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Running title: Adherence barriers in Japanese patients with COPD and asthma

Differences in Adherence Barriers to Inhaled Medicines between Japanese Patients with Chronic Obstructive Pulmonary Disease and Asthma Evaluated using the "Adherence Starts with Knowledge 20" (ASK-20) Questionnaire

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Abstract (249 words)

Objective: This multicenter, cross-sectional, non-interventional trial aimed to investigate adherence barriers to inhaled medicines when compared with oral medicines in Japanese patients with chronic obstructive pulmonary disease (COPD) and asthma.

Methods: The self-reporting “Adherence Starts with Knowledge 20” (ASK-20) questionnaire was administered for adherence barriers of inhaled and oral medicines to outpatients with regular clinic attendance.

Results: Patients with COPD and asthma reported different adherence barriers to inhaled medicines. Independent adherence barriers (odds ratio [95% confidence interval]) to inhaled medicines relative to those for oral medicines among patients with COPD and asthma were those related to item Q8 (“I know if I am reaching my health goals”; 2.49 [1.39–4.47]; p = 0.0022) and item Q2 (“I run out of my medicine because I do not get refills on time”; 2.69 [1.26–5.75]; p = 0.0127), respectively. Among patients with poor adherence to only inhaled medicines, those with COPD and asthma recognized item Q3 (“consuming alcohol and taking medicines”; 6.63 [1.27–34.7]; p <0.05) and item Q1 (“forget to take medicines only sometimes”; 4.29 [1.83–10.0]; p <0.05), respectively, were recognized as independent adherence barriers to inhaled medicines. The total ASK-20 scores and total barrier counts in

patients with poor adherence to inhaled medicines were significantly higher than in those without poor adherence among patients with asthma (p = 0.0057) but not those with COPD (p >0.05).

Conclusion: These results will aid in personalizing education on adherence to inhaled medicines among patients with COPD and asthma.

Key words: adherence barrier, inhaled medicine, COPD, asthma

Introduction

Inhaled medicines play a central role in the long-term treatment of chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma.[1,2] The improvement of pharmacological adherence (adherence) to inhaled medicines might contribute to a better prognosis, as poor adherence often causes disease exacerbation and affects mortality in patients with COPD and asthma.[3–8] Previous reports have demonstrated that adherence to inhaled medicines is worse than that to oral, injected, and transdermal medicines.[9–12] In Japan, adherence to inhaled medicines has been reported to be significantly poorer than that to oral medicines in patients with COPD and asthma.[13]

The Adherence Starts with Knowledge 20 (ASK-20) questionnaire was developed by Hahn et al. (2008) to identify adherence barriers. [14,15] The Japanese version of the ASK-20 questionnaire has already been validated in Japanese patients with asthma.[16] Previous studies have demonstrated a good correlation between adherence and adherence barriers in patients with asthma using the ASK-20 questionnaire.[14–16] However, adherence barriers to inhaled medicines compared with oral medicines are still unclear in Japanese patients with COPD.

In this regard, we have formulated three hypotheses. First, patients who require regular use of inhaled medicines, such as those with COPD and asthma, have

different barriers to inhaled medicines than they do to oral medicines. Second, there are differences in barriers to inhaled medicines between patients with COPD and asthma. Third, there are also differences in barriers to inhaled medicines between patients with COPD and asthma among patients with poor adherence to only inhaled medicines.

The Kyushu Asthma Seminar Investigator Group conducted this multicenter, cross-sectional, non-interventional trial to investigate the adherence barriers to inhaled medicines among Japanese patients with COPD and asthma using the ASK-20 questionnaire. Understanding adherence barriers to inhaled medicines will help personalize education about adherence to medicines in Japanese with COPD and asthma.

Methods

Ethical approval

The study was conducted in accordance with the Good Clinical Practice guidelines and was approved by the ethics board of each institute. The trial was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. R000015329) on February 13, 2014. Physicians obtained written informed consent from every patient who met the inclusion criteria.

Patients

Outpatients with COPD (>40 years of age) and asthma (>20 years of age) who met the inclusion criteria—regular medication with prescriptions of at least one inhaled and one oral medicine each and regular clinic attendance with medical records since giving their consent to participate within at least six months before the start of the study—were enrolled at each institute. To investigate adherence in each patient, one inhaled and one oral medicine each was selected as the most important medicine among all regularly prescribed agents by each physician, without consulting with the patient (Supplementary Table 1). Patients with higher brain disorders, such as dementia, were excluded. Elderly patients (≥80 years of age) and those <20 years old were also excluded. Patients with other chronic pulmonary diseases, such as

bronchiectasis, interstitial pneumonitis, and pneumoconiosis, and other active pulmonary infectious diseases, such as mycobacterium and fungal infections, were also excluded.

Study design

After providing their written consent, patients were required to complete the Japanese version of the self-reported ASK-20 questionnaire for adherence to the selected inhaled and oral medicines.[16] Two types of modified ASK-20 questionnaires (one for the inhaled medicines and one for the oral medicines) (Supplementary Table 1) were completed by each patient. To ensure the accurate completion of the ASK-20 questionnaire, technical nurses or pharmacists at each institute provided support for the patients' responses regarding inhaled and oral medicines. The nurses and pharmacists worked independently from the physicians and investigators.

Patient characteristics—including the age, sex, body mass index (BMI), smoking habits, presence of comorbid diseases, disease control levels, adherence levels to the selected inhaled and oral medicines, and information on all regular inhaled and oral medications—were recorded.[13,17] The presence of COPD was defined based on the following criteria: 1) age >40 years; 2) smoking history >0 pack-years; 3) fixed airflow obstruction with a forced expiratory volume in 1 s

(FEV$_1$)/forced vital capacity (FVC) ratio <70%; and 4) reversibility of FEV$_1$ <12% and <200 mL after administration of bronchodilators in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.[1] The presence of asthma was defined based on a diagnosis by the physician in accordance with the Global Initiative for Asthma (GINA) guidelines.[2] Poor disease control was recognized by a total COPD assessment test (CAT) score >10 points among patients with COPD[18-20] and by well, partially, or uncontrolled asthma in accordance with the GINA guidelines among patients with asthma.[2] Comorbid diseases were defined based on interview findings and information regarding all regular medicines prescribed to the total population (Supplementary Table 3). From medical records, physicians selected the best pre-bronchodilation values of FVC and FEV$_1$ during stable disease status. Adherence to the selected inhaled and oral medicines within 6 months before enrolment was assessed based on the questionnaire findings and prescription refill methods, and poor adherence to medicines was defined as <80% of adherence to inhaled or oral medicine, as determined by either method.[13, 21-24] All data were those values from within six months before enrolment.

However, patients with asthma-COPD overlap (ACO) were excluded from the study. Physicians excluded patients with suspected ACO based on the presence of asthmatic factors, such as variable changes in the respiratory symptoms and the lung

function, among the patients with COPD at enrollment. However, 26 patients (12.3%) who had COPD-like features (suspected ACO) based on the criteria according to the GOLD guidelines[1] after subsequent analyses among patients with asthma were accepted as having asthma in accordance with the physician's diagnosis. Patients who required long-term home oxygen therapy and non-invasive positive pressure support ventilation were also excluded from the subsequent analyses.

Statistical analyses

Patient characteristics were expressed as the number (percentage) of patients or mean ± standard deviation (SD). The total ASK-20 scores and total barrier counts (TBCs) were calculated in accordance with the methods described in previous studies (Supplementary Table 2).[14–16] To identify the independencies of adherence barriers to inhaled medicines, the proportions of patients who reported TBCs for each item were compared between inhaled and oral medicines by univariate and multivariate analyses. Patients were divided into two groups: those with and without poor adherence only to selected inhaled medicines, with the latter group including patients with good or poor adherence to the selected inhaled and oral medicines and poor adherence to only selected oral medicines. Adherence barriers for poor adherence to only inhaled medicines in each questionnaire item were identified by univariate and

multivariate analyses as follows: Dummy scores for the presence and absence of TBCs for inhaled or oral medicines were set as 1 and 0, respectively. When the dummy scores for inhaled medicines were higher than those for oral medicines, they were recognized as indicating the presence of barriers only to inhaled medicines. Data were compared between the groups using the unpaired *t*-test and chi-square test or the Fisher exact test with an expected frequency of <5.0 in cells >20%. To identify barriers for adherence to inhaled medicines, the odds ratio (OR) (95% confidence interval [CI] and p value) of each questionnaire item for inhaled medicines was analyzed by the chi-square or Fisher's exact test in univariate and multivariate analyses. The nonparametric Spearman rank test was used for the correlation (r) analysis. Differences of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the software package JMP version 9.0® (SAS Institute Japan Inc., Tokyo, Japan).

Results

Of the 381 patients (COPD, n = 140; asthma, n = 241) who gave their written consent, 335 (COPD, n = 114; asthma, n = 221) were ultimately analyzed in this study (Fig. 1). The numbers (OR [95% CI]; p value) of patients with poor adherence to inhaled medicines (n = 25) (poor adherence to only inhaled medicines [n = 19] and poor adherence to both inhaled and oral medicines [n = 6]) among patients with COPD (5.31 [1.46–19.2]; p = 0.0135) and asthma (n = 57) (poor adherence to only inhaled medicines [n = 17] and poor adherence to both inhaled and oral medicines [n = 40]; 9.53 [3.70–24.6]; p <0.0001) were significantly greater than those with poor adherence to oral medicines (11 patients with COPD: poor adherence to only oral medicines [n = 5] and poor adherence to both inhaled and oral medicines [n = 6]; and 24 patients with asthma: poor adherence to only oral medicines [n = 17] and poor adherence to both inhaled and oral medicines [n = 7]) (Fig. 1).

Table 1 presents a comparison of characteristics between patients with COPD and asthma. Patients with COPD were significantly older and had higher proportions of men (91.2%), smokers, and incidences of poor disease control than patients with asthma, whereas patients with asthma had significantly higher proportions of patients with chronic and seasonal rhinosinusitis and exhibited significantly better lung functions than patients with COPD. In regular treatment, the number of inhaled but

not oral medicines in the COPD group was significantly higher than that in the asthma group. In the comparison of diseases, the TBCs, but not the total ASK-20 scores, for oral medicines in patients with asthma were significantly higher than those in patients with COPD, whereas the total ASK-20 scores and TBCs showed no significant differences among the disease groups. However, regarding the correlation (r) between the ASK-20 questionnaire scores and adherence levels (%) via refill methods, the total ASK-20 scores and TBCs showed significantly negative associations with adherence with respect to inhaled ($r = -0.29$, $p < 0.0001$ and $r = -0.29$, $p < 0.0001$, respectively) but not oral medicines ($r = 0.07$, $p = 0.4800$ and $r = 0.10$, $p = 0.3784$, respectively) among patients with asthma. There was no correlation between inhaled ($r = -0.05$, $p = 0.6333$ and $r = -0.08$, $p = 0.4317$, respectively) and oral ($r = -0.02$, $p = 0.8112$ and $r = 0.10$, $p = 0.4982$, respectively) medicines in patients with COPD.

Fig. 2 presents the results of a comparison of the proportion of patients with adherence barriers identified for each ASK-20 item between inhaled and oral medicines. There were no significant differences in the total ASK-20 scores or TBCs between inhaled and oral medicines among the disease groups (Supplementary Fig. 1). In the total study population, markedly high proportions of patients with adherence barriers to inhaled medicines reported adherence barriers because of items Q3 (“My

use of alcohol gets in the way of taking my medicine") and Q8 ("I know if I am reaching my health goals"), whereas a relatively high proportion of patients with adherence barriers to oral medicines reported barriers because of item Q20 ("Have you not had your medicine with you when it was time to take it?"). In the COPD group, items Q7 ("I feel confident that each of my medicines will help me") and Q8 were found to be related to higher proportions of patients with adherence barriers to inhaled medicines than oral medicines, whereas items Q1 ("I forget to take my medicines only sometimes"), Q6 ("I have felt sad, down, or blue during the past month"), and Q20 were related to higher proportions of patients with adherence barriers to oral medicines than inhaled medicines. In the asthma group, item Q2 ("I run out of my medicine because I do not get refills on time") was related to higher proportions of patients with barriers to inhaled medicines than oral medicines, whereas item Q20 was related to higher proportions of patients with adherence barriers to oral medicines than inhaled medicines.

The results of multivariate analyses (Table 2) revealed that, among the total study population and among patients with COPD, items Q3 (OR, 3.81 [95% CI, 1.40–10.4]; p = 0.0087) and Q8 (2.49 [1.39–4.47]; p = 0.0022), respectively, were more frequently independent adherence barriers to inhaled medicines than to oral medicines. However, among patients with asthma, only item Q2 (2.69 [1.26–5.75]; p =

0.0127) was found to be an adherence barrier to inhaled medicines in a univariate analysis.

Fig. 3 presents the results of a comparison of the total ASK-20 scores and TBCs for inhaled medicines between patients with (n = 59 [COPD, 19; asthma, 40]) and without (n = 276 [COPD, 95; asthma, 181]) poor adherence to only selected inhaled medicines. As shown in Fig. 3A, the total ASK-20 scores among patients with poor adherence to inhaled medicines were significantly higher than those among patients without poor adherence in the total study population (p = 0.0077) and in the asthma group (p = 0.0057) but not in the COPD group (p = 0.2881). As shown in Fig. 3B, the TBCs among patients with poor adherence to inhaled medicines were significantly higher than those among patients without poor adherence in the total study population (p = 0.0005) and in the asthma group (p = 0.0004) but not in the COPD group (p = 0.2452).

Table 3 presents the ORs (95% CIs) for each item among adherence barriers to inhaled medicines in patients with poor adherence to only inhaled medicines relative to that in patients without poor adherence. The results of multivariate analyses revealed that, among patients with COPD, item Q3 (6.63 [1.27–34.7]; p = 0.0250) was an independent adherence barrier to inhaled medicines. In contrast, among the total study population and patients with asthma with poor adherence to inhaled medicines,

item Q1 was an independent adherence barrier to inhaled medicines (3.07 [1.60–5.88] and 4.29 [1.83–10.0]; p = 0.0007 and 0.0008, respectively).

Discussion

To our knowledge, this is the first report to compare adherence barriers between inhaled and oral medicines among Japanese patients with COPD and asthma using the ASK-20 questionnaire. The ASK-20 questionnaire is useful for identifying the patient-specific adherence barriers using the total ASK-20 scores and TBCs.[14-16] We demonstrated that the adherence to inhaled medicines was poorer than to oral medicines in patients with COPD and asthma.[13] However, we were unable to identify the differences in the barriers between the different drug formulations based on the total ASK-20 scores and TBCs in patients with COPD and asthma.

In the comparison of diseases, only the TBCs for oral medicines among patients with asthma were significantly higher than among those with COPD. The risk factors for higher TBCs in patients with asthma were not determined, although the correlations between high TBCs for oral medicines and the patient characteristics, including the age, gender, smoking status, disease control, lung function, and number of medicines, were analyzed (unpublished observation). The ASK-20 questionnaire includes the domains of lifestyles (item Q1 to Q6), attitude and behavior (Q7 and Q8), support from others or communication with the healthcare team (Q9 to Q12), barriers for medicines (Q13 to Q 15), and adherence to medicines (Q16 to Q20).[14, 15] Evaluating the score for each individual item in these domains may facilitate the

identification of patient-specific adherence barriers more efficiently than the total ASK-20 scores and TBCs.

Personalized interventions to adherence barriers may help improve adherence to medicines, although adherence barriers may vary among patients.[3, 25] Our study showed that the total ASK-20 scores and TBCs were negatively associated with adherence levels with respect to only inhaled medicines, as per the refill method in patients with asthma. The weak correlation between adherence barriers and adherence levels may be due to our assessment of the last six months of adherence, as previous studies demonstrated a good correlation between the daily or most-recent-two-week barriers and adherence.[3, 14-16] In addition, our finding of no correlation between adherence barriers and adherence levels in patients with COPD may have been due to the sample size.

A previous study reported embarrassment or annoyance regarding using or carrying medicines to be a barrier to inhaled medicines;[26] however, that study did not investigate adherence barriers among patients with COPD. Identifying patient-specific adherence barriers is important for managing patients with chronic diseases.[14, 15] In our study, the results indicated differences in independent adherence barriers to inhaled medicines compared with those to oral medicines among the total population, patients with COPD, and those with asthma. The total population is recognized as a

cohort of patients who require the regular use of inhaled medicines. These patients considered alcohol consumption to be an independent barrier to inhaled medicines to a greater extent than to oral medicines; however, why alcohol consumption was considered a barrier to adherence to inhaled medicines is unclear. Patients may simply forget to take their inhaled medicines or may be concerned with the interactive effects between alcohol and inhaled medicines during or after alcohol consumption. In comparing COPD and asthma patients, patients with COPD reported that reaching their health-related goals was an independent adherence barrier to inhaled medicines. Our study showed that the patients with COPD included a significantly larger population with poorly controlled diseases that used a larger variety of regular inhaled medicines than the patients with asthma. Furthermore, the patients with COPD seemed more likely to recognize their own respiratory disease as incurable and their own inhaled medicines as insufficient treatments than those with asthma. Recognition of diseases and medication beliefs may affect adherence barriers for inhaled medicines in patients with COPD, because patients with COPD may recognize their own disease as an incurable disease.[27-29]

In addition, most patients with COPD enrolled in this study were older than those with asthma. Aging is a predictor of poor adherence to medicines in patients with COPD.[30, 31] Albrecht et al. reported that depression reduced adherence in older

patients with COPD.[32] Aging and mood disorders may affect the recognition of personal health goals;[30, 32] however, the interaction between aging and the recognition of heath goals is still unclear. In contrast, patients with asthma reported that they refilled inhaled medicines in a timely manner after depleting their stocks less frequently than for oral medicines. The characteristics of asthma, not but COPD, seem to explain why patients do not take inhaled medicines when they are depleted. Asthmatic symptoms vary despite regular treatments. Indeed, a better controlled disease and less-frequent treatment due to a lack of perceived symptoms are known to be the main reasons for poor adherence in asthma.[33, 34] As such, less-intense symptoms may lead to a patient forgetting to take inhaled medicines.

Poor adherence to inhaled medicines is affected by barriers to inhaled medicines.[16, 27] In our study, patients with poor adherence to only inhaled medicines had significantly higher total ASK-20 scores and TBCs to inhaled medicines than those without poor adherence in the total population and the asthma group but not in the COPD group. Poor adherence to medicines may be linked to adherence barriers. Among patients with COPD, those with poor adherence to inhaled medicines recognized alcohol consumption as a greater independent barrier to inhaled medicines than to oral medicines. However, the proportion of patients with TBCs for item Q3 was small (<10%) among patients with COPD. An individual's alcohol

consumption may contribute to the development of a personalized education approach for inhaled medicines in patients with poor adherence to inhaled medicines among those with COPD. Among patients with asthma, those with poor adherence to inhaled medicines recognized forgetfulness about taking their medicines sometimes as a greater independent barrier to inhaled medicines than to oral medicines. As previously mentioned, forgetting to take inhaled medicines may be associated with asthmatic symptoms and the degree of control among patients with poor adherence, similar to our findings in the cohort of patients with asthma.[31, 34] Reminders or electronic trackers as interventions may help improve adherence to inhaled medicines, if patients with poor adherence simply forget to take their medicine.[35]

This study has some limitations. First, a selection bias might have influenced the results, as we selected patients with good pharmacological persistence. The absence of differences in the total ASK-20 scores or TBCs was possible, as over 70% of the enrolled patients had good adherence to inhaled and oral medicines. Previous studies have reported persistence rates of 10%–15% for inhaled medicines after a year among patients with asthma.[36, 37] Second, since there are no specific tools available for the measurement of adherence barriers to inhaled medicines, we used the ASK-20 questionnaire with some modifications. Third, pharmacological adherence was evaluated not by direct methods but rather by indirect methods (i.e.

questionnaire and prescription refill surveys). Fourth, the characteristics of patients with suspected ACO were not assessed in this study. Fifth, among all inhaled and oral medicines, we only selected one medicine each for the comparison of adherence between the two medication types. This selection bias might have affected our results. Sixth, the sample size of the COPD group might be considered inadequate for the statistical analyses (Supplementary Appendix). Further studies are necessary to address these limitations.

In conclusion, we comparatively analyzed adherence barriers to inhaled and oral medicines among patients with COPD and asthma using the ASK-20 questionnaire. We observed differences in the underlying factors for adherence barriers between patients with COPD and asthma. In addition, among patients with COPD and asthma, those with and without poor adherence to inhaled medicines differed in terms of some barriers to inhaled medicines. We believe that our results will aid in the personalization of education for adherence to inhaled medicines among Japanese patients with COPD and asthma who require inhaled medications.

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Author contributions

All authors contributed to the data analysis, drafting, and critical revision of the paper and agree to be accountable for all aspects of the work. Each author mainly contributed as follows: Dr. T. Toyama contributed to the protocol design, analysis, and writing of the manuscript; Dr. T. Kawayama contributed to the protocol design and

editing of the manuscript; Dr. T. Kinoshita contributed to the analysis; Dr. Y Imamura contributed to the analysis; Dr. M. Yoshida contributed to the data collection and editing of the manuscript; Dr. K. Takahashi contributed to the data collection and editing of the manuscript; Dr. K. Fujii contributed to the data collection and editing of the manuscript; Dr. I Higashimoto contributed to the data collection and editing of the manuscript; Prof. T. Hoshino supervised the protocol design and edited the manuscript.

Disclosure (conflicts of interest and funding sources)

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Table 1 Characteristics of the total study population and patients with COPD or asthma

Characteristics	Total n = 335	COPD n = 114	Asthma n = 221	COPD vs asthma p value
Age, years	64.5 ± 12.3	71.1 ± 6.2	61.1 ± 13.3	< 0.0001
Male, n (%)	186 (55.5)	104 (91.2)	82 (37.1)	< 0.0001
Body mass index, kg/m^2	23.3 ± 4.7	21.6 ± 4.2	24.2 ± 4.7	< 0.0001
Smoking habit, Cu/ex/non, n (%)	42/147 /146 (12.5/43.9/43.6)	15/99/0 (13.2/86.8/0)	27/48/146 (12.2/21.7/66.1)	< 0.0001
Smoke index, pack-year	25.6 ± 32.9	57.9 ± 29.3	8.9 ± 19.6	< 0.0001
No. of comorbid diseases per patient	2.6 ± 2.0	2.6 ± 1.9	2.6 ± 2.0	1.0
No. of patients with chronic and seasonal rhinosinusitis, n (%)	55 (16.4)	8 (7.0)	47 (21.2)	0.0006
Poor controlled diseases, n (%)	129 (38.5)	74 (64.9)	55 (24.9)	< 0.0001
Lung function tests				
FVC, L	2.8 ± 0.8	2.8 ± 0.7	2.8 ± 0.8	0.5
% predicted FVC, %	92.2 ± 19.3	87.0 ± 21.9	94.9 ± 17.2	0.0003
FEV_1, L	1.7 ± 0.7	1.3 ± 0.6	1.9 ± 0.7	< 0.0001
%FEV_1 predicted, %	70.5 ± 25.4	50.2 ± 22.0	80.9 ± 20.2	< 0.0001
FEV_1/FVC ratio	61.3 ± 17.4	45.5 ± 14.3	69.5 ± 12.6	< 0.0001
Treatment for COPD or asthma	335 (100)	114 (100)	221 (100)	
ICS alone	38 (11.3)	0 (0)	38 (17.2)	< 0.0001
LABA alone	14 (4.2)	14 (12.3)	0 (0)	< 0.0001
LAMA alone	26 (7.8)	26 (22.8)	0 (0)	< 0.0001
ICS–LABA combinations	186 (55.5)	16 (14.0)	170 (76.9)	< 0.0001
ICS–LAMA combinations	5 (1.5)	5 (4.4)	0 (0)	0.0043
LAMA–LABA combinations	21 (6.3)	21 (18.4)	0 (0)	< 0.0001
ICS–LABA–LAMA triplets	45 (13.4)	32 (28.1)	13 (5.9)	< 0.0001
No. of regular inhaled medicines (devices), n (range)	1.3 ± 0.5 (1 to 3)	1.5 ± 0.5 (1 to 3)	1.1 ± 0.4 (1 to 3)	< 0.0001
No. of regular oral medicines, n (range)	4.5 ± 3.4 (1 to 19)	4.9 ± 4.0 (1 to 19)	4.3 ± 3.0 (1 to 18)	0.1
ASK-20 questionnaire				
For inhaled medicines				
Total ASK-20 scores	35.1 ± 9.1	34.1 ± 9.2	35.4 ± 9.0	0.5
TBCs	3.1 ± 2.6	2.9 ± 2.5	3.4 ± 2.6	0.1
For oral medicines				
Total ASK-20 scores	34.0 ± 9.0	33.5 ± 9.0	34.9 ± 8.7	0.1
TBCs	2.9 ± 2.5	2.6 ± 2.5	3.5 ± 2.6	0.0008

Notes: Data are presented as numbers (percentages) of patients and mean ± standard deviation. For asthma, the number (%) of patients with steps I, II, III, IV, and V, based on GINA treatment steps, were

0 (0), 40 (11.9), 113 (33.7), 48 (14.3), and 20 (6.0), respectively. For COPD, the number (%) of patients with mild (%FEV_1 predicted $\geq$80%), moderate (50% $\leq$ %FEV_1 predicted <80%), severe (30% $\leq$ %FEV_1 predicted <50%), and very severe (%FEV1 predicted <30%) airflow obstruction levels based on the GOLD guideline were 11 (9.6), 44 (35.6), 33 (28.9), and 26 (22.8), respectively. The mean (SD) total CAT score was 14.1 (8.1) in patients with COPD.

Abbreviations: COPD, chronic obstructive pulmonary disease; Cu/Ex/Non, current/ex/non-smoker; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; TBCs, total barrier counts

Table 2 Odds ratio (95% CI) of each ASK-20 item between patients with adherence barriers to inhaled when compared with oral medicines by univariate and multivariate analyses

Item		Univariate analyses		Multivariate analyses	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Total study population					
Q3.	My use of alcohol gets in the way of taking my **inhaled or oral** medicines.	3.97 (1.46, 10.8)	0.0057[a]	3.81 (1.40, 10.4)	0.0087[a]
Q8.	I know if I am reaching my health goals.	1.39 (1.01, 1.89)	0.0480[a]	1.35 (0.99, 1.85)	0.1
COPD					
Q7.	I feel confident that each one of my **inhaled or oral** medicines will help me.	2.63 (1.23, 5.65)	0.0173[a]	1.59 (0.69, 3.66)	0.3
Q8.	I know if I am reaching my health goals.	2.84 (1.66, 4.87)	0.0002[a]	2.49 (1.39, 4.47)	0.0022[a]
Asthma					
Q2.	I run out of **inhaled or oral** medicine because I do not get refills on time.	2.69 (1.26, 5.75)	0.0127[a]		

Notes: In univariate analyses, odds ratio (95% CI; p value) for each item was calculated on the basis of comparison between patients with barriers to inhaled and oral medicines by the Fisher exact test (Full data in Supplementary Table 4). The bolded words were arranged in each ASK-20 item by investigators.

[a] $p < 0.05$ when compared with oral medicines, [b] $p < 0.05$ when compared with inhaled medicines

Abbreviations: ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; COPD, chronic obstructive pulmonary disease

Table 3 Odds ratio (95% CI) of each ASK-20 item on barriers to inhaled medicines in patients with poor adherence to only inhaled medicines relative to patients without poor adherence

Items		Univariate analyses		Multivariate analyses	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Total study population					
Q1.	I forget to take my **inhaled or oral** medicines only some times.	4.21 (2.33, 7.60)	< 0.0001[a]	3.07 (1.60, 5.88)	0.0007[a]
Q4.	I worry about how the **inhaled or oral** medicines will affect my sexual health.	3.36 (1.15, 9.83)	0.0317[a]	2.05 (0.58, 7.26)	0.3
Q5.	I sometimes forget things that are important to me.	2.57 (1.36, 4.86)	0.0051[a]	1.39 (0.68, 2.85)	0.4
Q16.	Have you taken an **inhaled or oral** medicine more or less often than prescribed?	2.91 (1.64, 5.18)	0.0003[a]	1.71 (0.90, 3.26)	0.1
Q17.	Have you skipped or stopped taking an **inhaled or oral** medicine because you did not think it was working?	4.13 (1.71, 9.94)	0.0024[a]	2.10 (0.69, 6.40)	0.2
Q18.	Have you skipped or stopped taking an **inhaled or oral** medicine because it made you feel bad?	3.78 (1.45, 9.86)	0.0089[a]	1.32 (0.39, 4.52)	0.7
COPD					
Q3.	My use of alcohol gets in the way of taking my **inhaled or oral** medicines.	8.18 (1.66, 40.2)	0.0144[a]	6.63 (1.27, 34.7)	0.0250[a]
Q17.	Have you skipped or stopped taking an **inhaled or oral** medicine because you did not think it was working?	4.80 (1.16, 19.9)	0.0410[a]	3.72 (0.81, 17.1)	0.1
Asthma					
Q1.	I forget to take my **inhaled or oral** medicines only sometimes.	5.76 (2.64, 12.5)	< 0.0001[a]	4.29 (1.83, 10.0)	0.0008[a]
Q4.	I worry about how the **inhaled or oral** medicine will affect my sexual health.	3.55 (1.07, 11.8)	0.0451[a]	2.18 (0.52, 9.14)	0.3
Q5.	I sometimes forget things that are important to me.	2.34 (1.07, 5.15)	0.0407[a]	1.10 (0.45, 2.70)	0.8
Q16.	Have you taken an **inhaled or oral** medicine more or less often than prescribed?	3.06 (1.52, 6.18)	0.0023[a]	1.79 (0.82, 3.91)	0.1
Q17.	Have you skipped or stopped taking an **inhaled or oral** medicine because you did not think it was working?	3.82 (1.24, 11.7)	0.0237[a]	1.64 (0.38, 6.99)	0.5
Q18.	Have you skipped or stopped taking an **inhaled or oral** medicine because it made you feel bad?	3.55 (1.07, 11.8)	0.0451[a]	1.00 (0.20, 4.95)	1.0

Notes: In univariate analyses, odds ratio (95% CI; p value) for each item was calculated on the basis of comparison between patients with barriers to inhaled medicines and oral medicines by the Fisher exact test (Full data in Supplementary Table 5).

[a] $p < 0.05$ when compared with patients without poor adherence to only inhaled medicines.

Abbreviations: ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; COPD, chronic obstructive pulmonary disease

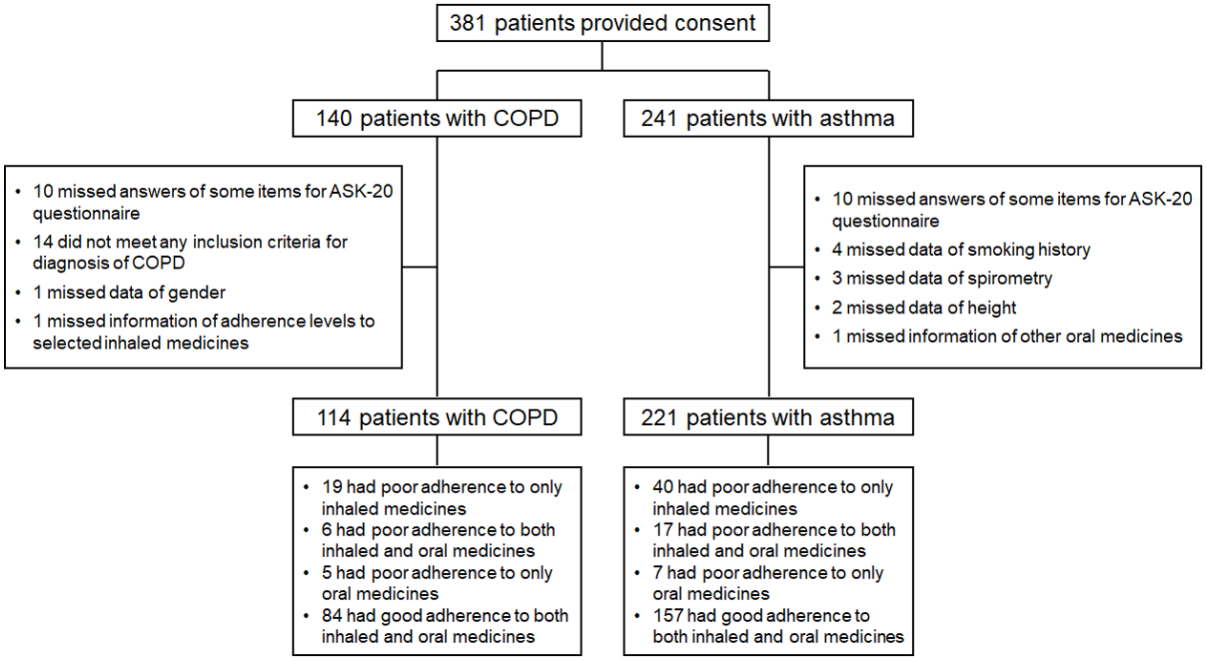

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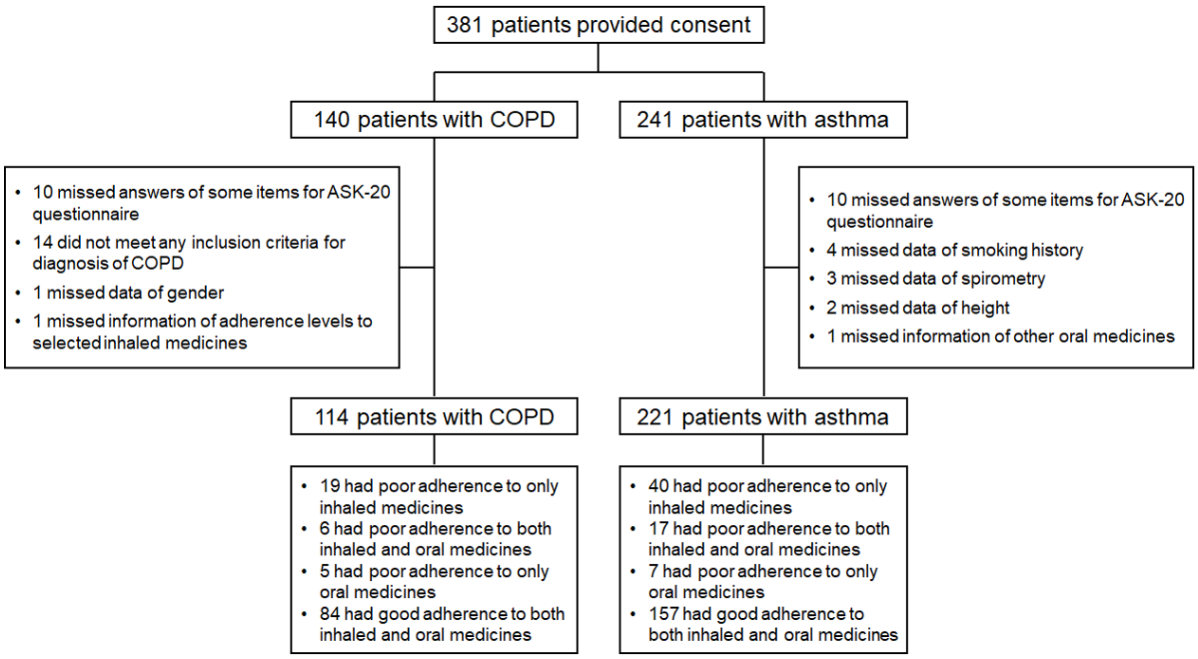
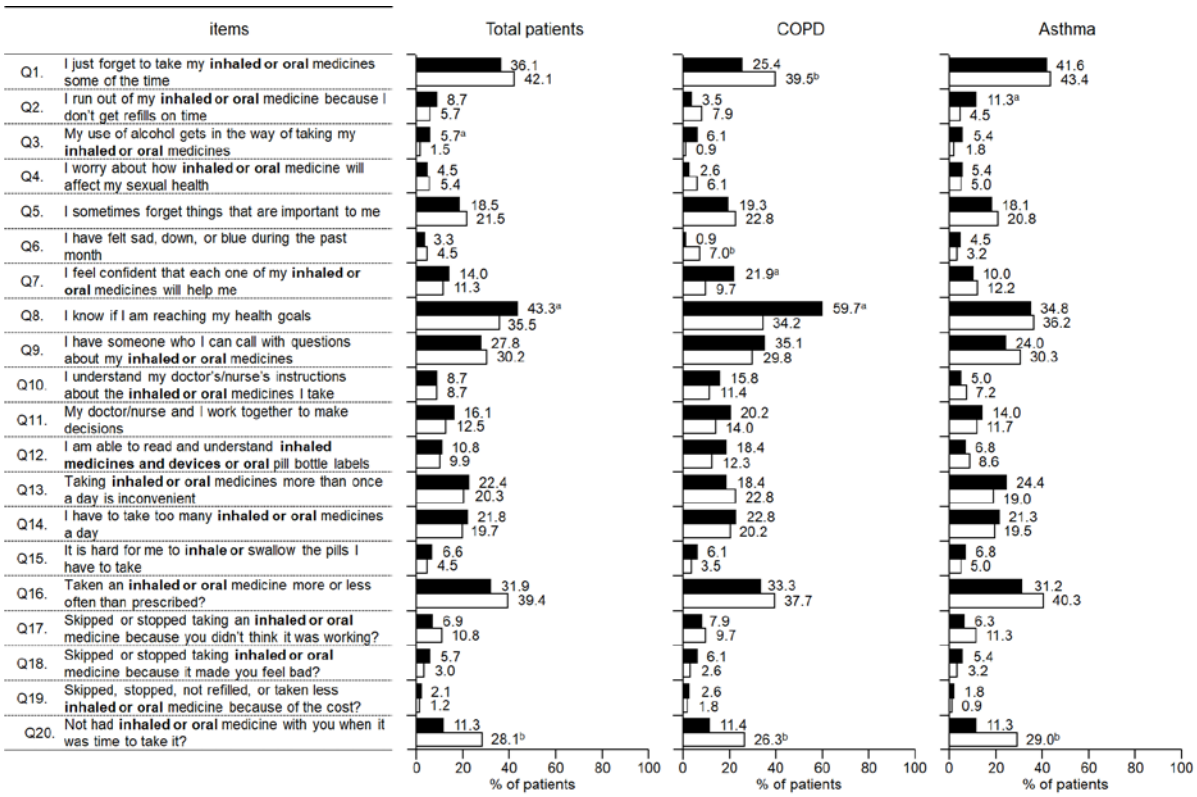
Figure Legends

Fig. 1. Study design.



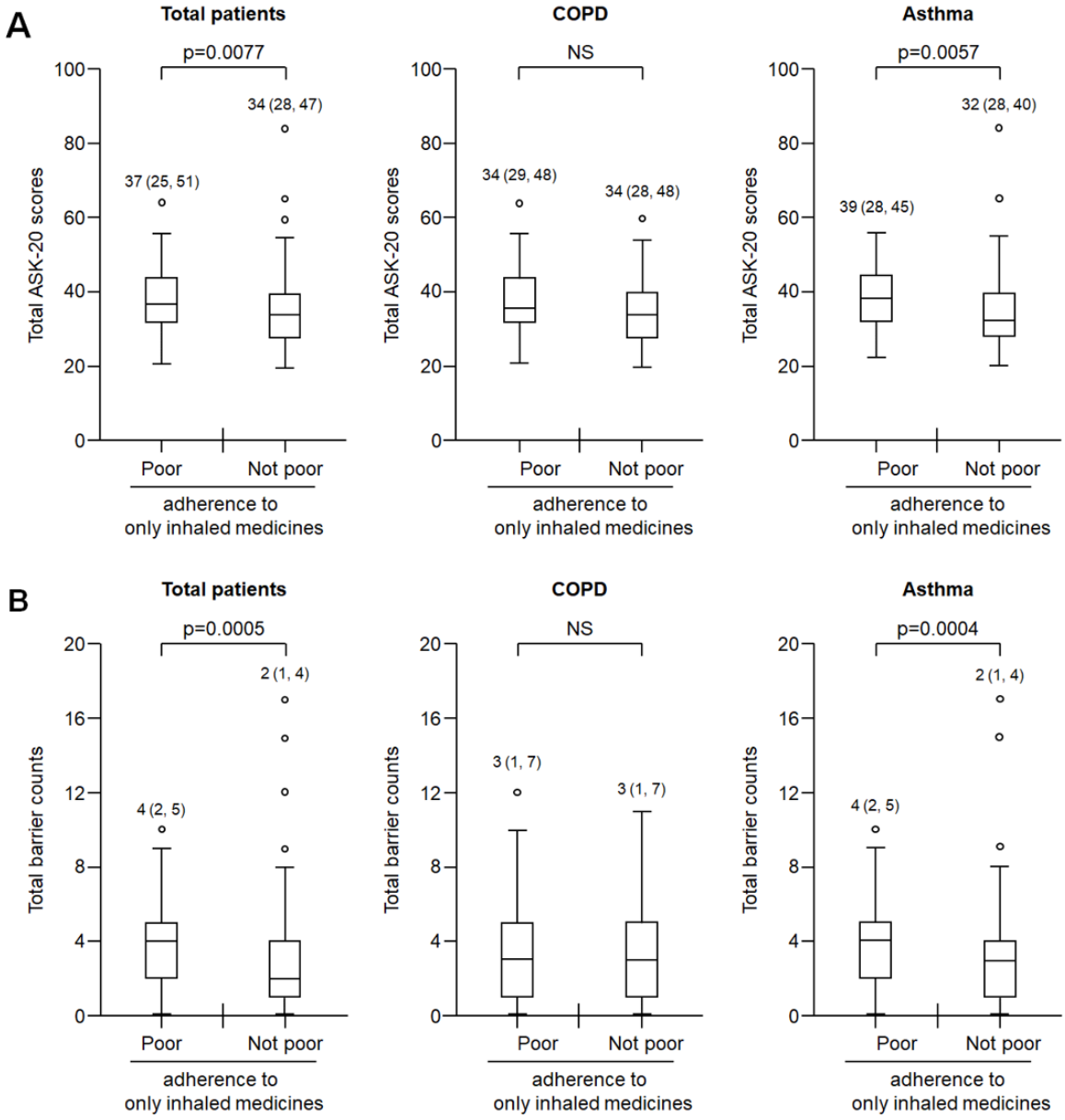
ASK-20, Adherence Starts with Knowledge 20; COPD, chronic obstructive pulmonary disease.

Fig. 2. A comparison of the proportion of patients with an adherence barrier indicated for each ASK-20 item between inhaled and oral medicines.



The proportions of patients (%) are presented as bars with values. Patients with adherence barriers to inhaled and oral medicines are represented by black and white bars, respectively. The bolded words were arranged in each AKS-20 item by investigators. [a]p <0.05 when compared with oral medicines, [b]p <0.05 when compared with inhaled medicines. ASK-20, Adherence Starts with Knowledge 20; COPD, chronic obstructive pulmonary disease.

Fig. 3. A comparison of the total ASK-20 scores (A) and total barrier counts (B) to inhaled medicines between patients with and without poor adherence to only inhaled medicines.



The values are presented as the median and 95% confidence interval (CI). The median values (upper and lower quintiles) are presented as boxes, and the maximum and minimum values of the 95% CI are presented as the upper and lower whiskers, respectively. Box-and-whisker plots with solid and dotted lines present the values for patients with and without poor adherence to only inhaled medicines, respectively. Outlier values are presented as open dots. ASK-20, Adherence Starts with Knowledge 20; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NS, not significant.