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SHORT COMMUNICATION

Changes in Side Effect Risk Communication in Patient Information Leaflets over the Past Decade: Results of a Survey

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Abstract

Introduction Patients' perceptions of side effect risks are important influences on their medicine-taking behaviour. A previous survey of Patient Information Leaflets (PILs) showed considerable variation in the terms used to communicate risks.

Objective Our objective was to assess the methods used to describe risk of side effects in recent PILs and to compare them with PILs sampled in 2006.

Method We sampled PILs for the 50 most frequently dispensed medicines in England and Wales in 2012 and PILs for the 50 most recently licensed medicines. We assessed the use of risk frequency terms or numbers, and the use of the risk format recommended by the European Medicines Agency (EMA).

Results A majority (76 %) of PILs for the most frequently dispensed medicines included a risk frequency descriptor, with 66 % using the recommended format. No difference was seen between PILs for branded and generic medicines. All 50 PILs for the most recently licensed medicines used the EU recommended risk format. PILs from the 2012 sample were much more likely than those from the 2006 sample to include risk descriptors and to use a consistent approach.

Conclusion The increased use and consistency of risk descriptors in PILs should benefit patients, particularly those using multiple medicines produced by different market authorisation holders. A need remains for further research evaluating the risk format recommended by the EMA. There is also a need for research evaluating spoken information and other sources of printed risk information about medicines that is available to patients.

Key Points

A majority of patient information leaflets (PILs) for the most frequently dispensed medicines include information on the frequency of side effects.

Compared with a sample of PILs in 2006, those in 2012 were much more likely to include risk frequency information and to use a consistent approach.

The consistent use of risk frequency formats should benefit patients, although a need remains to further evaluate patients' interpretations of risk information.

1 Introduction

In EU countries, it is a legal requirement that all licensed medicines must be provided with a patient information leaflet (PIL) inside the pack [1]. The content of the PIL is approved as part of the medicine's licence approval process, and must include the following headings [2]:

1. What X is and what it is used for
2. What you need to know before you take X

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3. How to take X
4. Possible side effects
5. How to store X
6. Contents of the pack and other information.

PILs therefore potentially serve a number of functions for the patient, including provision of information important for safety, such as contraindications and interactions. They also have potential to aid patient decision making, not least by informing about possible adverse effects of the medicine and advising on what patients should do if they experience one [3].

The list of adverse effects included in PILs is important to patients—research has reported it is the most often read section of PILs, although it may be perceived as negative [4, 5]. If the information on adverse effects is to have the potential for patients to use it to inform discussions or decisions around their medicines, it is essential that the information is provided in a useful and usable format. In addition, if the information is consistent across PILs, patients can then become familiar with the format.

The 1999 EU Guidance on the presentation of adverse effects in PILs suggested grouping adverse effects within a PIL according to five frequency bands, each described using one of five verbal terms (such as 'rare' and 'common') [6]. The guidance was updated in 2006 and 2009, and licence holders were then recommended to convey risks by combining each of the five verbal terms with a numerical frequency to form combined expressions such as 'Common: may affect up to 1 in 10 patients'. The guidance also said that the most serious side effects "need to be listed prominently first with clear instructions to the patients on what action to take (e.g. to stop taking the medicine and/or seek urgent medical advice)" [2]. However, it is notable that the effects of the EU recommended risk expressions have not been evaluated formally [7]. The use of verbal terms alone (e.g. 'rare' or 'common') has been shown to be problematic [8], and questions exist about the extent to which frequency bands (e.g. 'may affect up to 1 in 10 patients') or percentages (e.g. 'may affect 3 % of patients') are more effective methods of communicating risks [9].

The aims of the EU recommendations on adverse effects were to increase the usability of PILs for patients—without frequency information, patients would be unable to gauge the chance of an adverse effect occurring—and to increase uniformity of information across manufacturers. The latter should be of benefit particularly to patients taking more than one medicine, who may well be reading PILs for medicines produced by different companies.

EU requirements for manufacturers to "consult with target patient groups to ensure that it (the leaflet) is legible, clear and easy to use" came into force for new medicines in 2005. This is most commonly undertaken using the User Testing method, and should have resulted in improvements to PILs in terms of both their content and their format since 2005 for new medicines across the EU. However, in some countries, such as the UK, the national regulators required that existing leaflets also be tested. The UK gave a 3-year window to achieve this (2005–2008).

In 2006, pre-dating the User Testing activity across Europe, we surveyed the PILs for the 50 most frequently prescribed medicines in England and Wales [10]. We found substantial variation in the methods used to communicate adverse effects information to patients, including a wide range of verbal terms to convey risk, and that only a minority (8 %) of PILs provided any form of numerical indication of risk.

Given the recent publication of revised regulatory guidance and the undertaking of User Testing of PILs across Europe, it would be helpful to know whether the quality of information available to patients on potential adverse effects has improved over the period. Thus, the main aim of this study was to survey a sample of current PILs to assess whether the presentation of information on adverse effects has changed since the previous survey in 2006. We sampled PILs for the most frequently dispensed medicines in order to gain an insight into the PILs that the greatest number of patients see and compared them with PILs for newly licensed medicines to look for information quality in the PILs most recently written (given that PILs are not always updated or re-written very frequently). Finally, among the most frequently dispensed medicines, we aimed to include PILs from both branded and generic medicines and to compare the PILs from these two sectors.

2 Method

2.1 Design

The study was a cross-sectional survey and content analysis.

2.2 Sample

The study used random quota sampling to derive a sample of 100 PILs for licensed medicines available in the UK. Quota sampling was used to obtain PILs from two representative groups of medicines:

- 50 most frequently dispensed medicines in England and Wales in 2012
- 50 most recently licensed medicines in the UK (the so-called 'black triangle' medicines, i.e. new medicines under intensive surveillance).

2.2.1 50 Most Dispensed Medicines

The list of the 50 most dispensed medicines was obtained from prescription costs analysis data collated by the UK Information Centre for Health and Social Care, which includes items dispensed in community pharmacies in England and Wales. We excluded non-specific medicines for which a PIL might not be available (e.g. 'Other emollient preps') and, when a medicine was excluded the next item on the list was chosen instead. Once the list of 50 medicines was finalised, it was then ordered randomly (using a random number list generator, http://www.random.org). The top 25 in the list were assigned to branded medicines and the bottom 25 to generic medicines (see Table 1).

We wanted to maximise the number of manufacturers covered in the sample, as PILs from the same manufacturer are generally similar in their content and format (although not exclusively). Hence, when we sampled the generic medicines, where there was more than one manufacturer of a medicine, we selected the first named. If that manufacturer had already been included in the sample, we selected the next named manufacturer not already included. If that was not possible, the manufacturer was included in the sample for a second time. When a selected medicine had no generic producer, the medicine was swapped with one from the branded medicines list.

The 25 branded medicines were included, regardless of whether a manufacturer had already been included in the sample.

2.2.2 50 Most Recently Licensed Medicines

The sample of the 50 most recently licensed medicines in the UK was identified from the UK Medicines and Healthcare products Regulatory Agency (MHRA) 'Drugs under intensive surveillance' list [8]. From this list of so-called 'black triangle' medicines (so named because of the symbol used on information for professionals about these medicines), we included only those medicines identified as a new substance or product. We excluded medicines for which the patient might not regularly receive a PIL (such as for vaccines), or for which existing patient information was in circulation (such as new combinations of drugs, different formulations for an existing route, bio-similar products and existing medicines with new additional use, e.g. the

Table 1 The included 50 medicines from the most frequently dispensed medicines in England and Wales in 2012

Medicine	Verbal descriptors?	Numerical descriptors?	Any frequency mentioned?
Branded medicines			
Fluticasone	Yes (EU)	Yes (EU)	Yes
Tiotropium	Yes (EU)	Yes (EU)	Yes
Salbutamol	Yes (EU)	Yes (EU)	Yes
Felodipine	Yes (EU)	Yes (EU)	Yes
Ibuprofen	Yes, but not for all	No	Yes
Warfarin sodium	No	No	No
Tamsulosin hydrochloride	Yes (EU)	Yes (EU)	Yes
Amlodipine	Yes (EU)	Yes (EU)	Yes
Perindopril	Yes (EU)	Yes (EU)	Yes
Bisoprolol	Yes (EU)	Yes (EU)	Yes
Diclofenac	Yes (EU)	Yes (EU)	Yes
Fluoxetine	Yes (EU)	Yes (EU)	Yes
Alfacalciferol	No	Yes	Yes
Citalopram	Yes (EU)	Yes (EU)	Yes
Doxazosin	Yes (EU)	Yes (EU)	Yes
Paracetamol	No	No	No
Lansoprazole	Yes (EU)	Yes (EU)	Yes
Atorvastatin	Yes (EU)	Yes (EU)	Yes
Cetirizine	Yes (EU)	Yes (EU)	Yes
Digoxin	Yes (EU)	Yes (EU)	Yes
Prednisolone	No	No	Yes
Candesartan Cilexetil	Yes (EU)	Yes (EU)	Yes
Senna	No	No	No
Gliclazide	No	No	No
Clopidogrel	Yes (EU)	Yes (EU)	Yes
Generic medicines			
Omeprazole	Yes (EU)	Yes (EU)	Yes
Hydrocortisone	No	No	Yes
Alendronic acid	Yes (EU)	Yes (EU)	Yes
Lactulose	Yes (EU)	Yes (EU)	Yes
Atenolol	No	No	No
Co-codamol	No	No	No
Levothyroxine	No	No	No
Beclomethasone	Yes (EU)	Yes (EU)	Yes
Losartan	Yes (EU)	Yes (EU)	Yes
Lisinopril	Yes (EU)	Yes (EU)	Yes
Zopiclone	No ('rarely' is mentioned once, but with no qualifier)	No	Yes
Naproxen	Yes (EU)	Yes (EU)	Yes
Flucloxacillin	Yes (EU)	Yes (EU)	Yes
Aspirin	No	No	No
Folic acid	No	No	Yes
Isosorbide mononitrate	No	No	No
Furosemide (injection)	No	No	No
Amoxicillin	Yes (EU)	Yes (EU)	Yes
Bendroflumethiazide	No	No	No
Diazepam	Yes (EU)	Yes (EU)	Yes
Ramipril	Yes (EU)	Yes (EU)	Yes
Simvastatin	Yes (EU)	Yes (EU)	Yes
Amitriptyline hydrochloride	No	No	No
Tramadol	Yes (EU)	Yes (EU)	Yes
Metformin	Yes (EU)	Yes (EU)	Yes

EU means that the EU-recommended format was used

addition of paediatric use, or new route of administration, or change or addition to therapeutic indication). As all 'black triangle' listed medicines are newly licensed, this list comprised only branded medicines, as it was too early for generic versions to be available. The included medicines are listed in Table 2.

Sampling took place in January 2013.

2.3 Data Collection

A copy of each of the 100 PILs was obtained from the UK Electronic Medicines Compendium (EMC; http://www.medicines.org.uk/emc). For each PIL, we assessed the way information on the chance of adverse effects was organised and described, including the use of frequency terms (verbal descriptors such as 'common', 'often', 'sometimes') and/or numbers (i.e. percentages, frequencies or proportions). We also assessed whether EU recommended combined terms had been used. We recorded whether the most serious side effects were listed first in the PIL section, with instructions on what action the patient should take. Finally, we recorded the stated date of the last PIL update.

2.4 Data Analysis

Data from the 100 PILs were described according to the proportions of PILs in the two lists that used different forms of frequency descriptor, and whether the EMA-recommended terms had been used. We compared the 50 most frequently prescribed and 50 newly licensed medicines by using the Chi-squared (χ^2) statistic and, among the 50 most recently dispensed medicines, also compared branded and generic medicines by the χ^2 statistic.

3 Results

3.1 Most Frequently Dispensed Medicines

For the 50 most dispensed medicines, 38 (76 %) PILs included some form of frequency descriptor, of which 33 (66 %) used the EMA-recommended method of combining words and natural frequencies.

Additionally, in 38 (76 %) PILs, the adverse effects were ordered by severity, having a separate warning about the most severe adverse effects, irrespective of their frequency. Five (10 %) of the PILs ordered the adverse effects by organ system e.g. 'skin', 'stomach and gut', 'heart'.

Comparing branded and generic medicines, 18 of the 25 branded medicine PILs followed the EMA guidelines, whereas 15 of the generic medicine PILs did so; the difference was not statistically significant ($\chi^2 = 1.39$, $df = 1$, $p = 0.239$). PILs for generic medicines were more likely than branded medicines to include no numerical indicators of risk (11/25 vs. 6/25), but the difference was not statistically significant ($\chi^2 = 1.43$, $df = 1$, $p = 0.232$).

The PILs for the most frequently dispensed medicines had last been updated between July 2009 and November 2012 (for generic medicines), a mean of 18.2 months before sampling, and between December 2009 and September 2012 (for branded medicines), a mean of 11.0 months before sampling.

3.2 Newly Licensed (Black Triangle) Medicines

All 50 (100 %) of the black triangle medicines included frequency descriptors, with all 50 using the EMA-recommended method of combining words and numbers. Of these, 45 (90 %) PILs had a separate warning about the most serious adverse effects, ordered by severity. In one (2 %) of the black triangle PILs, the serious adverse effects were ordered by organ system. The black triangle medicine PILs had last been updated in the period October 2010 to February 2013, a mean of 6.6 months before sampling.

3.3 Comparison of the Two Sets of Patient Information Leaflets (PILs)

Newly licensed black triangle medicine PILS were more likely to include frequency information (50 vs. 38; $\chi^2 = 13.64$, $df = 1$, $p = 0.0002$) and to follow recommendations on reporting frequency (50 vs. 33; $\chi^2 = 9.49$, $df = 1$, $p = 0.0021$). More black triangle medicine PILs prioritised information on severe side effects and the action to take, although the difference was not statistically significant (45 vs. 38; $\chi^2 = 3.74$, $df = 1$, $p = 0.062$). Fewer black triangle medicine PILs than PILs for the most dispensed medicines included adverse effect information ordered by organ system, although the difference was not statistically significant (1 vs. 5; $\chi^2 = 2.84$, $df = 1$, $p = 0.092$).

3.4 Comparison with the 2006 PILs Sample

Comparing the PILs from the 50 most dispensed medicines in 2012 and the top 50 from 2006 (see Carrigan et al. [10]), many more PILs in the recent sample (33 vs. 6) followed the EMA guidelines ($\chi^2 = 9.49$, $df = 1$, $p < 0.0001$). PILs in the recent sample were much less varied in their method of describing frequency: in 2006, 20 from 50 PILs used a form of verbal frequency descriptor other than that recommended; in the recent sample only 20 from 50 did so ($\chi^2 = 10.45$, $df = 1$, $p = 0.0012$). Numerical indicators of adverse effect risk were almost absent in the 2006 sample [being included in only four PILs (8 %)]; in the recent sample, they were included in a majority of PILs [33 (68 %)] ($\chi^2 = 33.63$, $df = 1$, $p < 0.0001$).

Table 2 The included 50 medicines from the UK Medicines and Healthcare products Regulatory Agency 'black triangle' list of recently licensed medicines

Medicine	Verbal descriptors?	Numerical descriptors?	Any frequency mentioned?
Deferasirox Exjade	Yes (EU)	Yes (EU)	Yes
Pasireotide	Yes (EU)	Yes (EU)	Yes
Fampridine	Yes (EU)	Yes (EU)	Yes
Perampanel	Yes (EU)	Yes (EU)	Yes
Canakinumab	Yes (EU)	Yes (EU)	Yes
Mifamurtide	Yes (EU)	Yes (EU)	Yes
Bromfenac	Yes (EU)	Yes (EU)	Yes
Velaglucerase	Yes (EU)	Yes (EU)	Yes
Palifermin	Yes (EU)	Yes (EU)	Yes
Ticagrelor	Yes (EU)	Yes (EU)	Yes
Natalizumab	Yes (EU)	Yes (EU)	Yes
Fingolimod	Yes (EU)	Yes (EU)	Yes
Indacaterol	Yes (EU)	Yes (EU)	Yes
Belimumab	Yes (EU)	Yes (EU)	Yes
Idursulfase	Yes (EU)	Yes (EU)	Yes
Exenatide	Yes (EU)	Yes (EU)	Yes
Telaprevir	Yes (EU)	Yes (EU)	Yes
Temsirolimus	Yes (EU)	Yes (EU)	Yes
Ruxolitinib	Yes (EU)	Yes (EU)	Yes
Pazopanib	Yes (EU)	Yes (EU)	Yes
Boceprevir	Yes (EU)	Yes (EU)	Yes
Rifaximin	Yes (EU)	Yes (EU)	Yes
Prucalopride	Yes (EU)	Yes (EU)	Yes
Bivalirudin	Yes (EU)	Yes (EU)	Yes
Vinflunine—Javlor	Yes (EU)	Yes (EU)	Yes
C1 inhibitor (human)	Yes (EU)	Yes (EU)	Yes
Cannabidiol	Yes (EU)	Yes (EU)	Yes
Erdosteine	Yes (EU)	Yes (EU)	Yes
Ranolazine	Yes (EU)	Yes (EU)	Yes
Bendamustine	Yes (EU)	Yes (EU)	Yes
Conestat alfa	Yes (EU)	Yes (EU)	Yes
Axitinib	Yes (EU)	Yes (EU)	Yes
Fondaparinux	Yes (EU)	Yes (EU)	Yes
Tolcapone	Yes (EU)	Yes (EU)	Yes
Tocilizumab	Yes (EU)	Yes (EU)	Yes
Agomelatine	Yes (EU)	Yes (EU)	Yes
Certolizumab pegol	Yes (EU)	Yes (EU)	Yes
Ferumoxytol	Yes (EU)	Yes (EU)	Yes
Aclidinium	Yes (EU)	Yes (EU)	Yes
Tapentadol	Yes (EU)	Yes (EU)	Yes
Rilpirivine	Yes (EU)	Yes (EU)	Yes
Ofatumumab	Yes (EU)	Yes (EU)	Yes
Fidaxomicin	Yes (EU)	Yes (EU)	Yes
Asenapine	Yes (EU)	Yes (EU)	Yes
Apixaban	Yes (EU)	Yes (EU)	Yes
Cabazitaxel	Yes (EU)	Yes (EU)	Yes
Bevacizumab	Yes (EU)	Yes (EU)	Yes
Abiraterone	Yes (EU)	Yes (EU)	Yes
Varenicline	Yes (EU)	Yes (EU)	Yes
Dronedarone	Yes (EU)	Yes (EU)	Yes

EU means that the EU-recommended format was used

4 Discussion

The survey of PILs for the most frequently dispensed medicines in 2012 and the most recently licensed medicines found high levels of consistency of included risk information, as well as frequent use of the EU-recommended risk descriptor terms. The EU terms were used in all the newly licensed 'black triangle' medicines. PILs for branded and generic medicines did not differ in their approach. Among the most dispensed medicines, comparing the 2012 and 2006 samples, the recent sample had much more likelihood of risk frequency being included at all, much greater consistency in the format of risk communication, and much greater use of the EMA-recommended descriptors.

The difference in PILs over the 7 years between the two studies is positive, since an increase in consistency among PILs should be of benefit to patients. In a cross-sectional survey such as this it is not possible to identify the factor(s) effecting this change, although they are likely to include increased awareness of recommendations on expressing the likelihood of side effects, the requirements of medicines regulators that PILs should follow a certain format [11], and the requirement for PILs in Europe to undergo user testing for readability. This last explanation carries some weight, based on a small study showing that, overall, PILs in Germany had improved levels of readability before and after the period of required user testing [12].

PILs are the only information on licensed medicines that must be available to patients; in the EU, legislation not only requires their provision but largely defines their format and content. However, PILs have been subject to significant levels of criticism: about readability (that they often contain difficult language and use small print size), content (most importantly that they may not meet patients' needs), inconsistency, and timing (that provision with the dispensed medicine prevents their use for informing a discussion about the medicine between the patient and prescriber). Some of these aspects have changed in recent years, and user testing legislation should have resulted in PILs that are more readable. Furthermore, the availability of PILs electronically (such as in the EMC, used in this study) increases the potential for doctors and other prescribers to use them as aids in discussions with patients about treatment options. The findings of this study—that compared with 7 years earlier, PILs are now more likely to contain risk frequency information and to use a consistent format—suggests that there is now greater potential for their effective use in decision making by patients and by practitioners in consultation with patients, although research evaluating this would be greatly welcomed.

4.1 Study Limitations

The sampling method was chosen to give an insight into the information available to patients using frequently dispensed licensed medicines—whether prescribed or bought without prescription. It is possible that information would be different in less frequently dispensed medicine PILs; this seems unlikely, although a 2010 sample of PILs for various antidepressants did report some variation in the reporting of adverse effects, which questions our assumption [13]. Sampling the most recently licensed medicines gave an insight into PILs that have been written most recently and submitted as part of a licence application, and the data suggest that most current PIL authors in pharmaceutical companies—and the regulators who assess them—are aware of current recommendations on risk communication. It also suggests that there may be a degree of inertia in manufacturers of less recent PILs, with risk terms not universal in PILs despite them having been updated an average of only 14 months before inclusion in the study. However, the lack of reliable side effects incidence data for some older medicines may explain the lack of frequency information in their PILs.

5 Conclusions

The EMA-recommended format for communicating risks associated with medicines is now used extensively in PILs for licensed medicines, which represents a significant and positive change since our previous survey of PILs conducted in 2006. The PILs for the sample of recently licensed medicines was more likely to use the EMA-recommended format than PILs for the most frequently dispensed medicines, suggesting that PILs may need to be updated more frequently. Use of the risk format has occurred despite a lack of empirical backing for it and indeed suggestions that it may lead to misjudgements of risk in some patients [7]. A need remains for further research to test alternative formats for risk communication in this setting. Furthermore, if this format of risk communication in PILS is that most commonly seen by patients, it would be valuable to know whether other sources of information—including spoken information from practitioners, written information from health services, and the news media—are using a similar format or something different, which might confuse patients. This question would be worthy of research.

Compliance with Ethical Standards

Research ethics The manuscript does not contain clinical studies or patient data, and so Research Ethics committee approval was not required.

Declarations of interest Katherine Harris has no conflicts of interest that are directly relevant to the content of the study. Rebecca Dickinson has no conflicts of interest that are directly relevant to the content of the study. David K. Raynor is co-founder and academic advisor to Luto Research, which develops, refines and tests health information materials. Jan MacDonald has no conflicts of interest that are directly relevant to the content of the study. Peter Knapp has no conflicts of interest that are directly relevant to the content of the study.

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