			Laboratory						
Cohort		Code	Characteristic	Patients	Mean ± SD	Std diff	Patients	Mean ± SD	Std diff
	1 2	4548-4	Hemoglobin A1c (Hb A1c) %	22,690 248,694	7.5 +/- 2.0 6.1 +/- 1.8	0.776	17,427 17,174	7.3 +/- 2.0 7.1 +/- 2.0	0.100
	1 2	9083	BMI	22,948 649,696	36.4 +/- 8.5 29.4 +/- 20.6	0.443	18,247 18,414	36.1 +/- 8.5 35.6 +/- 8.9	0.057
Cohort		Code	Characteristic	Patients	% of Cohort	Std diff.	Patients	% of Cohort	Std diff.
	1 2	4548-4	HbA1c: 0 - 6.50 %	14,313 223,213	49.2% 22.6%	0.578	11,287 12,099	48.1% 51.5%	0.069
	1 2	4548-4	HbA1c: 6.50 - 9 %	15,936 38,212	54.8% 3.9%	1.349	11,145 10,823	47.5% 46.1%	0.027
	1 2	4548-4	HbA1c: 9 - 0 %	10,873 23,261	37.4% 2.4%	0.977	6,900 6,255	29.4% 26.6%	0.061
	1 2	9083	BMI: 0 - 25 kg/m2	3,629 264,421	12.5% 26.7%	0.365	3,069 2,810	13.1% 12.0%	0.033
	1 2	9083	BMI: 25 - 40 kg/m2	18,586 472,858	63.9% 47.8%	0.329	14,779 15,231	63.0% 64.9%	0.040
	1 2	9083	BMI: > 40 kg/m2	10,478 80,942	36.0% 8.2%	0.712	7,663 8,017	32.6% 34.2%	0.032