



Real-world Prescription Patterns and Patient Satisfaction Regarding Maintenance Therapy of Gastroesophageal Reflux Disease: An Observational, Cross-sectional, Multicenter Study

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Background/Aims

Gastroesophageal reflux disease (GERD) is a common chronic gastrointestinal disorder that typically requires long-term maintenance therapy. However, little is known about patient preferences and satisfaction and real-world prescription patterns regarding maintenance therapy for GERD.

Methods

This observational, cross-sectional, multicenter study involved patients from 18 referral hospitals in Korea. We surveyed patients who had been prescribed proton pump inhibitors (PPIs) for GERD for at least 90 days with a minimum follow-up duration of 1 year. The main outcome was overall patient satisfaction with different maintenance therapy modalities.

Results

A total of 197 patients were enrolled. Overall patient satisfaction, patient preferences, and GERD health-related quality of life scores did not significantly differ among the maintenance therapy modality groups. However, the on-demand therapy group experienced a significantly longer disease duration than the continuous therapy group. The continuous therapy group demonstrated a lower level of awareness of potential adverse effects associated with PPIs than the on-demand therapy group but received higher doses of PPIs than the on-demand therapy group. The prescribed doses of PPIs also varied based on the phenotype of GERD, with higher doses prescribed for non-erosive reflux disease than erosive reflux disease.

Conclusion

Although overall patient satisfaction did not significantly differ among the different PPI maintenance therapy modality groups, awareness of potential adverse effects was significantly different between the on-demand and continuous therapy groups. (J Neurogastroenterol Motil 2023;29:470-477)

Key Words

Gastroesophageal reflux; Maintenance; Proton pump inhibitors

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition that is becoming increasingly prevalent worldwide.¹ Proton pump inhibitors (PPIs) are commonly used as the first-line treatment for GERD and are among the most frequently prescribed drug classes globally. However, > 70% of patients experience recurrence of GERD within 6 to 12 months after discontinuing initial treatment.^{2,3} Consequently, many patients with GERD require long-term maintenance therapy to manage symptoms and facilitate healing of esophageal erosions. However, there are concerns regarding potential misuse and overuse of these drugs as their use becomes more widespread.⁴ Additionally, long-term use of PPIs may cause adverse effects, raising concerns among patients and physicians.⁵ Given the chronic nature of GERD and its negative impact on quality of life and economic burden,⁶ recent guidelines recommend using the lowest effective dose of PPIs for patients requiring long-term maintenance therapy to manage symptoms and facilitate healing of reflux esophagitis.⁷

PPIs are recommended for long-term maintenance therapy according to recent GERD guidelines.⁷⁻⁹ Maintenance therapy is available in several modalities, including continuous therapy in which PPIs are taken daily, on-demand therapy in which PPIs are taken only when symptoms occur, and intermittent therapy in which PPIs are taken for a certain period after the recurrence of symptoms.⁹ However, the level of evidence supporting on-demand therapy as a long-term maintenance therapy modality is low, despite its inclusion in recent guidelines.⁷ Furthermore, little is known about patient preferences and satisfaction and real-world prescription patterns regarding maintenance therapy for GERD. Therefore, we conducted a national multicenter survey of patients in South Korea to investigate their level of satisfaction, preferences for maintenance therapy, and awareness of potential adverse effects of PPIs. Ad-

ditionally, we surveyed physicians to determine their real-world prescription patterns and the factors influencing their prescription decisions.

Materials and Methods

Study Population

Between September 2020 and December 2022, a multicenter survey was conducted in Korea, involving patients and physicians from 18 referral hospitals. The inclusion criteria were as follows: (1) patients aged > 19 years; (2) patients who received PPI maintenance therapy for GERD for at least 90 days with a minimum follow-up duration of 1 year; and (3) patients with symptoms of heartburn or regurgitation confirmed on their medical record within 1 year. The exclusion criteria were as follows: (1) patients taking PPIs for a disease other than GERD (such as active peptic ulcer, gastrointestinal bleeding, malignancy, eosinophilic esophagitis, or prevention of NSAID-induced ulcer); (2) patients with a history of primary esophageal motility disorder; (3) patients with a history of resection of the gastrointestinal tract (except for a history of primary repair and endoscopic resection); (4) patients with a history of untreated malignancy prior to enrollment; (5) patients with clinically significant disorders in the hepatic, renal, cardiovascular, respiratory, endocrine, or central nervous systems; and (6) patients with a history of drug or alcohol abuse within 1 year. Written informed consent was obtained from all patients before their enrollment in the study. The study protocol was approved by the institutional review boards of each participating institution (3-2020-0131), and the study was registered at cris.nih.go.kr (KCT0005810). All authors had access to the study data and reviewed and approved the final manuscript.

Maintenance Therapy Modality

Continuous therapy group defined as administering a daily dose of a PPI regardless of symptom resolution. The continuous therapy group is defined as patients receiving a daily dose of a PPI regardless of symptom resolution. The on-demand therapy group is defined as patients taking a daily PPI dose when symptoms reoccur and discontinuing treatment upon symptom relief. The intermittent therapy group is defined as patients taking a regular daily PPI dose upon symptom relapse and continuing it for a specified period (typically 1 week or 2 weeks), irrespective of symptom response. The on-demand therapy and intermittent therapy groups are categorized to the non-continuous group.

Questionnaires and Contents

For the baseline characteristics of the patients, we investigated their demographic data, medical history, and concomitant medications. Two different questionnaires were developed for the present study: a 25-item multiple-choice questionnaire for patients and a 7-item multiple-choice questionnaire for physicians. The patient

questionnaire included questions regarding the type of maintenance therapy modality; reasons for choosing the current modality; overall satisfaction with, preference for, and convenience of the modality; and perceptions of potential adverse effects associated with PPIs. The physician questionnaire included questions regarding the indication and intention for prescribing the PPI, dose and components of the prescribed PPI, drugs combined with the PPI, and attempts to perform step-down therapy. In addition to these questionnaires, we administered the self-evaluation questionnaire for GERD symptoms (SEQ-GERD), GERD-health-related quality of life (GERD-HRQL) questionnaire, and Hospital Anxiety and Depression Scale. The SEQ-GERD was developed in Korea and has been internally and externally validated.¹⁰ The GERD-HRQL is a well-validated questionnaire used to evaluate symptomatic outcomes and therapeutic effects in patients with GERD.¹¹

Outcomes

The primary outcome of this study was the overall satisfaction of patients according to maintenance therapy modality. Meanwhile, the secondary outcomes included symptom control, convenience

Table 1. Baseline Characteristics of Patients

Variable	Category	Total (N = 197)	Maintenance therapy modality			P-value
			Continuous (n = 133)	On-demand (n = 53)	Intermittent (n = 11)	
Age (yr)		62.7 ± 12.6	62.7 ± 12.9	63.8 ± 12.0	56.3 ± 11.5	0.198 ^a
Sex	Male	110 (55.8)	74 (55.6)	31 (58.5)	5 (45.5)	0.728 ^b
	Female	87 (44.2)	59 (44.4)	22 (41.5)	6 (54.6)	
Height		163.4 ± 9.2	163.2 ± 9.2	164.3 ± 9.0	160.6 ± 8.5	0.455 ^a
Weight		66.4 ± 12.4	66.6 ± 12.4	66.5 ± 12.8	65 ± 10.1	0.917 ^a
Smoking	Yes	79 (40.5)	52 (39.7)	24 (45.3)	3 (27.3)	0.513 ^b
Drinking	Yes	69 (35.4)	50 (38.2)	18 (34)	1 (9.1)	0.148 ^b
Coffee	Yes	122 (62.6)	87 (66.4)	28 (52.8)	7 (63.6)	0.226 ^b
Underlying diseases						
Diabetes	Yes	37 (18.8)	28 (21.1)	8 (15.1)	1 (9.1)	0.45 ^b
Hypertension	Yes	78 (39.6)	55 (41.4)	22 (41.5)	1 (9.1)	0.104 ^b
Kidney disease	Yes	7 (3.6)	4 (3)	2 (3.8)	1 (9.1)	0.465 ^c
Neurological and psychiatric diseases	Yes	4 (2.0)	3 (2.3)	0 (0.0)	1 (9.1)	0.179 ^c
Heart and lung disease	Yes	23 (11.7)	18 (13.5)	5 (9.4)	0 (0.0)	0.34 ^b
Osteoporosis	Yes	17 (8.6)	10 (7.5)	6 (11.3)	1 (9.1)	0.546 ^c
History of gastrointestinal surgery	Yes	4 (2.0)	1 (0.8)	2 (3.8)	1 (9.1)	0.058 ^c
Stroke	Yes	3 (1.5)	2 (1.5)	1 (1.9)	0 (0.0)	1.000 ^c
History of cancer	Yes	24 (12.2)	14 (10.5)	9 (17.0)	1 (9.1)	0.453 ^b
Other chronic diseases	Yes	35 (17.8)	21 (15.8)	12 (22.6)	2 (18.2)	0.544 ^b

^aOne-way analysis of variance.

^bChi-square test.

^cFisher's exact test.

Data are presented as mean ± SD or n (%).

of medication administration, patient preference, total score on the SEQ-GERD and GERD-HRQL questionnaires, and awareness of adverse effects associated with PPIs according to maintenance therapy modality. Additionally, we investigated real-world physician prescription patterns, such as the indication and intention for prescribing the PPI, dose and components of the PPI, drugs combined with the PPI, and attempts to perform step-down therapy for the PPI.

Statistical Methods

Categorical data are presented as frequencies and percentages (%), while continuous data are presented as means and standard deviations. One-way analysis of variance was used to compare continuous variables across the three groups. The chi-squared test or Fisher's exact test was used to compare categorical variables, with Fisher's exact test being used when there were > 20% of cells with an expected frequency of ≤ 5. The Cochran-Armitage trend test was used to compare ordered categorical variables, such as indication, maintenance therapy modality, and dose of PPI. Cohen's Kappa was used to measure the classification accuracy of physician

intentions and patient compliance. The statistical programs used were SAS (version 9.4; SAS Institute, Cary, North Carolina, USA) for analysis and R (version 4.2.2; R Project for Statistical Computing, Vienna, Austria) for graphing. All tests were performed at a significance level of 0.05.

Results

Patient Characteristics

A total of 197 patients were enrolled and surveyed in the study, with 133 in the continuous therapy group, 53 in the on-demand therapy group, and 11 in the intermittent therapy group. Table 1 summarizes the characteristics of the patients. The patients had a mean age of 62.7 years, and 55.8% of them were men. There were no significant differences in the demographic characteristics among the 3 groups.

Primary and Secondary Outcomes

There were no significant differences in overall satisfaction,

Table 2. Outcomes According to Maintenance Therapy Modalities

Variable	Category	Total (N = 197)	Maintenance therapy modality		P-value
			Continuous (n = 133)	Non-continuous (n = 64)	
Overall satisfaction	Very dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	0.454 ^a
	Dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	
	Neither dissatisfied or satisfied	49 (24.9)	33 (24.8)	16 (25.0)	
	Satisfied	104 (52.8)	67 (50.4)	37 (57.8)	
Symptom control	Very satisfied	44 (22.3)	33 (24.8)	11 (17.2)	< 0.001 ^b
	Very dissatisfied	2 (1.0)	1 (0.8)	1 (1.6)	
	Dissatisfied	2 (1.0)	0 (0.0)	2 (3.1)	
	Neither dissatisfied or satisfied	46 (23.4)	32 (24.1)	14 (21.9)	
Convenience	Satisfied	100 (50.8)	64 (48.1)	36 (56.3)	< 0.001 ^b
	Very satisfied	47 (23.9)	36 (27.1)	11 (17.2)	
	Very inconvenient	0 (0.0)	0 (0.0)	0 (0.0)	
	Inconvenient	1 (0.5)	0 (0.0)	1 (1.6)	
Preference	Neither inconvenient or convenient	43 (21.8)	34 (25.6)	9 (14.1)	0.003 ^b
	Convenient	99 (50.3)	57 (42.9)	42 (65.6)	
	Very convenient	54 (27.4)	42 (31.6)	12 (18.8)	
	Very dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	
	Dissatisfied	5 (2.5)	2 (1.5)	3 (4.7)	
	Neither dissatisfied or satisfied	57 (28.9)	41 (30.8)	16 (25.0)	
	Satisfied	97 (49.2)	64 (48.1)	33 (51.6)	
	Very satisfied	38 (19.3)	26 (19.6)	12 (18.8)	

^aChi-square test.

^bFisher's exact test.

Data are presented as n (%).

degree of GERD symptom control, or preference for the current maintenance therapy modality among the continuous, on-demand, and intermittent therapy groups. However, the level of convenience of taking PPIs was greater in the continuous therapy group than in the non-continuous therapy groups (31.6% vs 18.8%, respectively; $P = 0.025$) (Table 2). The total scores for the SEQ-GERD and GERD-HRQL questionnaire did not differ between the 3 groups. However, there was a difference in the reason for using current maintenance therapy modality among these groups. In the continuous group, 84.2% of patients chose their treatment modality based on their own volition (patients driven), whereas 68.7% of patients in the non-continuous group chose their treatment modality for the same reason (Supplementary Table 1). Interestingly, the continuous therapy group had a significantly shorter duration of GERD than the non-continuous therapy groups (Fig. 1). It is worth noting that patients with a longer duration of GERD were more likely to receive non-continuous therapy, such as on-demand therapy.

Awareness of the potential adverse effects associated with PPIs did not affect overall patient satisfaction, GERD symptom control, or the convenience of taking PPIs. However, patients who were

aware of the adverse effects associated with PPIs showed a higher preference for the current maintenance therapy modality than those who were not aware (Table 3). The continuous therapy group showed a significantly lower awareness of adverse effects associated with PPI than the non-continuous therapy groups (18.8% vs

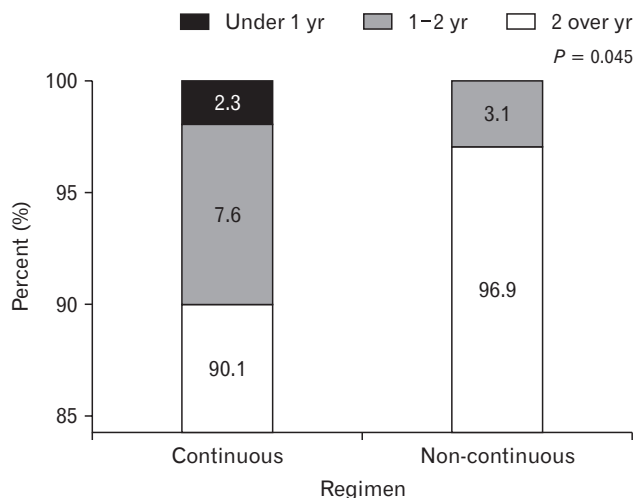


Figure 1. Duration of gastroesophageal reflux disease.

Table 3. Outcomes According to Awareness of Adverse Effects Associated With Proton Pump Inhibitor

Variable	Category	Total (N=197)	Awareness of adverse effects		P-value
			Yes (n=54)	No (n= 143)	
Overall satisfaction	Very dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	0.520 ^a
	Dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	
	Neither dissatisfied or satisfied	49 (24.9)	12 (22.2)	37 (25.9)	
	Satisfied	104 (52.8)	27 (50)	77 (53.9)	
Symptom control	Very satisfied	44 (22.3)	15 (27.8)	29 (20.3)	0.833 ^b
	Very dissatisfied	2 (1.0)	1 (1.9)	1 (0.7)	
	Dissatisfied	2 (1.0)	0 (0.0)	2 (1.4)	
	Neither dissatisfied or satisfied	46 (23.4)	11 (20.4)	35 (24.5)	
Convenience	Satisfied	100 (50.8)	29 (53.7)	71 (49.7)	0.109 ^b
	Very satisfied	47 (23.9)	13 (24.1)	34 (23.8)	
	Very dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	
	Dissatisfied	1 (0.5)	1 (1.9)	0 (0.0)	
Preference	Neither dissatisfied or satisfied	43 (21.8)	8 (14.8)	35 (24.5)	0.004 ^b
	Satisfied	99 (50.3)	26 (48.2)	73 (51.1)	
	Very satisfied	54 (27.4)	19 (35.2)	35 (24.5)	
	Very dissatisfied	0 (0.0)	0 (0.0)	0 (0.0)	
	Dissatisfied	5 (2.5)	3 (5.6)	2 (1.4)	
	Neither dissatisfied or satisfied	57 (28.9)	7 (13.0)	50 (35.0)	
	Satisfied	97 (49.2)	29 (53.7)	68 (47.6)	
	Very satisfied	38 (19.3)	15 (27.8)	23 (16.1)	

^aChi-square test.

^bFisher's exact test.

Data are presented as n (%).

45.3%, respectively; $P < 0.001$) (Fig. 2).

Physician Prescription Patterns

There were no significant differences in the indication for prescribing the PPI among the 3 groups, and the most common

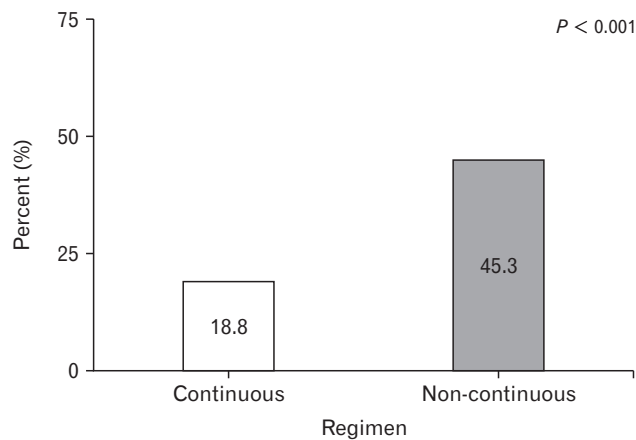
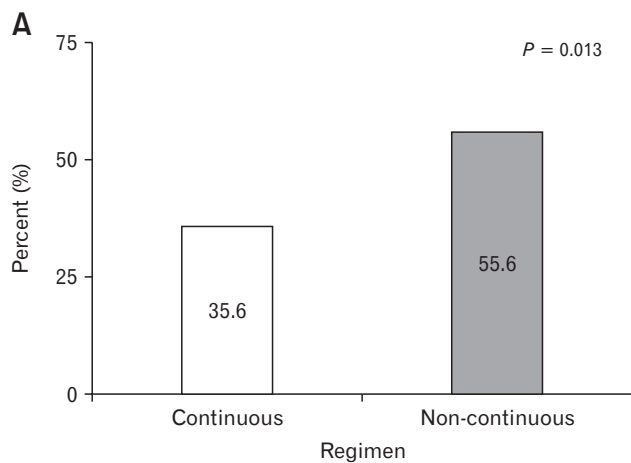


Figure 2. Maintenance therapy modality and awareness of adverse effects associated with proton pump inhibitor.



indication for all groups was nonerosive reflux disease (NERD) (continuous, 62.7%; on-demand, 53.9%; and intermittent, 72.7%) (Supplementary Table 2). Meanwhile, the dose of the prescribed PPI was higher in the continuous therapy group than in the non-continuous therapy groups (78.3% vs 54.0%, respectively; $P = 0.001$), as shown in Supplementary Figure 1A. The dose of the prescribed PPI was also higher in the NERD group than in the erosive reflux disease (ERD) group (74.8% vs 62.9%, respectively; $P = 0.043$), as shown in Supplementary Figure 1B and Supplementary Table 3. The trial and success rates of strategies for step-down therapy, including reducing the dose of PPI or changing the maintenance therapy modality from continuous to on-demand or intermittent, were significantly lower in the continuous therapy group than in the non-continuous therapy groups. The main reason for the failure of step-down therapy in the continuous therapy group was poor symptom control (66.0%), as shown in Figure 3.

Discussion

GERD is a chronic disease, and PPIs are widely considered the primary medical treatment for GERD. We investigated patient

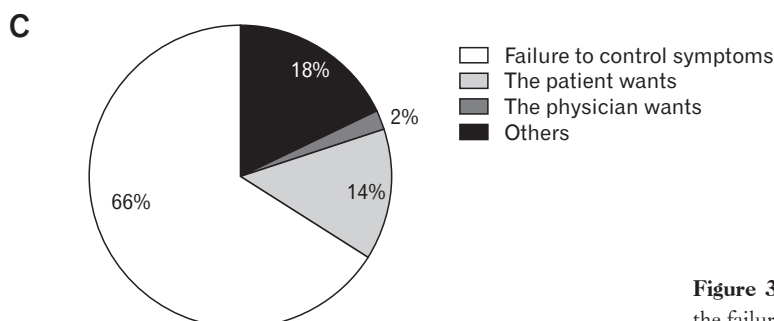
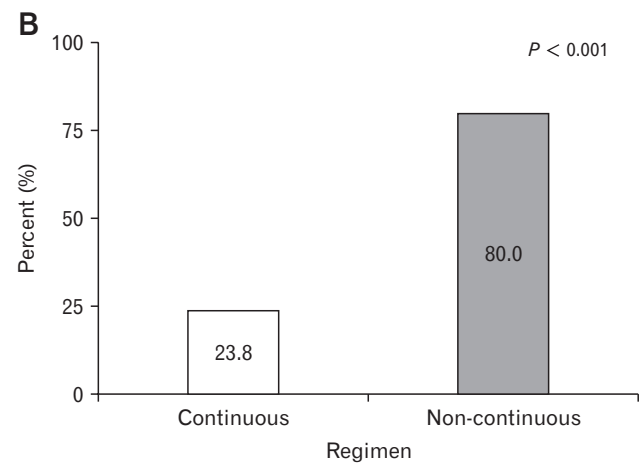


Figure 3. Step-down therapy. (A) Trial, (B) success, (C) reason for the failure of step-down therapy.

satisfaction, preference for maintenance therapy, and awareness of adverse effects associated with PPIs, as well as real-world physician prescription patterns and the factors that influence their prescription decisions. In our study, although overall patient satisfaction was similar among the different maintenance therapy modality groups, differences in the awareness of adverse effects associated with PPIs and physician prescription patterns were observed among the groups.

GERD often recurs after discontinuation of the initial treatment; thus, long-term maintenance therapy is required to control symptoms and prevent relapse.^{2,3} Various maintenance therapy modalities are available but current guidelines recommend attempting to switch to on-demand therapy for patients without severe erosive esophagitis or Barrett's esophagus once symptoms have resolved with PPI treatment.^{7,9} According to the Seoul consensus on GERD, on-demand therapy has comparable efficacy with continuous therapy for the long-term management of patients with NERD or mild ERD.⁹ Similarly, recent meta-analyses have demonstrated the effectiveness of on-demand therapy for the long-term management of patients with NERD or mild ERD.¹² Although the level of evidence supporting the efficacy of on-demand maintenance therapy for GERD is low, many guidelines recommend its use because of the potential adverse effects associated with the long-term use of PPIs, as well as the economic burden caused by frequent use of PPIs.^{6,7,9}

Several epidemiological studies have revealed associations between the long-term use of PPIs and adverse effects such as pneumonia, *Clostridium difficile* infection, bone fractures, dementia, and kidney diseases.¹³⁻¹⁶ However, most of these studies cannot definitively establish causality because of confounding factors. Nonetheless, recent studies have shown that patient and physician concerns regarding potential adverse effects associated with PPI can influence prescription patterns and long-term treatment strategies.^{1,4,17} Our study revealed that patients receiving continuous therapy had a lower level of awareness of potential adverse effects associated with PPIs than those receiving on-demand therapy. Notably, approximately 81.2% of patients in the continuous therapy group, whose GERD symptoms were controlled, were unaware of these potential adverse effects. Step-down therapy, which involves providing an adequate explanation regarding the potential adverse effects of PPIs and considering a switch to on-demand therapy, should be attempted for these patients.

Our study also revealed that patients in the continuous therapy and NERD groups were prescribed higher doses of PPIs than those in the on-demand therapy and ERD groups. Typically, pa-

tients who undergo successful reduction of their PPI dose may consider switching to on-demand therapy.¹⁸ However, attempts to reduce the PPI dose have a high probability of failure due to poor control of symptoms, resulting in patients remaining in the continuous therapy group. It is also likely that patients with NERD were prescribed higher doses of PPIs for a similar reason. However, further research is required to investigate these associations.

Our study showed that many patients in the on-demand therapy group experienced GERD symptoms for a prolonged period of time. A possible explanation is that patients may have been concerned about the potential adverse effects of the long-term use of PPIs. As the duration of maintenance therapy for GERD increases, patients may become more aware of and concerned about the potential adverse effects of PPIs. Additionally, patients may recognize GERD as a chronic condition that often recurs, requiring "continual management" rather than a "definite cure." Therefore, patients who have experienced GERD symptoms for a longer duration are more likely to choose on-demand therapy as a treatment modality.

Based on our research findings, patients in South Korea generally adhere well to the intended prescription of their physician (Kappa = 0.578; $P < 0.001$). However, we found that many patients (22.0%) who were initially prescribed on-demand therapy for GERD eventually switched to continuous therapy of their own volition because of inadequate symptom control (Supplementary Fig. 2). This finding highlighted the importance of close monitoring of GERD symptoms for successful step-down therapy. Even for patients receiving on-demand therapy, it is advisable to monitor for any recurrence of symptoms and consider non-pharmacological treatments, such as lifestyle modifications.

This study had several limitations that must be considered. First, our results were restricted to South Korea and cannot be generalized to other races and countries. Second, the study had inherent biases due to its cross-sectional design. The nature of this study design, involving a comprehensive cross-sectional survey, may have contributed to a perceived lack of focus in certain aspects of the study. Third, while validated questionnaires such as GERD-HRQL or SEQ-GERD were used, we also developed our own questionnaires specifically for this study and used them for data collection. So, the use of some non-validated questionnaires can be a notable limitation of our study. Fourth, there exists a discrepancy in the ratio of 'patients driven' between the continuous and non-continuous groups (continuous 84.2% and non-continuous 68.7%). This difference could have influenced the outcomes of the study. Lastly, the study included patients and physicians only from referral hospitals. Nevertheless, the study involved a multi-institutional

national survey that provided valuable insights into the current state and realities of maintenance therapy for GERD through various questionnaires targeting both patients and physicians.

In conclusion, overall patient satisfaction was not different among the modalities of PPI maintenance therapy. Long-term use of PPIs for GERD can result in high economic costs and potential adverse effects. Therefore, it is important for physicians to have proactive discussions with their patients regarding the risks and benefits of PPIs and consider step-down therapy for appropriate patients because the perception of adverse effects may affect patient preferences for maintenance therapy.

Supplementary Materials

Note: To access the supplementary tables and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm23088>.

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Conflicts of interest: None.

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