

Supplementary Material

A nationwide hospital claims database analysis of real-world patterns of laxative use for opioid-induced constipation in Japanese patients with cancer

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Table S1. Definition of opioids for database analysis

Class	Generic name	Route of administration
Strong	Oxycodone Hydrochloride Hydrate	Oral (extended release)
		Injection
	Tapentadol Hydrochloride	Oral
	Hydromorphone hydrochloride	Oral (extended release)
		Injection
	Fentanyl	Transdermal
	Fentanyl Citrate	Injection
		Transdermal
	Buprenorphine hydrochloride	Injection
	Methadone hydrochloride	Oral
Weak	Morphine Hydrochloride Hydrate	Oral (extended release)
		Injection
	Morphine Sulfate Hydrate	Oral
	Codeine Phosphate Hydrate	Oral
	Dihydrocodeine Phosphate	Oral
	Tramadol Hydrochloride	Oral
		Injection
	Pentazocine	Injection

Table S2. Definition of laxatives for database analysis

Group	Agent	Generic name	Route of administration
Osmotic laxatives	Magnesium Oxide	Magnesium Oxide	Oral
	Lactulose	Lactulose	Oral
	Polyethylene glycol	Macrogol 4000, sodium chloride, sodium bicarbonate and potassium chloride	Oral
	Other osmotic laxatives	Magnesium Sulfate Hydrate	Oral
Stimulant laxatives	Bisacodyl	Bisacodyl	Suppository
	Senna	Senna	Oral
		Senna extract	Oral
		Senna, Senna fruit	Oral
		Rhubarb, Senna combination drug	Oral
	Sennoside	Sennoside	Oral
	Picosulfate	Sodium Picosulfate Hydrate	Oral
PAMORA	Naldemedine	Naldemedine Tosilate	Oral
Others	Linacotide	Linacotide	Oral
	Lubiprostone	Lubiprostone	Oral
	Kampo	Daikenchuto extract	Oral
		Daiokanzoto extract	Oral
		Mashiningan extract	Oral
	Elobixibat	Elobixibat hydrate	Oral
	Glycerin	Glycerin	Suppository
	Other stimulant laxatives	Castor Oil	Oral
		Aromatic castor oil	Oral
	Others	Drugs with WHO-ATC code: A06A and not classified above groups.	All

Table S3. Baseline characteristics of patients receiving first-line laxatives for strong opioids in early and non-early medication groups

First-line laxative	Early medication			Non-early medication		
	Osmotic (N=3,466)	Stimulant (N=1,055)	PAMORA (N=1,059)	Osmotic (N=1,097)	Stimulant (N=1,323)	PAMORA (N=318)
Age (mean $\pm$ SD)	68.5 $\pm$ 12.2	70.5 $\pm$ 11.8	68.2 $\pm$ 12.5	68.5 $\pm$ 12.2	70.1 $\pm$ 12.4	68.5 $\pm$ 12.2
Male	2,025 (58.4%)	613 (58.1%)	588 (55.5%)	610 (55.6%)	771 (58.3%)	173 (54.4%)
Female	1,441 (41.6%)	442 (41.9%)	471 (44.5%)	487 (44.4%)	552 (41.7%)	145 (45.6%)
Cancer type						
Lung	403 (11.6%)	104 (9.9%)	129 (12.2%)	116 (10.6%)	139 (10.5%)	27 (8.5%)
Colon	172 (5.0%)	49 (4.6%)	49 (4.6%)	71 (6.5%)	58 (4.4%)	20 (6.3%)
Gastric	128 (3.7%)	52 (4.9%)	39 (3.7%)	36 (3.3%)	83 (6.3%)	14 (4.4%)
Breast	116 (3.3%)	42 (4.0%)	35 (3.3%)	34 (3.1%)	46 (3.5%)	6 (1.9%)
Uterine	57 (1.6%)	11 (1.0%)	28 (2.6%)	21 (1.9%)	11 (0.8%)	13 (4.1%)
Multiple	1,063 (30.7%)	285 (27.0%)	288 (27.2%)	343 (31.3%)	327 (24.7%)	98 (30.8%)
Other	1,527 (44.1%)	512 (48.5%)	491 (46.4%)	476 (43.4%)	659 (49.8%)	140 (44.0%)
Patient status at opioid initiation						
Inpatient	1,739 (50.2%)	657 (62.3%)	492 (46.5%)	495 (45.1%)	854 (64.6%)	129 (40.6%)
Outpatient	1,727 (49.8%)	398 (37.7%)	567 (53.5%)	602 (54.9%)	469 (35.4%)	189 (59.4%)
Opioids						
Oral						
Oxycodone	2,545 (73.4%)	630 (59.7%)	700 (66.1%)	673 (61.3%)	615 (46.5%)	176 (55.3%)
Hydromorphone	172 (5.0%)	67 (6.4%)	161 (15.2%)	65 (5.9%)	85 (6.4%)	39 (12.3%)
Morphine	150 (4.3%)	44 (4.2%)	40 (3.8%)	36 (3.3%)	50 (3.8%)	14 (4.4%)
Tapentadol	87 (2.5%)	29 (2.7%)	38 (3.6%)	43 (3.9%)	32 (2.4%)	16 (5.0%)
Methadone	1 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	2 (0.2%)	1 (0.3%)
Transdermal						
Fentanyl	252 (7.3%)	138 (13.1%)	58 (5.5%)	162 (14.8%)	304 (23.0%)	40 (12.6%)

Injection						
Fentanyl	46 (1.3%)	29 (2.7%)	4 (0.4%)	33 (3.0%)	64 (4.8%)	2 (0.6%)
Oxycodone	43 (1.2%)	34 (3.2%)	13 (1.2%)	18 (1.6%)	49 (3.7%)	15 (4.7%)
Morphine	19 (0.5%)	25 (2.4%)	6 (0.6%)	19 (1.7%)	50 (3.8%)	4 (1.3%)
Buprenorphine	3 (0.1%)	1 (0.1%)	0 (0.0%)	4 (0.4%)	4 (0.3%)	1 (0.3%)
Hydromorphone	1 (0.0%)	6 (0.6%)	2 (0.2%)	3 (0.3%)	4 (0.3%)	1 (0.3%)
Combination*						
Oxycodone (oral) + Pentazocine (injection)	36 (1.0%)	10 (0.9%)	7 (0.7%)	7 (0.6%)	4 (0.3%)	2 (0.6%)

Data are shown as mean $\pm$ SD or n (%).

PAMORA, peripherally acting μ -opioid receptor antagonists; SD, standard deviation.

Table S4. Prescription period of first-line laxatives in early medication group

First-line laxatives	Osmotic (N=3,466)	Stimulant (N=1,055)	PAMORA (N=1,059)
Number of days of prescription (mean $\pm$ SD)	57.6 $\pm$ 29.6	31.0 $\pm$ 29.5	63.2 $\pm$ 28.6
Number of patients who changed or added other laxatives			
2 weeks	1,062 (30.6%)	429 (40.7%)	389 (36.7%)
1 month	1,558 (45.0%)	577 (54.7%)	580 (54.8%)
2 months	1,874 (54.1%)	677 (64.2%)	695 (65.6%)
3 months	2,019 (58.3%)	702 (66.5%)	729 (68.8%)

Data are shown as mean $\pm$ SD or n (%).

PAMORA, peripherally acting μ -opioid receptor antagonists; SD, standard deviation.

Table S5. Waiting period for prescribing first-line laxatives in non-early medication group

First-line laxatives	Osmotic (N=1,097)	Stimulant (N=1,323)	PAMORA (N=318)
Number of days of prescription (mean $\pm$ SD)	40.6 $\pm$ 26.0	13.9 $\pm$ 17.6	44.8 $\pm$ 26.6
Number of patients who initiated first-line laxatives			
2 weeks	549 (50.0%)	788 (59.6%)	173 (54.4%)
1 month	841 (76.7%)	1,073 (81.1%)	257 (80.8%)
2 months	1,011 (92.2%)	1,241 (93.8%)	301 (94.7%)
3 months	1,097 (100%)	1,323 (100%)	318 (100%)

Data are shown as mean $\pm$ SD or n (%).

PAMORA, peripherally acting μ -opioid receptor antagonists; SD, standard deviation.

Table S6. Laxatives use after initiating first-line laxatives in early medication group

First-line laxatives	Osmotic (N=3,466)	Stimulant (N=1,055)	PAMORA (N=1,059)
Second-line laxatives			
Osmotic	12 (0.3%)	258 (24.5%)	233 (22.0%)
Stimulant	1,338 (38.6%)	155 (14.7%)	332 (31.4%)
PAMORA	314 (9.1%)	100 (9.5%)	0 (0.0%)
Others	544 (15.7%)	265 (25.1%)	208 (19.6%)
None	1,258 (36.3%)	277 (26.3%)	286 (27.0%)
Number of different kinds of laxatives			
2 weeks	1.6±1.0	1.9±1.2	1.7±1.1
1 month	2.0±1.2	2.3±1.4	2.2±1.4
2 months	2.2±1.4	2.6±1.5	2.6±1.5
3 months	2.4±1.4	2.7±1.5	2.8±1.5
Lost to follow-up ^a			
2 weeks	19 (0.5%)	7 (0.7%)	10 (0.9%)
1 month	157 (4.5%)	50 (4.7%)	63 (5.9%)
2 months	984 (28.4%)	359 (34.0%)	325 (30.7%)
3 months	1,420 (41.0%)	516 (48.9%)	488 (46.1%)

Data are shown as n (%) or mean ± SD.

^a Patients with no data after each time point were defined as “Lost to follow-up”.

PAMORA, peripherally acting μ -opioid receptor antagonists; SD, standard deviation.

Table S7. Laxatives use after initiating first-line laxatives in non-early medication group

First-line laxatives	Osmotic (N=1,097)	Stimulant (N=1,323)	PAMORA (N=318)
Second-line laxatives			
Osmotic	6 (0.5%)	259 (19.6%)	70 (22.0%)
Stimulant	311 (28.4%)	196 (14.8%)	70 (22.0%)
PAMORA	75 (6.8%)	92 (7.0%)	0 (0.0%)
Others	167 (15.2%)	341 (25.8%)	57 (17.9%)
None	538 (49.0%)	435 (32.9%)	121 (38.1%)
Number of different kinds of laxatives			
2 weeks	0.7±0.9	1.1±1.2	0.8±1.0
1 month	1.2±1.1	1.7±1.3	1.4±1.2
2 months	1.7±1.2	2.2±1.4	2.0±1.3
3 months	1.9±1.2	2.4±1.3	2.2±1.4
Lost to follow-up ^a			
2 weeks	2 (0.2%)	1 (0.1%)	0 (0.0%)
1 month	48 (4.4%)	45 (3.4%)	14 (4.4%)
2 months	270 (24.6%)	423 (32.0%)	97 (30.5%)
3 months	448 (40.8%)	656 (49.6%)	154 (48.4%)

Data are shown as n (%) or mean ± SD.

^a Patients with no data after each time point were defined as “Lost to follow-up”.

PAMORA, peripherally acting μ -opioid receptor antagonists; SD, standard deviation.