How much information about the benefits of medicines is included in patient leaflets in the European Union? – A survey.

Abstract

Introduction

Patient information leaflets (PILs) are required with all licenced medicines throughout the European Union (EU) and they must include information about all side effects and their likelihood. This has led to criticism of a lack of balance, with little information included about potential benefits. Recent European Medicines Agency guidance proposed the inclusion of benefit information, and this study examined the current prevalence and type of such information in PILs in the EU.

Methods

A survey and content analysis of the English translation of PILs in the EU. Random quota sampling was used on the most frequently dispensed (n=50) and newly licenced medicines (n=50) in 2011/2. Leaflets were searched for benefit information meeting predefined criteria, and data synthesised and categorised into 10 categories.

Results

Eighty-five (85%) leaflets described how the medicine works, with 45 providing information about the rationale for treatment (more commonly for newly licensed (32/50) than most commonly dispensed medicines (13/50; $p<0.001$). Nearly half (47) did not describe whether the medicine was curative, symptomatic or preventative. The terms used to communicate uncertainty were imprecise (such as '*may help'*). None communicated numerical benefit information.

Conclusion

Current PILs do not appropriately communicate information about benefit. At the basic level, around a half did not include information about treatment rationale or whether the treatment was to treat symptoms, curative or preventative. However, for true informed decision making, patients need quantitative information about benefits and none of the leaflets provided this.

1. Introduction

In order for patients to make informed decisions about their medicines they need good quality information about the likelihood both of harms and benefits of treatments (Raynor et al 2007). Patient information leaflets (PILs), written by the manufacturer according to strict guidelines, are required to be supplied with all licenced medicines throughout the European Union (EU). The guidelines require that PILs should include information about all side-effects of a medicine and their likelihood (1). This information usually takes the form of both a verbal descriptor and a probability to form a combined risk expression, such as *Common: may affect up to 1 in 10 patients.*

A recent survey showed that all sampled EU medicine leaflets in 2013 provided such numerical indicators of the risk of side effects, with most using the format recommended by the European Commission (2).

A common criticism of PILs is that they are too negative and focus only on the side effects of the treatment (3). Alongside this, there is evidence that patients desire information about the benefits of their treatments in order to help them make informed decisions (4). There is also increasing evidence to support the notion that patients overestimate the benefits and underestimate the harms of their treatments, particularly in the absence of numerical information (5). If patients are unable to form accurate representations of the risk and benefits of their treatments this has an impact upon their ability to make truly informed decisions.

EU regulatory bodies have become increasingly interested in including additional information about the potential benefits of medicines in PILs (6-8). However, currently little is known about the extent to which PILs include benefit information and how this information is presented. Such information could range from basic information about the way the medicine works, through to numerical information about how likely are patients to benefit from the treatment. The aim of this study was to determine the extent to which information about the benefits of treatments was included in a sample of PILs for medicines currently provided in the EU, and to categorise the different types of benefit information provided.

2. Methods

This was a survey and content analysis of the 'benefit information' contained in medicine patient information leaflets. A quota sample was taken of the English version of 100 PILs currently available in the EU, with a desire to include both established and new medicines from a range of manufacturers (who write the leaflets). Hence the leaflets were obtained from two representative groups of leaflet types:

1] For the top 50 dispensed medicines: identified from national prescription cost analysis data which provides details of items dispensed in the community (

2011) (9), and reflecting the most common medicines that patients, and therefore the most common leaflets that people, receive. The list of top 50 dispensed medicines was randomised using a random list generator (www.random.org). The top half of the list (n=25) was allocated a leaflet from a branded medicine and the bottom half (n=25) a leaflet from a generic medicine, to determine if any differences were evident.

2] For the 50 newly licenced medicines (from the 'Black Triangle list): identified from the Medicines and Healthcare Products Regulatory Agency (MHRA; the UK medicines regulator) list of "Drugs under

intensive surveillance (2012)", by the date their marketing authorisation was granted. (This list is also known as the 'Black triangle' list and referred to as such in this paper).This group of medicines are newly licensed and as such provide a comparison to the older, commonly dispensed medicines. The rationale for including this group was to see whether the manufacturers of PILs were responding to regulatory moves towards the inclusion of benefit information.

Products such as vaccines, where a patient might not routinely receive a PIL were excluded, as were medicines that were new combinations, formulations, or routes of administration of existing medicines, or older medicines for which a new indication had been licensed. These medicines were excluded as they are not necessarily new treatments and might have existing PILs. Consequently it might mean that the patient information is older and changes relating to recent regulatory moves towards the inclusion of benefit information might be more difficult to identify.

The total sample therefore contained 75% branded leaflets (50% from the Black Triangle List and 25% from the top 50 dispensed group) and 25% generic leaflets (from the 50 top dispensed list). There was no overlap between the two lists (Figure 1).

Obtaining the leaflets.

The leaflets were accessed from the Electronic Medicines Compendium (eMC; www.medicines.org.uk) between 7th January and 20th February 2013. For branded medicines the British National Formulary (www.bnf.org.uk) was used to identify a single listed manufacturer. Where more than one manufacturer was listed, one was selected using a random number generator. Generic leaflets were chosen at random from the eMC; a random list generator was applied to the list of manufacturers and the leaflet that was randomly listed first chosen. For the next random selection, if it included a manufacturer previously used, this name was excluded in order to ensure a range of manufacturers were included. In instances where only one manufacture was available this PIL was included regardless of previous selection. Once a manufacturer had a PIL included in the sample, that manufacturer was not included again unless it was the only manufacturer of a medicine. This ensured a range of manufacturers were included in the sample.

Categorisation of benefit information

There is no agreed existing categorisation of the types of benefit information for medicines. Therefore the benefit information criteria used for this analysis were derived from two sources:

- Report of the European Medicines Agency on patient and professional expectations of information on the risk and benefits of medicines (7).
- Guidance from the MHRA on patient information about medicines (6).

To create a workable set of criteria to use as a framework for the analysis of the patient information leaflets, a content analysis and synthesis of the benefit information described by the two reports was undertaken. The documents were searched for definitions of benefit information and organised into 10 categories based on the words and numerical expressions used (Figure 2).

Data extraction and quality assurance

The information was extracted and entered into a database on which was recorded the frequency and type of information contained in the PILs. The lead researcher (RD) undertook the data extraction, and a random 10% check for accuracy was undertaken by another member of the research team (TR). The 10% check for accuracy was split into 2 X 5% checks. The first 5% check

revealed a small amount of missing data (in particular relating to identifying terms associated with conveying uncertainty). As a result RD rechecked the remaining data for any missing data. The final 5% check was consistent, with both reviewers identifying the same data for each criterion.

Statistical analysis

Data were categorical and the following tests were applied:

- Chi-square test
- Fisher's exact test – used when the assumptions of the chi-spared test were violated (when cells had an expected count of less than 5).

The Statistical Package for the Social Sciences (SPSS) version 19 was used to perform the analysis (10).

3. Results

One hundred PILs were obtained, with at least one leaflet from 59 different manufacturers. Table 1 shows the total number of benefit criteria met according to leaflet type. The findings are listed below under each criterion – differences between generic and branded and new versus commonly dispensed were not statistically significant unless stated.

Criteria 1 & 2: Does the leaflet describe what the medicine is for and does it describe how the medicine works?
All of the leaflets (n=100) described what the medicine was used for, and 85 described how it worked.

Criterion 3: Does the leaflet describe the rationale for why the medicine is being taken?
45 leaflets provided information about the rationale for treatment. Significantly more newly licensed medicines provided additional information about the rationale for treatment when compared to medicines which are commonly dispensed (n=32 compared to n=13, $p<0.001$). A *post hoc* analysis identified 4 different categories of rationale information (see figure 3).

Criterion 4: Does the leaflet describe what will happen if you don't take the medicine?
22 leaflets described what could happen if the patient did not take the medicine (including stopping taking after initially starting to take):

- 17 about the impact of not taking the medicine on the condition
- 3 reported the impact on symptoms
- 1 provided information on withdrawal
- 1 described the impact of stopping on HIV resistance.

17 of the leaflets explicitly described the impact of not taking the medicine, for example:

> *"Do not stop taking this medicine as your heart problem may get worse. Talk to your doctor if you want to stop"* (Digoxin, top 50 dispensed, branded – Lanoxin).

Three included some information about what might happen if the patient did not take the medicine, but it was imprecise, without reference to specific impact on conditions or symptoms. For example:

"If you stop taking lactulose the desired effects of the medicine may not be achieved" (Lactulose, top 50 dispensed, generic).

Criterion 5: Does the leaflet describe whether the medicine will cure or alleviate the symptoms or is preventative?

19 leaflets met this criterion, the majority of which were for symptom control medicines (n=13) and the remainder were preventative (n=6). Most of these statements (n=11) were explicit about whether symptomatic or preventative. For example:

"[This medicine] is used to help relieve the symptoms of mild, moderate and severe asthma, other chest illnesses and to avoid asthma symptoms brought on by exercise or other 'triggers'. Pulvinal must be used for the relief of your asthma symptoms only. You may have other medicines which you take regularly to prevent the symptoms of your asthma." (Salbutamol, top 50 dispensed, branded - Pulvinal)

Eight leaflets were more implicit about the nature of the treatment, for example:

"By blocking the activity of IL-1 beta, canakinumab leads to an improvement in these symptoms." (Canakinumab, black triangle, branded - Ilaris)

Criterion 6: Is the duration of treatment described as short term or long term?

53% of the leaflets described treatment duration, and this was more common in the black triangle group (n=33) than the most frequently dispensed group (n=20) (p= 0.069). In all, 23 of the 53 leaflets described a timescale for treatment. Sometimes this was described only as long-term or short-term treatment, for example:

"*Treatment with Cardicor is usually long-term. Cardicor is used to treat stable chronic heart failure."* (Perindopril, top 50 dispensed, branded - Cardicor)

Other leaflets specified a period of time, for example:

"It will be given to you twice a week (at least three days apart) for the first 12 weeks, then once a week for 24 more weeks". (Mifamurtide, black triangle, branded - Mepact)

Thirteen leaflets said that treatment should continue as long as the doctor recommends, with no specific timescale, However, some of these provided a helpful explanation for this uncertainty, for example:

"There is no time limit laid down as a general rule for treatment with Levact. Duration of treatment depends upon disease and response to treatment." (Bendamustine, black triangle, branded - Levact)

Seventeen further leaflets described some information about treatment length, but were not explicit or were unclear in their description of the duration.

A total of 47 leaflets did not describe the duration of treatment, nor recommend that patients seek advice about duration. This was more common in the top 50 dispensed category, where 30 leaflets provided no information on the duration of treatment compared to 17 in the black triangle group.

Criterion 7: Does the leaflet convey any uncertainty associated with the treatment?

A total of 37 leaflets (37%) presented information that conveyed uncertainty in some way. These were categorised into the following groups, *post hoc*:

[1] No uncertainty conveyed. This was the majority (n=63), where the leaflets tended to include information about the effects of the medicine, for example:

> *Arzerra is used to treat chronic lymphocytic leukaemia (CLL) (Ofatumumab – black triangle, branded – Arzerra)*

The remainder (n=37) used a mixture of terms to convey uncertainty and were categorised into the following groups:

*[2] Uncertainty about the impact of the treatment on the condition (associated with the effectiveness of the treatment).*Two different methods of conveying such uncertainty were noted. Several used words to qualify treatment effectiveness, such as 'helps'; others used modal auxiliary verbs, which are verbs which help to indicate modality or likelihood, such as 'may' (11).

> *2a: Implies uncertainty using the term 'help/s' (n=23) or 'contributes to' (n=1)* Examples include 'helps lower', 'helps prevent', 'helps protect' and 'contributes to lowering' n=1
>
> *2b: Implies uncertainty using the auxiliary verbs 'may', 'can' and 'should'* (n=14). Examples include
>
> - May treat n=2
> - May reduce n=2
> - May prevent / help control / relieve; all n=1
> - Should help / have an improvement; both n=1
> - Can reduce n=2
> - Can help / help relieve; both n=1
> - Can raise n=1
>
> The use of these terms in addition to 'help' such as 'may help' appears to add further uncertainty.

[3] Uncertainty associated with the likelihood of developing an illness. Some leaflets referred to the risk or chance of developing an illness. These leaflets referred to treatments 'reducing the risk or chance' of that illness. There appeared to be 2 levels of uncertainty:

> *3a: Implies uncertainty using the terms 'risk' or 'chance'* (n=10).The treatment '*reduces the risk' (n=8) 'reduces the chance'* of condition (n=2)
>
> *3b: Implies uncertainty using the terms 'risk' or 'chance' and uses an auxiliary verb:* 'may *reduce the risk/chance'* of a condition. (n=5); 'can reduce the risk' n=3, 'may reduce the risk' n=1, 'will increase your chances' n=1)

Criteria 8 and 9: Numerical presentations of benefit

None of the leaflets sampled included any numerical format of benefit information, i.e. information that illustrates the proportion of patients who will benefit and/or the extent of the benefit on the symptoms of the condition, or information that presents any mean benefits of the medicine on a particular measure, for example blood pressure.

4. Discussion

This study shows that benefit information is variably communicated in PILs, with a large majority providing information about how the medicine works and just less than half giving additional rationale about the treatment. Uncertainty about the likelihood of benefit was generally only implicit, with use of terms like 'may' and 'helps', but the actual likelihood of benefit was not included

in any leaflet, neither textually nor numerically. This is despite information being routinely presented in PILs about the likelihood of harm through side effects.

The information about the rationale for treatment was most commonly related to the illness, with newly licenced medicines more likely to communicate such information. Patients desire information which is set in context of their illness and this additional information can have a positive impact on people's judgements about the risks and benefits of their medicines (12-14) .This increase may reflect moves in recent years to balance what is perceived as negative information about side effects (15). This includes recent changes to the EU template for PILs (8), which now specifies that 'clear and condensed' information about the benefits of medicines can be included. However their suggested sub-heading ('How X works') and the examples given, show that the recommendation does not extend to numerical information about benefit likelihood and more about what the medicine does in the body.

The sample of 100 leaflets allowed us to obtain variation in leaflet type and manufacturer, and facilitate a historic comparison of the frequency and type of benefit information. The criteria were developed from two regulatory sources and it is possible that the consideration of additional sources of benefit information might have led to the development of different criteria to define benefit information. However, it is unlikely that this would affect the frequency of numerical benefit information observed in patient information leaflets.

Fundamental information for patient understanding of the medicine they are being expected to take is whether it is intended to cure the condition, alleviate symptoms or be preventative. Nearly half of leaflets did not explicitly communicate this. This is particularly worrying for those medicines intended to be taken indefinitely – an informed decision about whether to start taking such a medicine cannot be made without knowledge of this. Related to this, only a small proportion of leaflets provided detailed information about the duration of treatment of the medicine andsome of those that did used implicit terms which were unclear or non-specific. In slightly less than half of the leaflets there was no information about how long the treatment should be used. Again this is fundamental information for the patient if are they being expected to take the medicine for a few weeks or months, or for the rest of their lives?

It was apparent that the majority of leaflets either did not convey the uncertainty associated with treatments, or conveyed uncertainty in a way that was largely inadequate or unclear. For example, the use of the term 'helps', which appears to be used to convey uncertainty about the action of a treatment, can be confusing and seems to imply that the treatment works, but only in a contributory sense. It could be misconstrued as conveying that the treatment is effective, but only in conjunction with other treatments, when this is not necessarily the case.

The use of auxiliary verbs such as 'can' or 'may' were also used in some leaflets. This technique conveys uncertainty more clearly than using 'helps' alone. However it is still ambiguous because it is unclear how much the treatment will help or reduce the risk of a condition. There is also some redundancy with the use of auxiliary verbs (such as may or can) when combined with terms such as 'risk' or 'chance', which already suggest uncertainty. This might lead to misunderstanding about the potential effectiveness of the medicine. Further research into the linguistics of communicating uncertainty in PILs could determine more effective terminology.

There was a slight tendency for 'black triangle' leaflets to include more benefit information than the top 50 dispensed leaflets on most, but not all, criteria. For two criteria the differences were statistically significant. These were duration of treatment (criterion 3) and whether the leaflet described the rationale of the treatment (criterion 6). It is possible that this increased performance relates to the more complex nature of some of the newly licenced treatments, some of which were for use in treatments such as chemotherapy regimens. This might also reflect a trend for newer, more recently authorised, leaflets to produce better quality information in line with some of the recent recommendations about improvements to the communication of medicines information. (16, 17) This increased inclusion of benefit information might also reflect a better availability and quality of effectiveness data as a result of undertaking of bigger and better designed trials over recent years.

There was variation amongst the type and frequency of information included in the different leaflets. It is apparent that some providers of medicines information include more information about the benefits of a treatment than others. The use of terminology between the leaflets also varies. This has a potential impact on the reader receiving information about their medicines that varies from product to product and is inconsistent. The impact of this upon a patient's knowledge and understanding about their medicines is not known.

It is surprising that none of the leaflets conveyed benefit information in numerical terms. For patients to make informed decisions about their treatments it could be argued that they should be provided with information which is comparable with the presentation of information about the risk of harm. There is increasing evidence that patients underestimate the risk of harm and overestimate the potential for benefit of their treatments which has implications for informed decision-making (4, 5, 18). Patients desire information about the benefits of their treatments in order to counterbalance the impact of what is perceived to be negative risk information (4, 13, 14, 19). The inclusion of textual benefit information has been shown to partly address this imbalance, however the impact of providing numeric benefit information is more complex (19). There is evidence to support the idea that the risks and benefits of treatments are better understood when presented in a numerical format (20, 21) although it is apparent that this is not without impact with patients reporting emotional responses, such as anxiety and unease, about the inclusion of numerical benefit information in patient information leaflets (4, 18). While patients report a preference for textual benefit information, it is apparent that the provision of numeric information can encourage more accurate interpretations of risks and benefits (21, 22). The provision of well-written benefit information in this context would be an appropriate accompaniment to the numerical frequency of side-effects already presented in PILs (23, 24).

Policy makers should work towards standardising the definition of benefit information and provide regulated evidence-based guidelines on the type of information that should be provided in a PIL. While it is apparent that the provision of numeric benefit information is a complex process, the producers and regulators of medicines information need to consider how this type of information can be best incorporated into a PIL. The information provided must not be promotional but should aim to support the patient with their decision-making (16).

Conclusion

This study has shown that the majority of leaflets in the UK do not contain clear or adequate information about the potential benefits of medicines. Leaflets do not consistently provide simple benefit information such as the rationale for treatment, the duration of treatment or whether the treatment is intended to be preventative, curative or symptomatic. Uncertainty about treatment outcome is largely inadequately communicated, with leaflets using ambiguous terms that do not describe either the proportion of patients who are likely to benefit from the treatment, or the magnitude of benefit. There is a duty to attempt to inform patients regardless of whether or not the information being communicated is complex (24). It has been suggested that the package leaflet is an excellent place to communicate information about the benefits of medicines as it is something that is regulated and should be provided with all medicines (25). The manufacturers and regulators of medicines information need to address the lack of usable and comprehensive information about medicines' benefits in PILs.

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Table 1: Benefit criteria met (including statistical difference between leaflets for top 50 dispensed medicines and Black Triangle medicines).

Criteria	Total criteria met n=100	Top50 dispensed n (%)		50 Black Triangle n (%)	Chi-square statistic, probability (p) value. (df=1 for all comparisons)
		Generic n=25	Branded n=25		
1: Does it describe what the medicine is used for?	**100**	25 (100%)	25 (100%)	50 (100%)	-
2: Does it describe how the medicine works?	**85**	21 (84%)	21 (84%)	43 (86%)	.078 (p=0.779)
3: Does the leaflet describe the rationale for taking the medicine?	**45**	5 (20%)	8 (32%)	32 (64%)	14.586 (p<0.001)
4: Does the leaflet describe what will happen if you don't take the medicine?	**22**	7 (28%)	5 (20%)	10 (20%)	.233 (p=0.629)
5: Does the leaflet describe whether the medicine will cure or alleviate symptoms or is preventative?	**19**	5 (20%)	4 (16%)	10 (20%)	.065 (p=0.799)
6: Is the duration of the treatment described as either short term or long term?	**53**	8 (32%)	12 (48%)	33 (66%)	3.305 (p=0.069)
7: Does the leaflet convey any uncertainty associated with the treatment?	**37**	10 (40%)	10 (40%)	17 (34%)	.386 (p=0.534)
8: Does the leaflet illustrate the likely proportion of patients who will benefit and the extent of the benefit on the symptoms of the condition?	**0**	0	0	0	-
9: Does the leaflet present any mean benefits of the medicine on a particular measure?	**0**	0	0	0	-