Original Article

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Evaluation of rapid drug safety communication materials for patients in Japan

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SUMMARY Since 2011, pharmaceutical companies in Japan have been required to issue two types of documents regarding severe adverse drug reactions reported post-marketing, namely the Rapid Safety Communication Materials for Patients and the Related Materials. However, the adequacy of these documents has not yet been systematically assessed. The aim of this study was to evaluate the adequacy of these two types of materials. The Rapid Safety Communications for Patients were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website. The Related Materials were obtained from pharmaceutical companies or the PMDA website. Three assessors independently scored the Rapid Safety Communication for Patients and the Related Materials using the Centers for Disease Control and Prevention Clear Communication Index (CCI). In addition, the contents and descriptions of the materials were analyzed. In total, 13 materials for seven drugs were assessed. Almost all materials contained the "main message" and "call to action". However, the average CCI scores for the Rapid Safety Communication for Patients and Related Materials for Patients were 68.8 and 74.3 (out of 100), respectively. Further, none of the evaluated materials were scored above the CCI threshold score (*i.e.*, ≥ 90%). Descriptions regarding "language", "state of science", and "risk" were not adequate. In particular, the terminology used in materials seemed difficult for patients to understand. In conclusion, the Japanese Rapid Communication Materials for Patients require improvement. Furthermore, a system for evaluating these materials prior to publication should be established.

Keywords Risk communication, Clear Communication Index, drug safety

1. Introduction

Japan has experienced several pharmaceutical drug-related disasters ("*Yakugai*" in Japanese), and a possible reason for these is the lack of prompt risk communication to the public, including patients. Risk communication refers to "communication intended to supply lay people with information they need to make informed, independent judgment about risks to health, safety, and the environment" (*1*). For effective risk communication, adequate drug safety information must be provided to patients, which can prevent severe adverse drug reactions.

In 2011, the Ministry of Health, Labour, and Welfare (MHLW) set up a risk communication framework for patients based on the post-marketing phase of drug evaluation, in addition to the framework already available for healthcare professionals. The MHLW requires pharmaceutical companies to immediately issue two types of special warning communication letter, for healthcare professionals and patients, when severe or fatal adverse drug reactions occur (*2*): the Rapid Safety Communication (Blue Letter) and the Emergent Safety Communication (Yellow Letter) (*3*). The latter is issued in more serious cases, especially when urgent safety measures are necessary. These communication

letters for patients are A4-sized, single-page documents, based on a template standardized by the MHLW. As of January 2020, seven Blue Letters for patients and no Yellow Letters have been issued. In addition, the MHLW requests that pharmaceutical companies prepare similar, easily understood Related Materials documents using their own format (*4*). Generally, these documents are handed directly to the patients at the medical institution and also made available on the website of the Pharmaceuticals and Medical Devices Agency (PMDA), which is the Japanese national regulatory body, or on that of the pharmaceutical companies. However, the quality of these communication letters has not yet been systemically evaluated.

Clarity is critical in order for written communication materials to be comprehensible to a general audience with varying literacy levels. Recently, governmental organizations in developed countries have introduced standards (criteria) for providing clear health information to patients. In the USA, "Clear & Simple" (*5*) from the National Institutes of Health and the "Toolkit for Making Written Material Clear and Effective" (*6*) are issued by the Center for Medicare and Medicaid Services. Furthermore, the Centers for Disease Control and Prevention (CDC) published the "CDC Clear Communication Index (CCI)" (*7*) in 2014. The CCI has been used to identify important communication characteristics that enhance clarity and help readers to understand public messages and materials (*8*). This index is the most comprehensive and widely used tool for assessing and developing such materials (*9-12*). However, to the best of our knowledge, no study has applied the CCI for the assessment or during the development of rapid safety communication materials intended for patients. In this study, we aimed to evaluate the adequacy of all Blue Letter and Related Materials documents in Japan using the CCI.

2. Materials and Methods

2.1. Target materials

We searched the PMDA website for Blue Letters (including the Blue Letters for Healthcare Professionals and Blue Letters for Patients) issued as of April 2017 for the following six drugs: RANMARK® Subcutaneous Injection, Careram® Tablets, YAZ®, XEPLION® Aqueous Suspension, SOVRIAD® Capsules, and Lamictal® Tablets. Because the Related Materials for Patients were not available on the websites of PMDA or the pharmaceutical companies, we obtained the respective Related Materials for Patients directly from the companies. In November 2019, we obtained the Blue Letter for Healthcare Professionals and Patients as well as the Related Material for Patients for another drug, Verzenio®, from the PMDA website.

2.2. Blue Letter basic information

The international nonproprietary names (INNs) and indications were extracted from the package insert for each drug by T.S. (a pharmacist). Thereafter, information regarding severe adverse reactions was extracted from the Blue Letters by T.S. in January 2020.

2.3. Format and contents of the Blue Letters for Patients and Related Materials for Patients

In January 2020, A.Y. (Master of Public Health, MPH) and T.S. independently counted the pages of the Related Materials for Patients and extracted the date of development as well as contents from each Related Materials for Patients document. Thereafter, the materials were assessed. To count the characters in the materials, the PDF documents were converted to Microsoft Word® format, and the software's character-counting tool was used.

2.4. Assessment of materials based on the CCI

The CCI was downloaded from the CDC website (*13*) along with the user's guide (*8*) and full index (*14*). The author and co-authors confirmed the criteria in the CDC CCI user's guide for the assessment of materials.

The CCI is divided into the following seven categories: main message and call to action, language, information design, state of science, behavioral recommendations, numbers, and risk. Each of these contains 20 items, with a rating of 0 or 1. The individual scores were converted to an overall score of 100. A CCI percentage score of ≥ 90 would indicate that the evaluated material is clear and understandable.

The materials were assessed between January 20 and February 26, 2020. A.Y. (MPH), M.Y. (Pharmacist), K.Y. (Pharmacist), and T.N. (MD) discussed and defined "the main message" and "call to action" in order to understand the details and factors that led to the issue of the document (*i.e.*, the Blue Letter), with a focus on severe adverse reactions as well as signs and symptoms. Furthermore, three assessors (A.Y., M.Y., and K.Y.) confirmed the "behavioral recommendations" and "risk" in these materials. Based on "the main message" and "call to action", the three assessors independently scored the Blue Letter for Patients and Related Materials for Patients, with one point for "yes" and zero for "no" per CCI item. After the first round of scoring, the first author (A.Y.) collected the scores from the other assessors and compared them. For items with different scores, each author described their reason for scoring, and the assessors once again scored the items independently (the second round of scoring). After discussing differences in the third round of scoring, the scores were revised to obtain the final scores. Finally, A.Y. compiled all the scores.

2.5. Statistics

The internal agreement of assessors for CCI scoring was computed using the Fleiss's κ-value (*15*). Other statistical analyses (the mean score and standard error of mean, *t*-test to assess the difference in the average scores of two materials) were performed using R® software version 3.4.3. and Microsoft Excel®.

3. Results

3.1. Materials obtained

Seven Blue Letters, one for each of the seven drugs, were issued before January 10, 2020. For each drug, the INN, indications, and severe adverse reactions list, as well as the issue date and the number of characters in the relevant Blue Letter for Patients, are summarized in Table 1. The number of characters varied between 636 and 1005.

In addition, we obtained seven Related Materials for Patients from pharmaceutical companies or the PMDA website. The material for XEPLION® Aqueous Suspension was not available, and we obtained two separate documents for Lamictal® Tablets.

3.2. Format and contents of the Related Materials for Patients

Table 2 presents a summary of the format and contents of the obtained Related Materials for Patients. Some patient materials did not contain an issue date. They varied in the number of pages (between 1 and 6) and characters (between 447 and 2832). All materials were presented in color, with illustrations lacking only in one. Three materials contained the indications of the relevant drugs. Two of the materials included photographs of the drug. All materials, excluding that for SOVRIAD® Capsules, contained information on the signs and symptoms of severe adverse reactions, and all materials contained the recommendation to consult a physician or pharmacist. We then searched materials for the contact information for the pharmaceutical companies and medical institutes. One material contained only the former, another included only the latter, three contained both, and two included no contact information at all.

3.3 Evaluation of materials in accordance with the CCI

The "main message" and "call to action" were defined as follows:

Main message: Because severe adverse reactions have occurred, be aware of the relevant signs and symptoms.

Call to action: If these signs and symptoms appear (or in the case of contraindication), consult your physician or pharmacist.

Table 1. Characteristics of Blue Letters[1]

Blue Letters for healthcare professionals							
Product name	RANMARK® Subcutaneous Injection	Careram® Tablets	YAZ®	XEPLION® Aqueous Suspension	SOVRIAD® Capsules	Lamictal® Tablets	Verzenio®
International Nonproprietary Name (INN)	Denosumab	Iguratimod	Drospirenone, Ethinyl estradiol	Paliperidone	Simeprevir	Lamotrigine	Abemaciclib
Indication[2]	Bone lesion associated with multiple myeloma or bone metastases from solid tumors	Rheumatoid arthritis	Dysmenorrhea	Schizophrenia	Chronic hepatitis C	Bipolar disorder, epilepsy	Breast cancer
Severe adverse reactions	Serious hypocalcemia	Serious bleeding	Thrombosis	Fatal cases	Hyperbilirubinemia	Serious skin disorders	Interstitial pneumonia
Issue date for professionals	2012.9.11	2013.5.17	2014.1.17	2014.4.17	2014.10.24	2015.2.4	2019.5.17
Blue Letters for Patients							
Material No.	1-1	2-1	3-1	4-1	5-1	6-1	7-1
Number of characters	1005	1002	657	636	639	696	646

[1]Blue Letters: Rapid Safety Communications. [2]Excerpt from the drug package inserts.

Table 2. Characteristics of the Related Materials for Patients

Product name	RANMARK® Subcutaneous Injection	Careram® Tablets	YAZ®	XEPLION® Aqueous Suspension	SOVRIAD® Capsules	Lamictal® Tablets	Verzenio®
Material No.	1-2	2-2	3-2	No material	5-2	6-2	6-3	7-2
Issue date for patients	Not found	2016.5	Not found		2016.5	2015.3	2015.6	2019.6
Number of pages	6	2	4		2	3	6	1
Number of characters	1732	855	764		1164	447	2832	513
Contents[1]								
Indication		○	○				○	
Contraindication		○			○			
Risk of severe adverse reactions	○	○	○			○	○#	○
Subjective symptoms of severe adverse reactions	○	○	○			○	○#	○
How to take the drug		○			○		○#	
Drug photo	–	○			○			
Recommendation to consult a doctor	○	○	○		○	○	○#	○
Recommended preventive behavior	○	○	○			○	○#	
Taking the drug as directed		○				○	○	
Contact information; pharmaceutical company	○	○	○					○
Contact information; medical institute	○	○				○		○
Others	● High-risk patients ● Mechanism of serious adverse reaction		● Be cautious of the adverse reactions in carriers of the card. ● Instruction to follow doctor's directions. ● Space for medical center use.		● How to store the medicine. ● Symptoms of main adverse reactions. ● Caution on pregnancy and breastfeeding during treatment.	Main adverse effects# #Mention in FAQ.		Supervisor

[1]Two reviewers extracted data from each material and summarized them.

Based on the "main message" and "call to action," three assessors graded the seven Blue Letters and six Related Materials for Patients with a score of 0 or 1 per CCI item. The assessment results are presented in Table 3.

The material for SOVRIAD® Capsules was excluded from CCI base assessment because it did not mention severe adverse events and only provided information on how to take the medicine. In total, 13 materials were assessed. Reliability analysis showed substantial agreement among the assessors ($\kappa = 0.64$). The average scores and standard errors of the means for the three assessors were 68.8 ± 2.8 and 74.3 ± 2.8 for the Blue Letters for Patients and Related Materials for Patients, respectively. None of the materials reached a CCI score of 90%, which is the threshold for patient materials to be considered comprehensible.

3.3.1. Core

The "main message" (item #1) and "call to action" (#5) were found in almost all the Blue Letters for Patients. All Blue Letters for Patients were evaluated with "No" for #4 (visual support). However, some of the illustrations supported the main message in four of the Related Materials for Patients. All text in the Related Materials for Patients was in the active voice (#6). In a few of the Blue Letters for Patients, the main message was written in the passive voice. Approximately half of the materials included words that are not commonly used by the primary audience (#7). Bulleted or numbered lists were included (#8), and the most important information (main message) was presented at the top of the materials (#10) in all documents evaluated. "What's known and what's not" (#11, state of science,) was explained in only one material (4-1).

3.3.2. Behavioral recommendation

"Call to action" was regarded as a "behavioral recommendation," and #12-14 were scored with "Yes" for all materials, except one (2-2).

3.3.3. Numbers and risk

We evaluated only the numbers related to severe adverse reactions. None of the materials were scored on this part. Thus, part C was excluded from the calculation of total score percentage. The nature of the risk (#18) was not explained in three of the Blue Letters for Patients and four of the Related Materials, while the risks and benefits of the recommended behaviors (#19) were not addressed in any of the materials.

4. Discussion

In this study, we evaluated the adequacy of two types of rapid safety communication materials regarding

Table 3. Clear Communication Index Scores for Blue Letters for patients and the Related Materials

Part	No.	Questions	Blue Letter for Patients[1]								Related Materials for Patients[2]							
			1-1	2-1	3-1	4-1	5-1	6-1	7-1	Mean score of 3 reviewers for 7 materials	1-2	2-2	3-2	5-2	6-2	6-3	7-2	Mean score of 3 reviewers for 6 materials
			No. of reviewers who answered 'Yes'								No. of reviewers who answered 'Yes'							
Part A: Core																		
Main Message and Call to Action	1	Does the material contain one main message statement?	3	3	3	3	3	3	3	3.0	3	2	3	-	3	3	3	2.8
	2	Is the main message at the top, beginning, or front of the material?	3	3	3	0	3	3	3	2.6	3	2	3	-	3	3	3	2.8
	3	Is the main message emphasized with visual cues?	3	3	3	0	3	2	3	2.4	3	2	2	-	3	3	3	2.7
	4	Does the material contain at least one visual that conveys or supports the main message?	0	0	0	0	0	0	0	0.0	3	0	0	-	3	3	3	2.0
	5	Does the material include one or more calls to action for the primary audience?	3	3	3	3	3	3	3	3.0	3	3	3	-	3	3	3	3.0
Language	6	Do both the main message and the call to action use the active voice?	1	1	3	1	3	3	3	2.1	3	3	3	-	3	3	3	3.0
	7	Does the material always use words the primary audience uses?	2	0	3	3	0	3	0	1.6	0	3	3	-	3	0	0	1.5
Information Design	8	Does the material use bulleted or numbered lists?	3	3	3	3	3	3	3	3.0	3	3	3	-	3	3	3	3.0
	9	Is the material organized in chunks with headings?	0	0	3	0	3	3	3	1.7	3	3	3	-	0	3	3	2.5
	10	Is the most important information the primary audience needs summarized in the first paragraph or section?	3	3	3	3	3	3	3	3.0	3	3	3	-	3	2	3	2.8
State of Science	11	Does the material explain what authoritative sources, such as subject matter experts and agency spokespersons, know and don't know about the topic?	0	0	0	2	0	0	0	0.3	0	0	0	-	0	0	0	0.0
Part B: Behavioral Recommendations	12	Does the material include one or more behavioral recommendations for the primary audience?	3	3	3	3	3	3	3	3.0	3	3	3	-	3	3	3	3.0
	13	Does the material explain why the behavioral recommendation(s) is important to the primary audience?	3	3	3	3	3	3	3	3.0	3	0	3	-	3	3	3	2.5
	14	Does the behavioral recommendation(s) include specific directions about how to perform the behavior?	3	3	3	3	3	3	3	3.0	3	3	3	-	3	3	3	3.0
Part C: Numbers	15	Does the material always present numbers the primary audience uses?																
	16	Does the material always explain what the numbers mean?																
	17	Does the audience have to conduct mathematical calculations?																
Part D: Risk	18	Does the material explain the nature of the risk?	3	0	3	3	0	0	0	1.3	3	0	0	-	0	0	3	1.0
	19	Does the material address both the risks and benefits of the recommended behaviors?	0	0	0	0	0	0	0	0.0	0	0	0	-	0	0	0	0.0
	20	If the material uses numeric probability to describe risk, is the probability also explained with words or a visual?																
		Mean total score % for 3 reviewers	68.8	58.3	81.3	62.5	68.8	72.9	68.8	68.8	81.3	62.5	72.9	-	75	72.9	81.3	74.3
		Standard error of mean	3.6	2.1	0.0	0.0	0.0	2.1	0.0	2.8	0.0	6.3	2.1	-	0.0	2.1	0.0	2.8
																	Overall κ-value	0.64

[1]Blue Letter for Patients; 1-1 RANMARK® Subcutaneous Injection, 2-1 Careram® Tablets, 3-1 YAZ®, 4-1 XEPLION® Aqueous Suspension, 5-1 SOVRIAD® Capsules, 6-1 Lamictal®. [2]Related Materials for Patients; 1-2 RANMARK® Subcutaneous Injection, 2-2 Careram® Tablets, 3-2 YAZ®, 5-2 SOVRIAD® Capsules, 6-2 Lamictal® Tablets, 6-3 Lamictal® Tablets

severe adverse reactions for patients in Japan and found that these materials have several areas that require improvement. In particular, none of the assessed materials achieved the threshold (≥ 90%) CCI score. Furthermore, the descriptions regarding "language," "state of science," and "risk" were not adequate. The effectiveness of risk communication is often judged based on whether the intended audience took effective action (*16*). Fischhoff (*16*) lists the following requirements for adequate risk communication: (a) the information needed for effective decision making, (b) accessibility of the information, and (c) comprehensibility. The results of our study suggest that, overall, Japanese rapid safety communication materials for patients have a few issues, particularly related to the comprehensibility of risks.

Most of the materials in the Blue Letters for Patients and Related Materials for Patients contained a "main message" (#1, *i.e.*, "the occurrence of severe adverse reactions and warning of the symptoms") and a "call to action" (#5, *i.e.*, "consult a physician or pharmacist"). These items are considered sufficient minimum information with which to make a decision (*16*). However, there was a lack of information on "what's known and what's not" provided by authorities (state of science, #11), such as the details and number of severe adverse reaction cases or the uncertainty of association between adverse reactions and the drug concerned, as well as on the "risks and benefits of the recommended behaviors" (#19). Davis reported that patients preferred specific, detailed information about adverse effects (*17*). According to Suka *et al.*, several Japanese lay people indicated that they believe all information should be disclosed (*18*). These patients' information needs should be considered.

In the current study, we did not find detailed information on adverse reaction frequency in any of the materials (Part C). The quality of information on severity and frequency affects risk perception in relation to adverse reactions (*19*). Further research is required to establish effective adverse reaction risk perception in Japanese patients.

Accessibility refers to the following two aspects: access to information sources (*i.e.*, drug safety materials) and access to message content (*i.e.*, main message and call to action) (*16*). The CCI user's guide highlights how to disseminate rapid safety communication materials, and Japanese authorities have requested that materials be widely disseminated to the public as well as patients. To the best of our knowledge, there are no studies assessing ease of access to rapid safety communication materials. Accessibility, defined as access to message content, can be evaluated based on CCI items #2-4 (*7,10*). The Blue Letters for Patients lacked visual components (#4), such as illustrations, due to the requirement for their rapid publication. Nevertheless, the materials were concise, and the main messages were accessible because they were presented in the front (#2) and emphasized with visual cues (#3), except for one material. In contrast, most Related Materials for Patients varied in format and content, were colorful, and had a user-friendly appearance. However, their main messages may be unclear to patients, due to the substantial amount of information distributed across several pages, including extensive information on dosage.

In the current study, we identified some key issues regarding the comprehensibility of Japanese rapid drug safety information materials for patients. First, the risks of severe adverse reactions were not explicitly mentioned in some of the materials. To prevent severe adverse reactions, it is of utmost importance that patients are able to perceive the signs and symptoms and take appropriate actions (*20*). However, some materials did not clearly explain the severity of health outcomes (for example, "interstitial pneumonia"). Second, some materials used only medical terms (for example, "jaundice"), while it is necessary to explain risks and symptoms in a manner that lay people can understand. Illustrations may help promote a better understanding of medical terms. Third, with regard to voice (#6 in the CCI), the main messages of some materials were presented in the passive voice, as in "the case was reported." Japanese people tend to use the passive voice more often than Westerners, due to the characteristics of the language. However, in the Japanese language, the passive voice is also used to imply possibility, spontaneity, and respect. For this reason, drug safety materials should be written in the active voice as much as possible, in order to improve comprehensibility among the broader readership.

The current study had some limitations. First, although the Related Materials were obtained from the pharmaceutical companies, some materials might have been developed with intentions other than warning patients about serious adverse reactions. Further, as pharmacists and/or MPH professionals, the assessors might have been generous in scoring item #7 "use words that the primary audience use."

In conclusion, several concerns regarding the comprehensibility of Japanese rapid safety communication materials on drugs for patients were identified in this study. In particular, the language used and the explanation of the nature of risks should be improved. In addition, Japanese authorities should build a system for evaluating materials for patients based on indices, such as CCI, for use prior to material publication.

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Supplementary Material

The Blue Letters for patients
1-1 https://www.pmda.go.jp/files/000148240.pdf
2-1 https://www.pmda.go.jp/files/000148446.pdf
3-1 https://www.pmda.go.jp/files/000148622.pdf
4-1 https://www.pmda.go.jp/files/000148732.pdf
5-1 https://www.pmda.go.jp/files/000147341.pdf
6-1 https://www.pmda.go.jp/files/000198340.pdf
7-1 https://www.pmda.go.jp/files/000229599.pdf