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Adequacy of Patient Information on Adverse Effects

An Assessment of Patient Information Leaflets in the UK

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Abstract

Background: One of the most important categories of information that patients want to know about the drug they are taking is the likelihood or probability of adverse effects. All patients should receive such information in the patient information leaflet that is supplied with all drugs. Anecdotal evidence suggests that most leaflets give little indication of the likelihood of adverse effects. The UK Medicines and Healthcare products Regulatory Agency (MHRA) suggests using a combination of words and numbers to convey this information. However, an EU guideline suggests using five verbal descriptors on a scale from common to rare, the use of which has been shown to lead to gross overestimation of the risk of adverse effects.

Methods: We assessed the leaflets supplied with the 50 most frequently prescribed drugs in England, to determine the extent to which the likelihood of adverse effects was described, and whether it met the requirements of the EU guidance and/or best practice. We examined both the method used to describe the likelihood of adverse effects, and the format of this information in the leaflet.

Results: Twenty of the 50 leaflets (40%) gave no indication of the likelihood of adverse effects occurring. Six (12%) used the recommended EU terms and a further 20 (40%) used a wide range of other verbal descriptors. Only four leaflets (8%) provided any form of numerical indication of risk. Over half (52%) presented long lists of adverse effects in paragraphs of continuous text.

Conclusions: Patient need is not being met in terms of the provision of usable information about the likelihood of adverse effects. Most patients receive no information, whereas some are given verbal descriptors, both of which lead to overestimation of the risk. Very few of the patient information leaflets assessed used currently described best practice, i.e. to present verbal descriptions alongside numerical information in the form of natural frequencies, e.g. 'rare (affects less than 1 in 1000 people)'.

Background

The adverse effects of drugs (otherwise known as adverse drug reactions) are one of the most important categories of drug information that patients want to be informed about.[1-3] EU legislation passed during the 1990s made it mandatory for drug packaging to contain a leaflet providing all the information that is provided to health professionals in the summary of product characteristics, including all adverse effects, but in a form understandable to the patient.[4] A recent study conducted by our research group indicated that around 40% of patients receiving a prescribed drug read at least some of the leaflet, but this figure rises to >70% of those receiving the drug for the first time.[5] Despite this high level of readership, patients generally invest low value in the leaflets and see them as secondary to spoken information provided by a health professional.[6]

For information about adverse effects to be useful, people need to be able to understand how likely they are to happen, and an EU guideline in 1998[7] suggested the frequency could be expressed using the verbal (non-numerical) terms 'very common', 'common', 'uncommon', 'rare' and 'very rare'. These terms were supposed to map onto percentage bandings used by pharmacovigilance specialists (see table I). However, in the past, the interpretation by potential patients of such verbal terms has been shown to be very variable.[8] This led us to undertake a series of studies with members of the public[9-11] and people taking medications,[12] which confirmed that the terms used in patient information leaflets did not allow people to estimate, with any accuracy at all, the likelihood of adverse effects.

Table I. Verbal descriptors of adverse effects and their corresponding probabilities (EU guidelines)

Verbal descriptor	Probability (%)
Very common	>10
Common	1–10
Uncommon	0.1–1
Rare	0.01–0.1
Very rare	<0.01

There was a universal overestimation of risk when this verbal terminology was used. For example, the adverse effect of constipation for atorvastatin occurs in 2.5% of people, but use of the word 'common' led people taking this drug to think that the incidence was 34% on average.[12] In addition, the range of responses given was considerable. The use of verbal terms also resulted in a greater perceived risk to health from the drug, less satisfaction with the information provided and made people significantly more likely to say it would affect their decision to take the drug.

Many patient information leaflets list 20 or more adverse effects, and some form of categorization is needed for the information to be accessible and understandable. Verbal terms describing likelihood of an adverse effect are one way in which a list of adverse effects can be categorized. Other ways are based on body system, urgency of any action required or severity. In addition, the individual adverse effects listed underneath category headings would benefit from being presented as a bulleted list.[13]

In reviewing the evidence, the UK Medicines and Healthcare products Regulatory Agency (MHRA) produced a set of guidelines for how best to present adverse effect frequency information in leaflets and other written materials.[14] The report suggested examples of how this might be achieved, using a combination of verbal terms and natural frequencies, such as "Very rarely (less than 1 in 10,000) patients treated…."[14] In common with the EU guideline, the terms recommended by the MHRA guidance appeared not to have been evaluated for their understanding by patients.

In this study, we determined the extent to which pharmaceutical companies had followed the EU guidance, in using the proposed verbal terms in their patient information leaflets or were adhering to gui-

dance in the MHRA report. We also looked at other, more subjective markers, including the identification of methods used for describing and categorizing adverse effects and the format in which the adverse effect information is presented. In addition, we identified any information about the benefits from taking the drug, as it has been suggested that balancing potential harm with potential benefit is necessary if patients are to be able to make an informed choice about their treatment.[14]

Methods

In order to select the leaflets most commonly supplied to patients, we obtained a list of the most prescribed drugs by volume in England[15] and obtained a copy of the leaflet for each of those drugs. We took no account of drugs available without prescription (often known as over-the-counter drugs), choosing only to select drugs according to prescription volume. Because at least 50% of drugs in the UK are now prescribed in a generic (non-branded) form, we randomly allocated 25 of the 50 drugs as branded products and 25 as generic drugs. For those allocated to a branded product, where the British National Formulary listed a single manufacturer, this leaflet was selected. Where there was more than one manufacturer, we selected at random a manufacturer for each drug. For generic drugs, we selected leaflets at random from the companies of the British Generic Manufacturers Association. To ensure that a range of branded and generic manufacturers was represented, once they had been selected once, we discounted them from subsequent random selections. When all manufacturers had been selected once, this process was repeated.

We obtained leaflets from the Electronic Medicines Compendium[16] or from the manufacturer. On receipt of the leaflet, the terminology used to describe adverse effect frequency was identified. We identified all verbal terms used to describe the frequency of adverse effects, and noted if they followed the EU or other guideline. In addition, we identified how, if at all, the adverse effects had been categorized, and whether any information on the benefits of the drug was included in the leaflet. The latter was defined as any information that described the potential benefit to health from taking the drug, over and above a simple description of how the drug worked.

Results

The 50 patient information leaflets analysed are listed in table II, along with the name of the manufacturer. All of the leaflets were dated from 1998 or later (with only two dated that year).

Verbal and Numerical Terms Used to Describe Risk

Figure 1 shows the leaflets categorized according to the way the risk of adverse effects is described. Twenty of the leaflets (40%) gave no indication of the likelihood of any adverse effect occurring. There were 26 leaflets that used verbal descriptors of risk. Of these, six (12%) used the EU terms. The remaining 20 (40%) used alternative verbal descriptions of risk. These included words such as ‘occasionally’ or ‘a small number of people’ (see table III). Although words such as ‘rare’ and ‘rarely’ were sometimes used in these 20 leaflets, it was clear from their context of use that they were not being used in the systematic way described in the EU guideline. Table IV shows one example of how the EU-recommended terms are used to describe the risk of adverse effects, and a second example in which no descriptors of the risk of adverse effects are provided.

Four (8%) of the leaflets assessed used natural frequencies (e.g. 1 in 100 people) to describe the risk of adverse effects, and three of these used natural frequencies in combination with other non-EU-recommended formats. One presented risk in both frequency and verbal terms (e.g. “Very rare side effects

Table II. List of leaflets surveyed indicating generic or brand, manufacturer name and date of last revision

Drug[a]	Generic/brand	Company	Date of last revision
Amoxicillin capsule 250 mg	Generic	Sandoz	Jul 2004
Angettes® tablet 75 mg	Brand	Bristol-Myers Squibb	Jun 2005
Aspirin dispersible tablet 75 mg	Generic	Sandoz	Oct 2003
Tenormin® tablets 50 mg	Brand	AstraZeneca UK	Jun 2003
Beclometasone inhaler 100 μg	Generic	Generics UK	Mar 2003
Bendroflumethiazide tablets 2.5 mg	Generic	Crescent Pharma	Jul 2005
Cetirizine tablets 10 mg	Generic	Ratiopharm UK	Mar 2005
Cipramil® tablet 20 mg	Brand	Lundbeck	Apr 2003
Co-codamol tablets 8 mg/500 mg	Generic	Wockhardt UK	Mar 1999
Co-dydramol tablets 10 mg/500 mg	Generic	IVAX Pharmaceuticals	Jan 2004
Voltarol® tablets E/C 50 mg	Brand	Novartis Consumer Health	Oct 2000
Lanoxin® tablets 125 μg	Brand	GSK Consumer Healthcare	May 2000
Ferrous sulphate tablets 200 mg	Generic	Ranbaxy (UK) Ltd.	Oct 2004
Prozac® capsules 20 mg	Brand	Eli Lilly & Co Ltd.	Jul 2003
Folic acid tablets 5 mg	Generic	Teva Pharmaceuticals	Jan 2004
Lasix® tablets 40 mg	Brand	Celltech Pharmaceuticals	Nov 2004
Gaviscon® liquid (original aniseed) S/F	Brand	Reckitt Benckiser Healthcare	Sep 2002
Diamicron® tablets 80 mg	Brand	Servier Laboratories Ltd.	Sep 1998
Brufen® tablets 400 mg	Brand	Abbott Laboratories Ltd.	Feb 2003
Lactulose solution	Generic	Generics UK	Oct 1998
Glucophage® tablets 500 mg	Brand	Merck Sharpe & Dohme	Dec 2003
Losec® capsule E/C 20 mg	Brand	AstraZeneca UK Ltd.	Jul 2005
Paracet tablets 500 mg	Generic	IVAX Pharmaceuticals	Jun 2004
Phenoxymethylpenicillin potassium tablets 250 mg	Generic	Kent Pharmaceuticals	Dec 2003
Tritace® capsules 10 mg	Brand	Aventis Pharmaceuticals	Jul 2003
Salbutamol Inhaler 100 μg (200 D) CFC free	Generic	Teva Pharmaceuticals	Apr 2000
Nylax	Generic	Alpharma	Aug 2000
Zocor tablets 20 mg	Generic	Merck Sharpe & Dohme	Sep 2005
Temazepam tablets 10 mg	Generic	Genus Pharmaceuticals	Jun 2004
Tramadol HCl capsules 50 mg	Generic	Pliva Pharmaceuticals	May 2004
Monotrim® tablets 200 mg	Brand	Solvay Healthcare Ltd.	May 2004
Warfarin sodium tablets 1 mg	Generic	Crescent Pharma Ltd.	Aug 2004
Zimovane® tablets 7.5 mg	Brand	Aventis Pharmaceuticals	Apr 2005
Amitriptyline HCl tablets 25 mg	Generic	Ivax	Aug 2000
Istin®	Brand	Pfizer	Aug 2004
Coversyl®	Brand	Servier	Dec 2003
Diazepam tablets 2 mg	Generic	Dr Reddy's	Aug 2002
Dihydrocodeine tartrate tablets 30 mg	Generic	Ranbaxy	Mar 2005
Erythromycin tab E/C 250 mg	Generic	Dr Reddy's	Jul 1998
Floxapen®	Brand	GlaxoSmithKline	Nov 2004
Fosamax® once weekly tablet 70 mg	Brand	Merck Sharpe & Dohme	Apr 2004
Lipitor® tablets 10 mg	Brand	Parke-Davis	Aug 2005
Microgynon® 30 tablets	Brand	Schering	Jun 2003

Continued next page

Table II. Contd

Drug[a]	Generic/brand	Company	Date of last revision
Seroxat®	Brand	GlaxoSmithKline	Dec 2004
Plavix®	Brand	Bristol Myers Squibb/Sanofi	Jan 2005
Prednisolone tablets E/C 5 mg	Generic	Kent	Feb 2002
Zantac®	Brand	GlaxoSmithKline	Jul 2004
Xalatan	Brand	Pharmacia	Oct 2004
Zoton capsules 15 mg	Generic	Cyanamid	Feb 2002
Cozaar tablets 50 mg	Generic	Merck Sharpe & Dohme	Nov 2005

a The use of trade names is for product identification purposes only and does not imply endorsement.

CFC = chlorofluorocarbon; **E/C** = enteric coating; **S/F** = sugar free.

that could happen to less than 1 in 10,000 people taking [this medicine] include [list].” A further leaflet presented potential adverse effect risk as a frequency and as a histogram. None presented the risk information as a percentage (figure 1).

The four leaflets that gave numerical indication of risk (in the form of natural frequencies) were all branded drugs. Other ways of indicating likelihood of adverse effects (no indication of likelihood; following the EU guideline; using alternative verbal descriptions) were used in similar proportions of leaflets for branded and generic drugs.

Grouping of Adverse Effects

The way in which adverse effects were grouped and formatted in the leaflets for both branded and generic drugs is shown in figure 2. The most popular form of grouping was by the type of action a patient needs to take if the adverse effect occurs (such as ‘seek medical help immediately’), with 18 (36%) using this format. This was followed by grouping according to frequency of occurrence in 14 (28%), with seven (14%) using the type of body system affected. Only two leaflets (4%) used severity of the adverse effect as a method of grouping. Eleven of the leaflets (22%) used no type of grouping. Again, the numbers were similar for both branded and generic drugs.

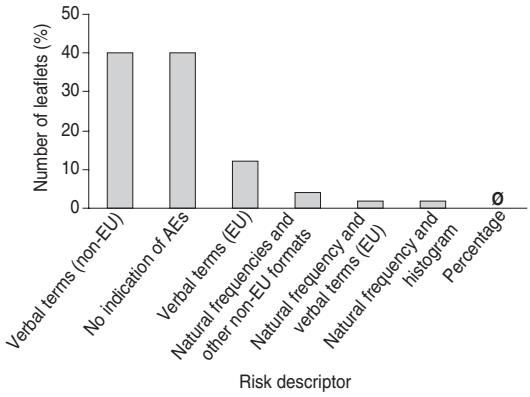

Fig. 1. Percentage of leaflets using various risk descriptors to describe likelihood of an adverse effect (AE). **Ø** indicates that no leaflets presented the information as a percentage.

Format of the List of Adverse Effects

A list of adverse effects can be presented as continuous text where each adverse effect is separated in a paragraph of text by a comma. Alternatively, each adverse effect can appear as an item in a bulleted list. It is also possible that both these formats can appear in the same leaflet, with some listed in a paragraph and some as a list. Over half (52%) of the leaflets used paragraphs of continuous text to present adverse effects. Fifteen (30%) of the leaflets used a combination of text and bullet-pointed lists and nine (18%) used only bullet-pointed lists to present adverse effects.

Figure 2 shows that there were differences in the way in which information was presented between leaflets for branded and generic drugs. A higher proportion of the branded-drug leaflets used bullet-pointed lists to present adverse effects (seven as

Table III. Verbal descriptors used in leaflets to describe risk (not based on EU guidelines)

Verbal descriptor	Number of leaflets
'Rarely' or 'very rarely'	10
'Occasionally'	5
'Rare' or 'very rare'[a]	4
'Most common'	4
'Less common'	2
'A [very] small number of people'	2
'A few people'	1

a Not in same context as these descriptors in the EU guideline.

opposed to two for generic drugs). Similarly, of the 26 leaflets that presented adverse effects in paragraphs of continuous text; almost twice as many were for generic drugs (17) as opposed to branded drugs (9).

Information on the Benefits of the Drug

Two of the 50 leaflets included some information of the benefits of the drug. In both cases, this consisted of a statement (e.g. "[drug] reduces the chance of spinal and other bone fractures") without any numerical data.

Discussion

If the information given to patients about adverse effects is to be useful to them, they need to understand how likely they are to happen. This study covers leaflets produced by all the major branded and generic pharmaceutical companies in the UK, and it is disturbing to find that 40% gave no indication at all of the likelihood of adverse effects. Few were following the flawed EU guidelines in using verbal descriptions alone; it is not clear if this is a result of inaction or disagreement with the guideline. Since the EU document is a guideline and not a directive, manufacturers are under no legal obligation to adhere to it.

Given the problems in using verbal descriptors, it may seem that the simple solution is to provide the information as numbers. However, as Knapp et al.[12] point out, verbal descriptors do have some advantages over numerical information. They can break up long lists of adverse effects into more manageable sections based on the frequency of occurrence. Furthermore, verbal descriptors can convey the inherent uncertainty of levels of risk and the variations in incident rates across trials. Finally, many people feel more comfortable with verbal descriptions than with numerical information, which can be seen as complex and intimidating.

Only four leaflets provided any numerical information in any form. Some authors have argued that verbal descriptors should be used in conjunction with numerical information in order to attenuate the difference between perceived and actual level of risk.[17] This has been proposed as current best practice,[14] although only one leaflet used such a combination of verbal terms and natural frequencies.

A further concern is that almost one-fifth of leaflets presented the adverse effects with no attempt to group or categorize them. Generally, peo-

Table IV. Extracts from selected leaflets to illustrate methods of adverse effect description

Method of presenting adverse effects	Example
Use of EU-recommended verbal terms	Common adverse effects: headache, diarrhoea, constipation, stomach ache, feeling sick, vomiting, wind Uncommon adverse effects: dizziness; pins and needles; light-headedness; feeling faint; sleepiness; trouble sleeping; liver disease, which may make your skin and eyes yellow; rash; itching; generally feeling unwell (Losec®)
No indication of adverse effect likelihood	The adverse effects that some patients have had with similar products are feeling sick, being sick, constipation, confusion, drowsiness, dizziness, giddiness, excitement, difficulty in passing water, dry mouth, sweating, facial flushing, slow heart rate, palpitations, feeling faint on standing up, low body temperature, restlessness, mood changes, hallucinations, pinpoint pupils, pressure on the brain, skin rashes, allergic reactions, kidney damage and blood disorders (Co-codamol)

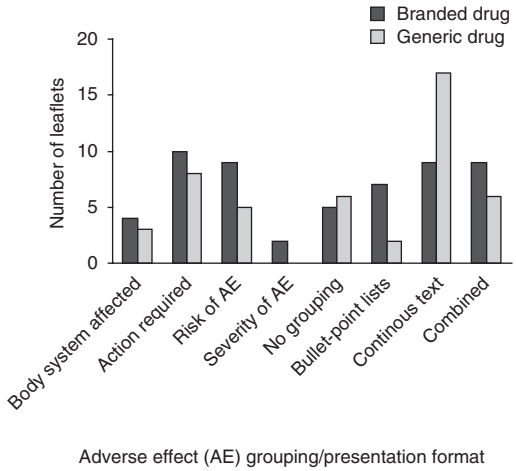

Fig. 2. Comparison of proprietary and generic drug patient information leaflets according to adverse effect grouping and presentation format.

ple find it difficult to understand and use risk information effectively.[18] However, a large body of research in cognitive psychology demonstrates the benefits for comprehension and memory of breaking up long lists of items into smaller groups or blocks.[19] Furthermore, presenting individual adverse effects as a bulleted list under sub-headings will make it easier to read, comprehend and remember.[13] Unfortunately, over half of the leaflets assessed presented long lists of adverse effects as continuous text in paragraphs. The most likely reason for presenting information in this way is to save space; however, in doing so, leaflets are placing further hurdles in front of patients' effective understanding.

Finally, only 2 of the 50 leaflets surveyed included any information on benefits related to taking the drug. Traditionally, drug manufacturers in the UK have not included information on benefits in the patient information leaflets, as they are prohibited from marketing their products. However, current legislation does allow for the inclusion of some information on benefits, and the MHRA guidelines actively encourage its use.[14] Previous research suggests that providing information on the benefits of drug can offset the impact of negative risk information, leading to a more accurate assessment of the objective risk.[20,21]

Given that the risk of adverse effects plays a major role in a patient's decision to take the drug or not,[22] accurately understanding the risk is paramount if the decision is to be an informed one. The findings suggest that a large number of leaflets do not allow patients to fully understand the risks they face from taking their drug, which compromises their ability to make informed choices about their healthcare. Certain groups of patients might be more sensitive to an inadequate communication of adverse effect risk, and this could be investigated in further research that selects leaflets for certain drugs, rather than those of the most prescribed drugs (as was done in this study). Further research is needed to augment the existing limited research that currently defines best practice in describing the likelihood of adverse effects. Such research might also examine patients' understanding of the words used to describe adverse effects and the effects that rewording this information has on the decisions. In addition, research is needed to determine how best to incorporate both harm and benefit information into drug leaflets.

Conclusion

The requirement patients have for information on the likelihood of adverse effects with their medication is not currently being met. Most leaflets provide no information on risk, while some use verbal risk descriptors, which lead to overestimation of the risk. Very few of the leaflets in current use apply described best practice for risk presentation, or follow the EU guidelines. The regulatory authorities should review their guidance on how the risk of adverse effects is conveyed in patient information leaflets, to take account of current best practice and encourage manufacturers to follow it. Replication of this work in other EU member states would be

beneficial to determine if the issues are the same across the EU. Further work is also needed to determine how best to incorporate information on benefits of the drug into patient information leaflets.

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