医薬品相互作用研究
一　般　論　文
42(1) 16-22 (2018)

Comparison of functional usability between brand-name and generic topical anti-inflammatory analgesics.

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(Received August 25, 2017; Accepted November 6, 2017)

For topical anti-inflammatory analgesics, it is not only the efficacy but also the functional usability which are important factors for patients in their choice of drugs. However, little information is available on the functional usability of generic drugs (GEs). The aim of the study was to compare the functional usability between brand-name drug (BR) and GEs topical anti-inflammatory analgesics in order to define any superiority in the functional usability of these drugs.

The questionnaire survey on the functional usability of BR and GEs of Ketoprofen Tape (patches) was conducted on patients having previously used the patch form of topical anti-inflammatory analgesics.

We received 245 responses from the patients. Respondents regarded "Efficacy", "Securely adhering" and "No rashes" as important. The most dissatisfaction with patch use was "Difficultly applying/re-applying". Respondents having used both BR and GE rated the functional usability for BR better than that for GE.

Respondents' dissatisfactions were indicated much more frequently in functional usability than in efficacy. Thus, the functional usability may be a trigger for the patient to change drugs. Further, a large individual difference was observed in patients' responses concerning the functional usability. Even with the use of the same type of patch, the functional usability perceived by each patient might differ.

This study revealed that functional usability differs among BR and GEs, and the patient's perception of functional usability patients also varies among patients, indicating that functional usability may be important when patients use a patch and that their needs for functional usability is varied.

Key Words: transdermal patches, ketoprofen, drug information, generic medicines, questionnaire survey

Introduction

Recently in Japan, the national medical care expenditure has increased more rapidly than the increase in national income due to advanced aging[1]; the year-specific estimated medical costs exceeded JPY 30 trillion in 2001 and reached JPY 40 trillion in 2014[2),3)]. In response to this situation, the Ministry of Health, Labour and Welfare (MHLW) addressed a reduction in drug cost as part of the strategy to make medical care more efficient, and the Ministry began to establish an environment to promote the use of generic drugs (GEs) by revising the prescription form in the 2006 Revision of Medical Fee[4]. The quantity share of GEs among the medical drug products was 46.9% in September 2013 and 56.2% as of September 2015[5]. To further reduce the drug cost, the MHLW set the target of this share at 80% or above as early as possible between 2018 and 2020[5]. GEs have been approved based on confirmed bioequivalence. However, medical staff are still concerned that GEs might be inadequate compared to brand-name drug (BR) in quality, information service by manufacturers and stable supply. This anxiety may prevents the promotion of GEs[1),6)].

Topical anti-inflammatory analgesics are commonly used to cure various types of pain[7]. Since the patches are applied directly to the skin, it was reported that not only anti-inflammatory and analgesic effects but the functional usability, such as removing and stretching were also

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important factors for drug change by patients and patient satisfaction[8),9)]. In the previous study which investigated the importance of 4 factors (“Efficacy”, “Safety”, “Economics” and “Functional usability”) when patients used or selected topical anti-inflammatory analgesic patch products[10)], 83.9% of patients using BR patches and 84.8% of patients using GEs patches replied that the functional usability was an “Important” or “Rather important” factor. The patients changed their patches mainly due to dissatisfaction with functional usability such as “Rash/skin irritation” and “Easily peeling during application”. Moreover, the patients requested to change their patches to another specific patch mainly due to dissatisfaction with the anti-inflammatory and analgesic effect and also because of “Easily peeling during application”. These results indicate that “Functional usability” may serve as an important criteria when patients select the drugs[10)]. However, bioequivalence has been observed between BR and GEs, without the evidence that functional usability would be the same level. Furthermore, it is difficult to evaluate functional usability based on the documents provided by manufacturers, such as the package insert or an interview form. We compared the functional usability of between BR and GEs of Ketoprofen Tape, one of the most popular topical anti-inflammatory analgesics, in order to evaluate the functional usability of these drugs.

Methods

We conducted a self-completed anonymous questionnaire for patients who have used BR-A or one of GE-B, -C, -D, or -E for Ketoprofen Tape 20 mg through 21 insurance pharmacies of the Maru Corporation.

The respondents received an explanation describing the purpose and contents of this study and anonymity of this questionnaire. They consented to reply to this questionnaire. This study was approved by the Ethical Review Board of the Graduate School of Pharmaceutical Science, Chiba University.

1. Questionnaire

The questionnaire consisted of the following questions: 1) characteristics of the respondent (age, sex and the patches used), 2) important factors related to using the patch, 3) satisfaction and dissatisfaction with the patch, 4) whether or not they had changed their patch and, if applicable, the reason for change, 5) previous use of BR and GEs and the name of GE used, 6) evaluation of the comparison of functional usability between BR and GEs, and 7) the reason for return to BR.

We obtained the responses in the form of multiple choice for [questions 1), 3), 4), and 5) (partially narrative)], selection of the top 1 to 3 [among the options for 2), 3), 7)], and rating of “Easiness to apply”, “Smell”, “Degree of adherence”, and “Easy removal” using 1 to 5 scale as well as “Pain severity with removal” using 1 to 5 scale for 6).

2. Statistical analysis

A chi-square test was performed for the proportion of BR versus GE users satisfied with their patch. The important factors using the patch, dissatisfaction with their patch, and the reasons for return from GE to BR, assuming that the top 1, 2, and 3 items was regarded as 3, 2, and 1 points, respectively, the mean score was calculated by dividing the total score by the number of respondents for each item. The resultant mean scores were examined according to the drug product used, gender, and age group based on the Mann-Whitney U-test. Differences in pain severity in the ratings of impression from using BR and GEs between the respective users were examined based on the Student’s t-test. The statistical significance level was set at a p-value below 0.05. All analyses were conducted using SPSS (version 20.0, IBM, Japan).

Results

1. Characteristics of respondents (age, sex and the patches used)

We conducted the questionnaire between December 2014 and March 2015 and obtained the responses from 274 subjects. The responses for 29 subjects, for whom some responses were related to missing baseline information, were not included; therefore the analysis set consisted of

245 subjects. Among the entire analysis set, the proportion of respondents aged 60 years or older was 81.6% (n = 200) and that of female was 68.2% (n = 167). BR users accounted for 78.4% (n = 192) of all responders; those aged 60 years or older 80.7% (n = 155) and females 71.4% (n = 137). GE users accounted for 21.6% (n = 53) of all respondents; those aged 60 years or older 84.9% (n = 45) and females 56.6% (n = 30).

Among 53 GE users, the product used was B in 9 users, C in 23, D in 4, and E in 17.

2. Important factors related to using the patch

Two hundred forty three of 245 respondents replied to the following question: "Q: On what important factors do you consider when using a patch to reduce pain or inflammation?".

The important factors related to the use of the patch are listed in Table 1. These factors were "Efficacy", followed by "No rash", and "Securely adhering" in BR users, while they were "Efficacy", followed by "Securely adhering", and "Easy removal" in GE users. According to the sex, the important factor using the patch was "Efficacy", followed by "Securely adhering", and "Medication as prescribed by physician" for males, while it was "Efficacy", followed by "No rash", and "Securely adhering" for females. According to the age group, the important factor was "Efficacy", followed by "Securely adhering", and "No rash" in respondents younger than 60 years, while it was "Efficacy", followed by "No rash", and "Securely adhering" in those aged 60 years or older. When comparing the individual items, the respondents younger than 60 years considered "Securely adhering" as more important compared to those aged 60 years or older ($p < 0.05$).

Table 1. The important factors using the patch (n = 243)
"Q: On what important factors do you consider when using a patch to reduce pain or inflammation?"

	BR n = 190	GE n = 53	*P*- value	Male n = 77	Female n = 166	*P*- value	Younger than 60 years n = 45	60 years or older n = 198	*P*- value
Efficacy	1.97±1.27	2.17±1.24	0.253	2.05±1.28	2.00±1.16	0.739	2.13±1.16	1.99±1.29	0.860
Securely adhering	0.73±1.05	0.70±1.03	0.922	0.81±1.08	0.68±1.03	0.290	1.02±1.10	0.65±1.03	0.015*
Easy removal (i.e., painless)	0.34±0.77	0.60±1.01	0.051	0.34±0.79	0.42±0.86	0.455	0.33±0.77	0.41±0.85	0.563
No rashes	0.81±1.11	0.53±0.87	0.148	0.65±0.97	0.80±1.11	0.452	0.87±1.16	0.72±1.05	0.461
No smell	0.36±0.76	0.26±0.66	0.442	0.10±0.38	0.45±0.84	0.001*	0.44±0.79	0.31±0.73	0.088
Smell	0.03±0.19	0.04±0.28	0.932	0.00±0.00	0.04±0.26	0.125	0.04±0.21	0.03±0.21	0.220
Easily applying /re-applying	0.49±0.89	0.57±0.95	0.631	0.47±0.82	0.52±0.94	0.931	0.31±0.76	0.55±0.93	0.088
Good stretchability	0.17±0.49	0.04±0.28	0.025*	0.13±0.47	0.14±0.44	0.435	0.16±0.42	0.14±0.46	0.491
Low cost	0.07±0.36	0.36±0.76	0.000*	0.14±0.56	0.13±0.46	0.777	0.20±0.55	0.12±0.48	0.216
Well-recognized name (pharmaceutical company)	0.04±0.28	0.04±0.19	0.500	0.08±0.42	0.02±0.13	0.319	0.02±0.15	0.04±0.28	0.899
Color	0.04±0.29	0.02±0.14	0.907	0.00±0.00	0.05±0.32	0.125	0.00±0.00	0.05±0.29	0.282
Prescribed by doctor	0.52±0.97	0.38±0.84	0.325	0.66±1.07	0.40±0.87	0.047*	0.36±0.91	0.52±0.95	0.116
Recommended by pharmacist	0.01±0.10	0.00±0.00	0.454	0.00±0.00	0.01±0.11	0.334	0.00±0.00	0.01±0.10	0.499
Recommended by family/friend	0.01±0.10	0.00±0.00	0.454	0.00±0.00	0.01±0.11	0.334	0.00±0.00	0.01±0.10	0.499
Others	0.04±0.30	0.00±0.00	0.358	0.04±0.34	0.02±0.22	0.943	0.00±0.00	0.04±0.29	0.407

Mean ± S.D. was calculated by dividing the total score by the number of respondents for each item, assuming the top 1, 2, and 3 items as 3, 2, and 1 points, respectively.

$P < 0.05$ (Mann-Whitney *U* test)

3. Satisfaction and dissatisfaction for the patch

Two hundred forty of 245 respondents replied to the following question: "Are you satisfied with the patch that you are now using?", 197 respondents (82.1%) answered "Yes" while 43 (17.9%) answered "No". The number of users who were satisfied was 154 (82.4%) for BR (n = 187), while it was 43 (81.1%) for GE (n = 53). In contrast, the number of users dissatisfied was 33 for BR and 10 for GE. The details of these dissatisfactions are shown in Table 2. The item indicated as a dissatisfaction was "Difficultly applying/re-applying", followed by "Rash", and "Efficacy" for BR users while "Difficultly applying/re-applying", followed by "Painful removal", "Efficacy", and "Rash" for GE users. There was no item associated with a significant difference between BR and GE users.

4. Experience of prescription change and the reason

Two hundred forty of 245 respondents replied to the following question: "Have you consulted with your doctor/pharmacist about changing the

Table 2. Satisfaction and dissatisfaction with the patch (n = 43)
"Q: Are you satisfied with the patch that you are now using?" (select 1, 2 or, 3 items.)

	BR n = 33	GE n = 10	*P*- value
Poor efficacy	0.52±1.12	0.60±1.27	0.921
Insecurely adhering	0.45±1.09	0.00±0.00	0.487
Painful removal	0.33±0.92	0.80±1.32	0.419
Rash	0.94±1.32	0.60±1.27	0.524
Unpleasantly strong smell	0.09±0.52	0.20±0.63	0.766
Too weak smell	0.00±0.00	0.00±0.00	-
Difficultly applying /re-applying	1.03±1.26	1.20±1.55	0.854
Bad stretchability	0.06±0.35	0.00±0.00	0.899
The product is GE.	0.00±0.00	0.00±0.00	-
Less recognized product name	0.03±0.17	0.00±0.00	0.899
Color	0.00±0.00	0.00±0.00	-
Others	0.27±0.88	0.40±0.84	0.681

Mean ± S.D. was calculated by dividing the total score by the number of respondents for each item, assuming the top 1, 2, and 3 items as 3, 2, and 1 points, respectively.

(Mann-Whitney *U* test)

patch for any reason leading to the change?", 53 (22.1%) respondents answered "Yes".

Fifty one of 53 respondents replied to the following question: "Q: Why did you ask to change prescription for the patch?".

The reason for change was primarily "Insecurely adhering" (29.4%), followed by "Rash" (29.4%), and "Change to GE to reduce drug cost" (27.5%) (Fig. 1).

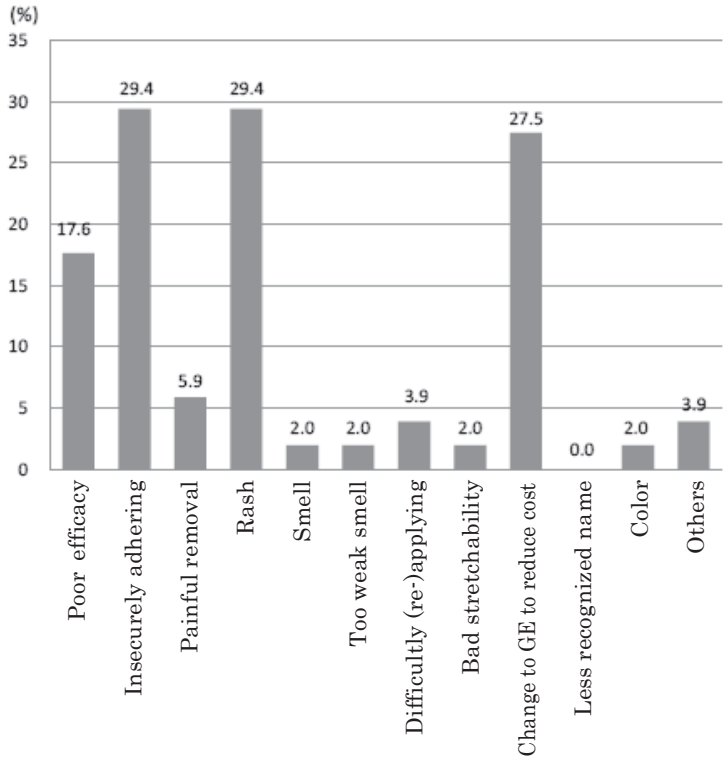

Fig.1. Experience of prescription change and the reason (n = 51)
"Q: Why did you ask to change prescription for the patch?"

5. Functional usability from using BR and GEs

We identified 46 respondents who had experienced both BR and GEs and information regarding the specific products that they had used. GE used was B in 9 respondents, C in 21, D in 6, and E in 10. Among them, 45 respondents, with the exception of those who provided no response, indicated their ratings based on 1 to 5 scale concerning "Easiness to apply", "Smell", "Degree of adherence", and "Easy removal" (Fig. 2A).

For "Easiness to apply", "Degree of adherence", and "Easy removal", BR was better rated than

either of GE-B, -C, -D, or -E. For “Easiness to apply”, GE-E (2.40 ± 0.84 [mean ± S.D.]) was best rated, followed by GE-C (2.29 ± 0.95), GE-D (2.14 ± 0.90), and GE-B (2.11 ± 0.93). For “Degree of adherence”, GE-E (2.70 ± 1.06) was best rated, followed by GE-D (2.57 ± 1.40), GE-B (2.33 ± 0.87), and GE-C (2.29 ± 1.20). For “Easy removal”, GE-B was best rated (2.67 ± 1.12), followed by GE-E (2.60 ± 0.70), GE-D (2.57 ± 1.40), and GE-C (2.43 ± 0.99). For “Smell”, GE-B, -C, -D, and -E were rated similarly to BR; GE-D (3.14 ± 0.38) followed by GE-C (2.92 ± 0.83), GE-E (2.90 ± 0.32), and GE-B (2.78 ± 0.67). However, for the Functional usability-related items other than “Smell”, GEs were all associated with a great S.D. with variation in the responses.

Among the 46 respondents experiencing both BR and either of GE-B, -C, -D, or -E, 44 respondents, except for those who provided no response, rated “Pain severity with removal” based on 1 to 5 scale (Fig. 2B). When comparing this item between BR and individual GEs, there was no significant difference in pain severity between any GE and BR.

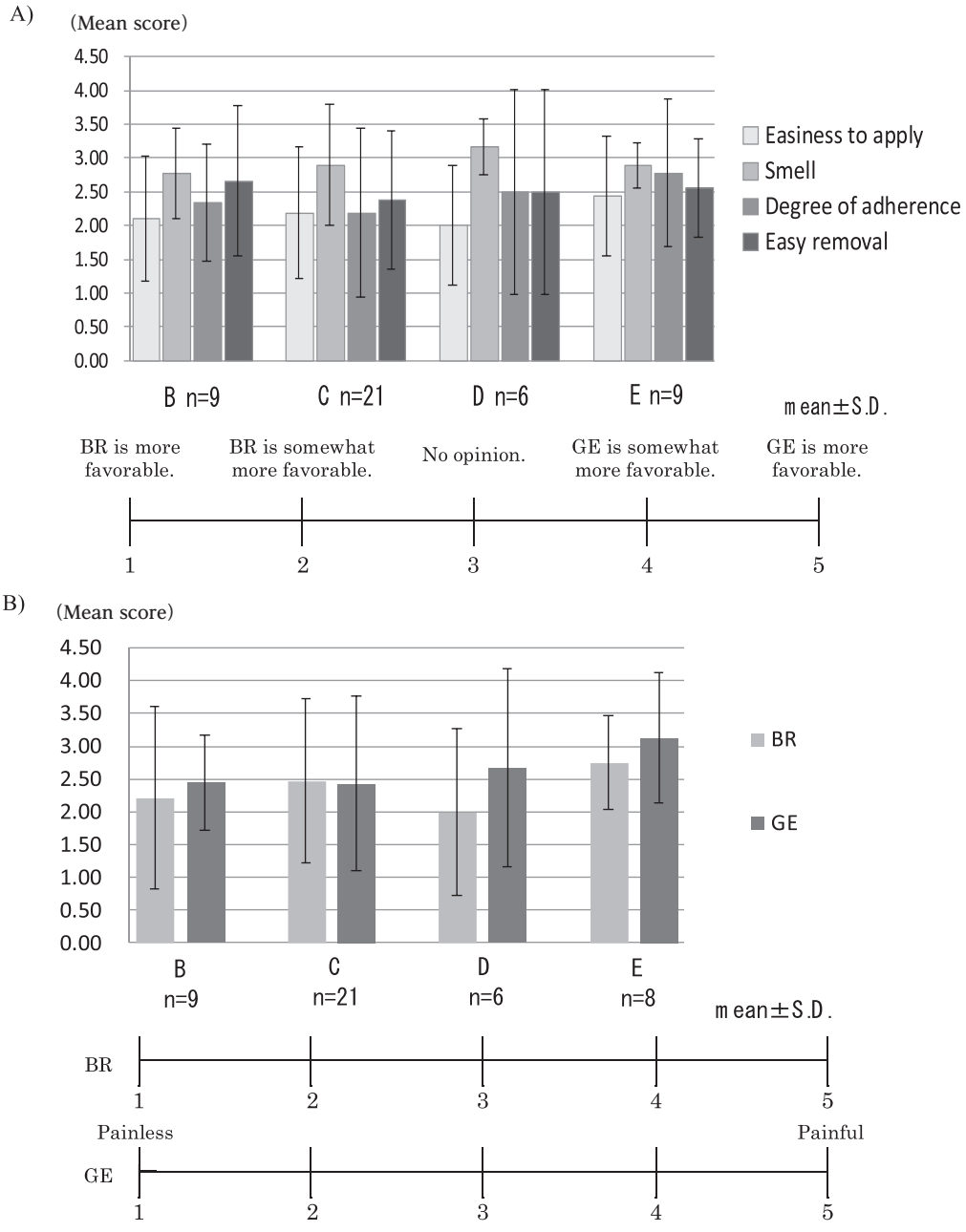

Fig.2: Evaluation of Functional usability for BR versus GE
A) Easiness to apply, Smell, Degree of adherence, and Easy removal (n = 45)
B) Pain severity with removal (n = 44)

6. The reason for return from GE to BR

Twenty-two respondents have experienced return from GE to BR. Their reasons to return from GE to BR are summarized in Table 3.

The reasons included “Insecurely adhering”, “Difficultly applying”, and “Rash”; male respondents indicated “Insecurely adhering”, “Difficultly applying”, and “Rash” while female respondents indicated “Insecurely adhering”, “Difficultly applying”, and “Painful removal”. According to the age group, “Insecurely adhering”, followed by “Difficultly applying”, and “Rash” were indicated by respondents younger than 60 years, while “Insecurely adhering”, followed by “Difficultly applying”, and “Poor efficacy” was given in those aged 60 years or older. There was no significant difference in the reasons between both sexes as well as between the age groups.

Table 3. Reasons for return from GE to BR (n = 22)
“Q. If applicable, for what reason did you return to BR?” (select 1, 2 or, 3 items).

	All respondents n= 22	Male n = 9	Female n = 13	*P*- value	Younger than 60 years n = 8	60 years or older n = 14	*P*- value
Poor efficacy	0.55±1.01	0.67±1.12	0.46±0.97	0.695	0.38±0.74	0.64±1.15	0.815
Insecurely adhering	1.09±1.31	1.00±1.32	1.15±1.35	0.896	1.25±1.49	1.00±1.24	0.664
Painful removal	0.55±1.06	0.56±1.13	0.54±1.05	1.000	0.50±0.93	0.57±1.16	1.000
Difficultly applying	0.95±1.36	1.00±1.32	0.92±1.44	0.794	1.13±1.36	0.86±1.41	0.616
Rash	0.59±1.14	0.78±1.20	0.46±1.13	0.601	0.63±1.19	0.57±1.16	0.920
Comparable cost	0.18±0.66	0.33±1.00	0.08±0.28	0.896	0.38±1.06	0.07±0.27	0.815
Unpleasant smell	0.00±0.00	0.00±0.00	0.00±0.00	-	0.00±0.00	0.00±0.00	-
Unfavorable color	0.00±0.00	0.00±0.00	0.00±0.00	-	0.00±0.00	0.00±0.00	-
Others	0.55±1.10	0.33±1.00	0.69±1.18	0.512	0.63±1.19	0.50±1.09	0.920

Mean ± S.D. was calculated by dividing the total score by the number of respondents for each item, assuming the top 1, 2, and 3 items as 3, 2, and 1 points, respectively.

(Mann-Whitney *U* test)

Discussions

This study revealed that patients put emphasis on “Efficacy” when using a patch, as well as the items related to functional usability from using, such as “Securely adhering” and “No rash”, regardless of the product used, gender, and age group. The respondents younger than 60 years rated “Securely adhering” as more significantly important compared to those aged 60 years or older. Kobayashi and Razia[11] reported that generally younger people are associated with a higher amount of sweating. A difference in the trends of responses according to the age group may be influenced by a difference in age-related skin condition.

Concerning the satisfaction of the patch that the respondents were currently using, they were highly satisfied for both BR and GEs, although about 20% of the respondents indicated that they were dissatisfied. In these respondents, we conducted a survey on what aspects of their patch about which they felt dissatisfied. Both BR and GE users had the top dissatisfaction for impression functional usability-related items of “Difficultly applying/re-applying” rather than “Efficacy”. The report by Abe et al.[12] suggested that BR and the individual GEs patches have distinctive physical features. This may result in a difference in functional usability from using and, in turn, influence the scores of satisfaction.

In the respondents experiencing prescription change, we examined the reasons. The 3 top responses were “Insecurely adhering”, “Rash”, and “Change to GE to reduce cost”. This result is similar to the important factor when using a patch product, as shown in Table 2. Therefore, such functional usability is likely to represent an important motivation of drug change by patients. Furthermore, in the respondents experiencing both BR and GEs and returning from GE to BR, the reason was “Insecurely adhering” and “Difficultly applying”, which were related to functional usability, rather than “Efficacy”. The motivation of return to BR may be related to functional usability. According to these results, it may be possible to propose an option to change from one GE to another GE based on considerations of the physical features specific to individual patch products, in

addition to the change from GE to BR product.

We compared the mean scores of functional usability rated by the respondents experiencing both BR and GEs. For "Easiness to apply", GEs were all rated lower compared to BR. For "Degree of adherence", GE-D and -E were rated similar to BR-A, although GE-B and -C were rated as low. For "Easy removal", GE-B, -D, and -E were rated as similar to BR-A although GE-C was rated as difficult removal. GEs used for this study were not rated as equivalent to or better than BR-A in the mean scores of "Easiness to apply", "Degree of adherence", and "Easy removal" among the respondents. However, a variation in individual responses was observed, and some responses indicated better functional usability of "Easiness to apply", "Degree of adherence", and "Easy removal" for GEs compared to BR. According to these results, it was suggested that the patient's impression of functional usability is individually different, even if with the same drug product. Since the report by Abe et al.[12] demonstrated physical features of the patch products, pharmacists are able to utilize the information on these physical features when selecting a patch product for patients who feel dissatisfied about the functional usability when using their product.

Conclusion

This study revealed differences in functional usability in using BR compared to GEs. When using the patch products, patients consider not only the efficacy but also such functional usability as important factors. Functional usability was found to be important in patients' satisfaction of the patch products as well as related to the motivation to change the patch product. Further, without classification of BR and GE, it was suggested that the individual patient's needs related to needs vary.

Conflicts of Interest: COI

The authors declare no conflicts of interest.

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