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Communicating the Risk of Side Effects to Patients

An Evaluation of UK Regulatory Recommendations

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Abstract

Background: All licensed medicines in the European Union must be provided with a Patient Information Leaflet that includes a list of all known side effects. Among patients who read the leaflet, the side effects section is the most often read. A UK government regulatory publication recommends providing medicine side effect risk information in a combined format, using verbal descriptors accompanied by numerical information.

Objectives: This study, with users of an existing popular patient information website, investigates the effectiveness of presenting medicine side effect risk information in different forms.

Design: Participants were randomly allocated to one of the three formats for representing risk information (*verbal* descriptors, e.g. 'common'; *absolute frequencies*, e.g. 'less than 1 in 10 people'; and a *combination* of verbal descriptors and frequency bands, e.g. 'common (affects less than 1 in 10 people)'.

Methods: Participants (n = 187) were recruited from users of the Cancer Research UK patient information website. They were asked to imagine that they had to take a cancer treatment (tamoxifen), estimate the risks of four side effects occurring, and complete Likert scales relating to their satisfaction with the information supplied and perceived likelihood of various outcomes.

Results: Those in the *absolute frequency* format demonstrated greater accuracy in estimating the likelihood of having two of four side effects than the other two formats. They were also more accurate at estimating the likelihood of themselves or the average person having any side effect from taking tamoxifen. Participants in the *absolute frequency* format rated the risk to health from tamoxifen as lower than those in the other two formats, were more satisfied with the information they received than those in the *verbal* format, and felt there would be less impact of the information on tamoxifen use than those in the *combined* format.

Conclusions: These findings fail to confirm that the recommended use of combined descriptors for medicine side effects is unequivocally superior to absolute frequency alone. They also add weight to the growing body of research highlighting the deficiencies in using verbal descriptors for conveying side effect risk, and the strength of using absolute frequency descriptors.

Background

There is growing evidence that involving patients in decisions about their healthcare leads to better health outcomes,[1] and increased patient involvement has been incorporated into the strategy of health services.[2] Since medicines are the most common form of healthcare intervention, providing patients with understandable information about treatment is an important part of this process. Patients want this information, especially when it relates to side effects,[3] and side effect information has the most influence on decisions regarding whether or not to take a medicine.[3-6]

This desire for information has been addressed, at least partially, by an EU directive stipulating that all medicines prescribed in Member States must be distributed with a comprehensive patient information leaflet (PIL) including details of all potential side effects.[7] In addition, there is a growing trend for such information to be made available on the internet.[8] In line with this trend, Cancer Research UK (CRUK) has developed a website for members of the public looking for general information on cancer or particular treatments for cancer (www.cancerhelp.org.uk).[9]

Despite advances in patient empowerment, from a situation in the 1970s when patients may not even have been told the name of the medicine they were prescribed,[10] there is much work still to be done to optimize the manner in which information about medication is presented. While the EU produced a guideline to improve the readability of PILs,[11] patients still have difficulty understanding the likelihood (or risk) of a side effect.[10] Various recommendations have emerged in the hope of improving the manner in which side effect information is presented. For example, the EU proposed five verbal descriptors for side effect risks.[11] The verbal descriptors and their corresponding probabilities are presented in table I. More recently, the UK Medicines and Healthcare products Regulatory Agency (MHRA)[12] incorporated the same descriptors into recommendations to medicine licence holders. They recommended that verbal descriptors of risk (e.g. 'very common') should only be used in conjunction with corresponding numerical information and be presented as a frequency band, e.g. 'very common (more than 1 in 10 people)'.

Problems with both the EU and MHRA guidelines are that they are not evidence-based and they are not consistently applied. In a review of the 50 most frequently prescribed medicines, for example, only 12% of provided leaflets used recommended EU terms and <1% followed MHRA guidelines.[13] Almost half the reviewed leaflets gave no information on the likely frequency of side effects.

The verbal descriptors recommended by the EU have been shown to lead to considerable overestimations of risk by patients, doctors and the general public.[14-19] For example, according to EU guidelines the term 'common' is assigned to side effects that occur in 1–10% of people taking the medicine (table I). Berry and colleagues[17,20] showed that, on average, patients

Table I. EU recommended verbal descriptors of side effect risk and their corresponding probabilities

EU recommended verbal descriptor	EU assigned probability of side effect occurrence
Very common	>10% (more than 1 in 10 people)
Common	>1% and <10% (less than 1 in 10 but more than 1 per 100)
Uncommon	0.1–1% (less than 1 per 100 but more than 1 per 1000)
Rare	0.01–0.1% (less than 1 per 1000 but more than 1 per 10 000)
Very rare	<0.01% (less than 1 in 10 000)

interpreted the word to mean around 45%, while doctors estimated the risk to be around 25%.

It is not just verbal descriptors that lead to overestimations of risk. One study showed that, even when given the risk of pancreatitis from taking atorvastatin as a percentage (0.04%), patients overestimated the risk of having the side effect (mean estimate 2.1%).[19] A more recent study[18] tested the MHRA recommendation of a combined description by presenting patients with the side effect risk either verbally (e.g. 'common', as recommended by the EU) or as a combination of verbal descriptors and percentage ranges (e.g. 'common, i.e. occurs in between 1 and 10% of people'), although this risk expression is not precisely the same as the MHRA recommends. The findings echoed those of previous research in that verbal descriptors resulted in overestimates of the risk of side effects but, interestingly, many of those in the combined format also overestimated the risk.[18]

Some researchers argue that percentages are abstract concepts that lack a concrete reference class, and the patient cannot then place the risk in a natural context.[21] To overcome this problem, they advocate the use of 'natural' or 'absolute' frequencies that always state a reference class. So rather than 'a 30–50% chance of developing a side effect', the information is presented as '3 to 5 people out of every 10 will develop a side effect' (absolute frequency) or 'if 10 people take this medicine, 3 to 5 of them will develop a side effect' (natural frequency). In these instances, people are the reference to whom the patient can relate. When rephrasing even quite complex conditional probabilities in this way, people become much better at finding the correct solution.[21] A recent study has shown that presenting risk as an absolute frequency results in more accurate assessments.[18]

It is not just estimates of side effect frequency that are affected by the way in which the risk information is presented. Several studies have found that the use of numerical information rather than verbal descriptors when presenting side effect risk significantly decreases perceived risk to health and increases intention to take the medicine.[14-17,19] Provision of numerical information (as opposed to verbal descriptors) also decreases perceived severity of side effects (e.g. Berry et al.[15]) and increases satisfaction with the information (e.g. Knapp et al.[19]). Satisfaction with information supplied about a drug has been shown to predict adherence to treatment,[22] albeit in a different condition to cancer, and it is important that we provide information to generate accurate perceptions of risk and in a manner that patients find satisfactory.

This research closely follows the methods used to compare the impact of side effect information in previous studies.[15,19] These studies reported that patients' perception of the risk of side effects when provided with the EU verbal descriptors was much higher than patients who received the same information as percentages; however, even the patients receiving information as percentages assessed the risk as higher than the actual risk. This study aimed to take this a step further by comparing risk estimates resulting from the presentation of risk side effects using (i) verbal descriptors; (ii) absolute frequencies; and (iii) a combination of verbal descriptors and frequency bands. We also measured satisfaction with information supplied, and whether the provided information would impact on the decision to take tamoxifen. In doing so, the aim was to test whether absolute frequencies or a combination of verbal descriptor and frequency bands lead participants to make more accurate assessments of side effect risk than verbal terms alone, and how presentation mode affected patient satisfaction, intention to take the medicine and other important outcomes. A key element of the approach was to attract participants who were actually in the process of seeking information about a medicine, whether for themselves, for others, or out of general interest. Accordingly, a web-based experiment was developed to be conducted with visitors to the CancerHelp UK website.[9]

Methods

Design

The study used an independent groups design with three risk formats (figure 1). Participants were recruited via a convenience sample, i.e. one not

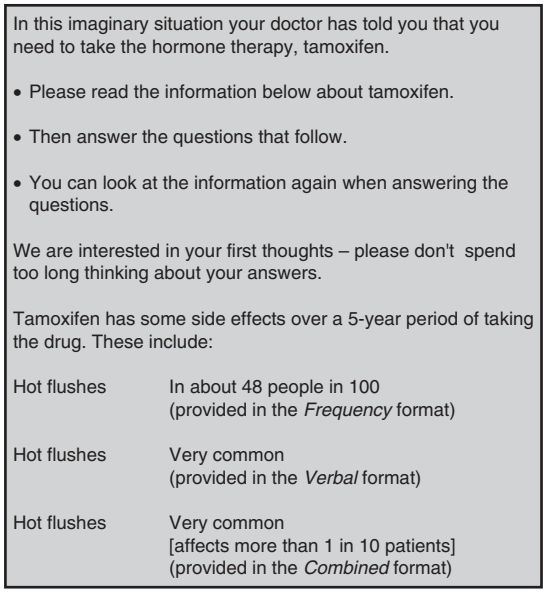

Fig. 1. Scenario given to participants and examples of the three allocated formats.

based on random sampling from a population. The *verbal* format presented the likelihoods of four side effects of tamoxifen according to the EU-recommended descriptors in table I. For example, the likelihood of hot flushes was presented as being 'very common'. The *frequency* format presented absolute frequencies, i.e. the number of people per 100 (or per 1000 or 10 000) who experience each side effect. For example, the likelihood of hot flushes was presented as being experienced 'in about 48 people in 100'. The *combined* format presented both the verbal descriptors (as described earlier) plus the EU-assigned probability band for that descriptor. For example, the likelihood of hot flushes was presented as being 'very common (affects >1 in 10 patients)'. The side effect risk information presented in the questionnaire was taken from the CRUK database of medicines used in cancer (March 2006).

Procedure

Each participant in the study took part via the internet and had no interaction with the researchers. The invitation to take part in the study was via a 'pop-up' window that appeared when participants navigated to the tamoxifen page on the CancerHelp UK website[9] during the period March–December 2006.

Participants were first given information about the purpose and nature of the study and given the opportunity to continue. They were also told they could withdraw at any time (by simply closing the window). Participants who agreed were then taken to the study's website and were randomly allocated by the computer (according to a random numbers schedule) to one of three formats. Participants in all three formats saw a webpage containing the same hypothetical scenario, followed by the likelihoods of four side effects expressed in a form according to the experimental format. Participants were then asked to complete the series of questions (outlined in the measures section). A final web page thanked participants, explained the study aims, and also told participants that the list of side effects was not exhaustive and provided a link and a telephone helpline if they wanted further information. Participants were invited to provide their email address if they wished to receive a summary of the study results. On completion, participants were returned to the tamoxifen webpage. No incentives were offered to participate in the study or complete it.

Materials

Participants were asked to imagine that their doctor had told them that they needed treatment with tamoxifen (figure 1). The side effects were selected to be as recognizable as possible, e.g. 'cataracts (clouding of the lens of the eye)'. Four side effects with incidence rates were used: 'hot flushes' (48%); 'cataracts' (3%); 'deep vein thrombosis [DVT]' (0.2%); and 'pulmonary embolism' (0.06%). We deliberately chose those whose rate corresponded to different EU frequency categories (>10%, 1–10%, 0.1–1% and 0.01–0.1%, respectively). We also chose to include side effects with rates of <1%, since there is some evidence that this can be more difficult to understand.[19]

Measures

Participants were asked to rate on 6-point Likert scales (figure 2):

- how satisfied they were with the presented information;
- how severe the perceived side effects were;
- how likely they were to experience a side effect;
- the general risk to health;
- the extent to which the information would affect their decision to continue treatment;
- how likely they thought it was that they would benefit from tamoxifen.

Participants were able to scroll back to the side effect information to help with their responses. They were also asked to make separate estimates of the probability that they would experience each of the side effects from taking tamoxifen. For example, participants were asked 'What do you think is the chance that *you* will have hot flushes from taking tamoxifen? Please state as a percentage in the box below'. In addition, participants were asked 'What do you think is the chance that *you* will have *any* side effect from taking tamoxifen?' and 'What do you think is the chance that *the average* person taking tamoxifen will have *any* side effects?' to look at any differences caused by perceived personal susceptibility. Participants were again asked to answer both questions by providing a percentage; a previous study showed that altering the response format (percentage or frequency) had no effect on risk estimates.[16] The actual rate of getting *any* of the four side effects was not known, but we calculated the maximal chance (when the occurrence of each side effect is independent of each other) to be 49.7% (figure 3).

The final page of the study asked participants for demographic information (sex, age, nationality, whether English was their first language, their job and why they were looking for information about tamoxifen). This page also asked participants to list, where relevant, any side effects they had themselves experienced while taking tamoxifen.

Statistical Analyses

Means (and standard deviations) were calculated for all variables by allocated format. A number of exploratory analyses were conducted to examine the possibility that age, cancer status or number of side effects experienced may

Overall, how satisfied are you with the information you have just read about the risk of side effects from tamoxifen?

Not satisfied at all 1 2 3 4 5 6 Very satisfied

Thinking about the information you have just read, how bad overall are the side effects of tamoxifen?

Not at all severe 1 2 3 4 5 6 Very severe

From the information you have just read, how likely is it that you would have a side effect from tamoxifen?

Not at all likely 1 2 3 4 5 6 Very likely

Thinking about the information you have just read, what do you think is the general risk to health from tamoxifen?

No risk at all 1 2 3 4 5 6 Very high risk

How much would the side effect information you have just read affect your decision to continue taking tamoxifen?

Definitely would not affect 1 2 3 4 5 6 Definitely would affect

How likely do you think it is that you will benefit from taking tamoxifen?

Not at all likely 1 2 3 4 5 6 Very likely

Fig. 2. Wording of Likert response items.

p (one or more side effects) = 1 – p (no side effects)

= 1 – [p (no hot flushes) × p (no cataract) × p (no DVT) × p (no PE)]

= 1 – [(1–0.48) × (1–0.03) × (1–0.002) × (1–0.0006)]

= 1 – [0.52 × 0.97 × 0.998 × 0.9994]

= 1 – 0.503089

= 0.497 = 49.7%

Fig. 3. Calculation for the maximal chance of having at least one side effect from tamoxifen (p). **DVT** = deep vein thrombosis; **PE** = pulmonary embolism.

act as co-variates when examining differences between experimental formats and outcome variables. The effect of these variables was assessed by entering them as co-variates in multiple analysis of co-variance (MANCOVA) analyses.

The effect of allocated format was tested by analysis of variance (ANOVA), with Tukey *post hoc* pairwise comparisons.

Research Ethics

The study was approved by the Faculty Research Ethics Committee at the University of Leeds, Leeds, UK.

Results

Participants

The study was accessed via the 'pop-up' window by 339 people who were allocated to one of the three formats (109 to *frequency*, 112 to *verbal*, 118 to *combined*). 187 (55.2%) people completed the study (52 participants were randomly allocated to *frequency*, 69 to *verbal*, 66 to *combined*). A Chi-squared test found no relationship between format allocation and study completion ($p > 0.05$).

Characteristics of the 187 participants (sex, age, location, language and cancer status) are reported in table II. We collected no data on other participant characteristics, such as educational attainment or household income. The three study allocations had similar proportions of participants on each of the demographic variables.

Likert Scale Responses and Risk Estimates

On the whole, participants were moderately satisfied with the information supplied, felt the side effects were moderately severe, and felt it was quite likely that they would have a side effect from taking it (table III). Overall, participants thought there was a moderate risk to health from taking tamoxifen, that the information would have a moderate impact on their decision to continue taking it, and that it was likely they would benefit from taking it. On average, participants felt the risk of personally experiencing hot flushes was around 60%, the risk of cataracts was around half this, and that the risk of DVT was around half this again. Overall, the perceived risk of PE was lowest at just under 12%. The perceived risk of personally experiencing any side effect from taking tamoxifen (56.5%) was slightly higher than the perceived risk of the average person (53.6%).

Adjustment for Co-Variates

There was no overall effect for any of age, cancer status or number of side effects experienced

Table II. Characteristics of the sample (n = 187)

Sex	180 female; 7 male
Age (y)	Mean 42.8 (SD 12.9); range 15–66
Location	156 UK; 15 US; 16 other
English as first language	182 yes; 5 no
Reason for visiting the webpage [n (%)]	45 (24.1) currently taking tamoxifen 27 (14.4) have cancer but not taking tamoxifen 6 (3.2) have previously taken tamoxifen 20 (10.7) about to take tamoxifen 50 (26.7) have a close relative or friend with cancer 16 (8.6) health professionals 23 (12.3) none of the above
Side effects experienced personally from tamoxifen among n = 51 current or past users [n (%)]	Study side effects: 43 (84.3) hot flushes 3 (5.9) cataract 0 (0) deep vein thrombosis 0 (0) pulmonary embolism Also reported: 5 (9.8) joint pain 5 (9.8) weight gain 4 (8) fatigue 45 (88.2) have experienced at least one side effect

Table III. Mean (SD) scores for participants' Likert scale item responses and side effect risk estimates (%)

Likert scale item	Format			F-value and Tukey *post hoc* pairwise comparisons[a]
	combined mean (SD) [n = 66]	*frequency* mean (SD) [n = 52]	*verbal* mean (SD) [n = 69]	
Satisfaction with side effect information	3.6 (1.42)	3.9 (1.3)	3.2 (1.5)	3.86* combined = frequency combined > verbal† frequency > verbal†
How bad overall tamoxifen side effects are	3.6 (0.9)	3.1 (1.2)	3.4 (1.1)	2.73 combined = frequency combined = verbal frequency = verbal
Likelihood of having a side effect	4.3 (1.4)	3.6 (1.2)	4.3 (1.4)	5.33** combined > frequency† combined = verbal frequency < verbal†
General risk to health from tamoxifen	3.3 (1.0)	2.9 (0.9)	3.3 (1.1)	3.74* combined > frequency† combined = verbal frequency < verbal†
Impact of information on decision to take tamoxifen	3.5 (1.5)	2.6 (1.5)	3.2 (1.5)	4.39* combined < frequency† combined = verbal frequency = verbal
Likelihood of benefit from taking tamoxifen	4.5 (1.1)	4.8 (1.1)	4.7 (1.3)	1.28 combined = frequency combined = verbal frequency = verbal
Side effect risk estimates (actual %)				
Personal chance of hot flushes (48%)	43.6 (37.5)	55.7 (23.0)	78.1 (23.9)	25.67*** combined < frequency† combined < verbal† frequency < verbal†
Personal chance of cataracts (3%)	20.8 (21.5)	12.1 (18.5)	49.4 (23.3)	52.10*** combined > frequency† combined < verbal† frequency < verbal†
Personal chance of DVT (0.2%)	11.2 (21.3)	12.2 (22.3)	21.7 (20.2)	5.14** combined = frequency combined < verbal† frequency < verbal†
Personal chance of pulmonary embolism (0.06%)	9.2 (19.7)	11.1 (20.2)	14.9 (21.2)	1.48 combined = frequency combined = verbal frequency = verbal
Personal chance of ANY side effect (maximum 49.7%)	42.9 (37.8)	52.9 (28.5)	72.2 (27.5)	15.35*** combined = frequency combined < verbal† frequency < verbal†
Average person's chance of ANY side effect (maximum 49.7%)	38.7 (34.0)	47.4 (21.3)	72.6 (24.0)	29.19*** combined = frequency combined < verbal† frequency < verbal†

a Pair-wise comparisons tested at $p < 0.05$. † indicates a statistically significant difference; for F-values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

when entered as co-variates in separate MANCOVAs examining responses to the Likert scale items. However, significant co-variation was identified between number of side effects experienced and risk estimates. Number of side effects experienced was significantly correlated with perceived risk of hot flushes (Pearson's correlation $r = 0.19$; $p < 0.01$); DVT ($r = 0.18$; $p < 0.05$); PE ($r = 0.18$; $p < 0.05$); or having any side effect ($r = 0.15$; $p < 0.05$). The number of side effects experienced was also significantly correlated with perceived risk of the average person experiencing any side effects ($r = 0.18$; $p < 0.05$). That is, participants who reported having more side effects generally gave higher frequency estimates of side effects occurring, regardless of experimental format. Consequent analyses therefore included the number of side effects experienced as a co-variate when examining risk estimates.

A MANOVA performed on responses to the six Likert scales showed a significant main effect of format on responses ($F [12\ 358] = 2.05$; $p < 0.05$).

Participants in the *frequency* format were significantly more satisfied with the information given about the side effects of tamoxifen than those in the *verbal* format. No significant differences existed between formats in terms of perceptions of how bad the overall side effects are. Participants in the *frequency* format felt it was significantly less likely that they would have a side effect from tamoxifen than the other two groups (although all groups had a mean rating above 3.5, indicating that having a side effect was likely overall). Participants in the *frequency* format rated the general risk to health as significantly lower than the other two groups. Participants in the *frequency* format felt that the side effect information would have less of an impact on their decision to continue taking tamoxifen than participants in the *combined* format (the difference between the *frequency* and *verbal* formats was not significant). No significant differences existed between formats in terms of the likelihood of benefiting from taking tamoxifen.

Table III also demonstrates that when participants were asked to give percentages for how likely they were to have the individual side effects or any side effect (both personally and for the average person), the estimates in the *verbal* format were higher than in the other two groups. The difference was most marked for the likelihood of having cataracts. In almost all cases, side effect risks were overestimates.

A MANCOVA controlling for number of side effects experienced showed a significant main effect of format on risk estimates ($F [12\ 358] = 11.90$; $p < 0.001$). It can be seen from the table that significant between-subjects effects exist for all risk perceptions except perceived chance of having a PE from taking tamoxifen. Those in the *verbal* format perceived that there was a significantly greater chance of experiencing hot flushes, cataracts, DVT and any side effect than with the other two formats. Those in the *verbal* format also perceived that there was a significantly greater chance of an average person having any side effects than with the other two formats. Those in the *frequency* format perceived their risk of having hot flushes to be significantly greater than those in the *combined* format, whilst the reverse was true for risk of having cataracts. No other significant differences existed between the risk perceptions of those in the *combined* and *frequency* formats.

Accuracy of Risk Estimates

To examine the accuracy of participants' ratings of the chance of each of the side effects, difference scores were computed by subtracting the actual risk of each side effect occurring (or, where relevant, of any side effect occurring) and each participant's perceived risk of that side effect. We disregarded the direction of any inaccuracy to facilitate comparisons between groups, so difference scores of <0 and >0 were given the same value. Therefore, scores closer to zero are more accurate.

The mean accuracy scores are shown in table IV. In general, risk perceptions of those in the *frequency* format appear most accurate. A MANCOVA controlling for number of side effects experienced showed a significant main effect of format on risk estimates ($F[12\ 358] = 16.95$, $p < 0.001$). Table IV shows the F-values for tests of between-subjects effects, and *post hoc* comparisons. With regard to perceived risk of experiencing hot flushes

Table IV. Mean (SD) risk estimate accuracy scores

Side effect risk estimates	Format			F-value and Tukey *post hoc* pairwise comparisons
	combined mean (SD) [n = 66]	*frequency* mean (SD) [n = 52]	*verbal* mean (SD) [n = 69]	
Personal chance of hot flushes	35.0 (13.4)	14.4 (19.4)	36.4 (12.2)	38.13*** combined > frequency† combined = verbal frequency < verbal†
Personal chance of cataracts	18.0 (21.3)	9.5 (18.3)	46.5 (23.1)	52.19*** combined > frequency† combined < verbal† frequency < verbal†
Personal chance of deep vein thrombosis	11.0 (21.3)	12.0 (22.3)	21.6 (20.2)	5.14** combined = frequency combined < verbal† frequency < verbal†
Personal chance of pulmonary embolism	9.1 (19.7)	11.1 (20.2)	14.8 (21.2)	1.48 combined = frequency combined = verbal frequency = verbal
Personal chance of ANY side effect	35.3 (14.6)	19.9 (20.4)	31.5 (16.1)	12.29*** combined > frequency† combined = verbal frequency < verbal†
Chance of average person having ANY side effect	32.9 (13.3)	13.3 (16.7)	29.0 (15.8)	25.87*** combined > frequency† combined = verbal frequency < verbal†

a Tukey pairwise comparisons tested at $p < 0.05$. † indicates a statistically significant difference; for F-values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

or any side effect, those in the *frequency* format were more accurate than those in either the *combined* or *verbal* formats, which were not significantly different from one another. The same pattern is evident for perceived chance of the average person having any side effects. Participants in the three formats differed significantly from one another in terms of how accurate their perceptions were regarding the chance of having cataracts. Those in the *verbal* format were significantly less accurate at judging their risk of DVT than the other two formats. Accuracy of risk judgements regarding PE did not differ between groups.

Discussion

This study was novel in examining how presenting side effect risks for tamoxifen using either verbal descriptors, absolute frequencies or a combination of verbal descriptors and frequency bands affected risk estimates. In line with previous research,[15,19] we found that those given just the verbal descriptors were significantly less satisfied with the information they received than those given numerical descriptors (although it is unclear what underlies this difference). As with previous studies, we also found that verbal descriptors resulted in a higher perceived likelihood of a side effect and a higher perceived risk to health (e.g. Berry et al.[15] and Knapp et al.[19]).

Giving a combination of verbal descriptors and frequency bands did not produce significantly different responses from verbal descriptors alone in terms of satisfaction with information; perceived severity of side effects; likelihood of a side effect; perceived risk to health; perceived impact of information on tamoxifen use; or perceptions of the likely benefits of tamoxifen. This

is in contrast to a previous study in a different setting,[23] which compared the impact of verbal descriptors with a combination of verbal descriptors and percentage bands when presenting the side effect risks of a new drug. This previous study found that the combined format resulted in greater satisfaction with information, lower perceptions of risk, more positive perceptions of the likely benefits, and increased likelihood of participating in a trial testing the new drug. It should be noted that the current study used frequency bands in the combined format rather than the percentage bands used in the previous study. Although the *frequency* format resulted in more satisfaction with information provided and lower perceptions of risk, there were no significant differences between the *combined* format and the *verbal* format for any of the Likert scale responses.

In line with previous research, participants generally overestimated the risk of side effects irrespective of how the information was presented (e.g. Berry et al.[15] and Knapp et al.[18]). One argument[19] is that participants may not have trusted the information they were given and believed that the side effect likelihood was much higher. It may also be that prior to taking part, participants may have read information on other forms of cancer treatment where the risk of side effects was higher, or their own experience of cancer treatment may have influenced their judgement. However, cancer treatments vary considerably both in their beneficial and harmful effects, and experience of treatment other than tamoxifen might not be relevant.

Another phenomenon noted here as previously (e.g. Berry et al.[15]), is that risk perceptions are more accurate when actual risks are greater. For example, participants overestimated the risk of hot flushes by approximately a quarter. In contrast, participants' mean estimate of the risk of PE was approximately 200-fold the actual risk. It may be that people find percentages <1 to be problematic, or there simply may be more room for error when actual risks are very small.

Relative Accuracy Between Formats

A major finding from this experiment is that participants who received side effect information in the *frequency* format were significantly more accurate at estimating the risk of side effects than the other two formats in four of six cases (i.e. hot flushes, cataracts, any side effect and the average person having any side effect). The only case where significant differences in accuracy between formats did not occur was when estimating the PE risk. When estimating the risk of DVT those in the *frequency* format were significantly more accurate than those in the *verbal* format but did not differ significantly from those in the *combined* format.

The finding that, in general, participants in the *verbal* format were less accurate than those in the *frequency* format is in line with much previous work (e.g. Knapp et al.[18]). However, the current study is the first, as far as the authors are aware, to include a format expressing side effect risk as a combination of frequency bands and verbal descriptors.

Although it seems intuitively understandable, there is no empirical evidence to suggest that the MHRA recommendation[12] of combining verbal descriptors with numerical values will generate any more accurate perceptions of side effect risks than presenting individuals with numerical values alone. Although a recent study reported that a combined descriptor generated significantly more accurate risk estimates than a verbal descriptor alone,[18] the current study has taken this research a step further by examining the relative merits of verbal versus combined versus numerical descriptors. By focussing on absolute differences (i.e. ignoring the sign of differences) between estimates and actual risks of side effects, we were able to compare accuracy across the three formats. This revealed that the *combined* format did not lead to more accurate side effect risk estimates than the *verbal* format in four of the six instances where participants were asked to estimate the risk of side effects. Therefore, it would appear preferable to represent side effect risk in terms of natural or absolute frequencies rather than combining verbal and frequency band descriptors, if we wish to generate more accurate risk perceptions amongst patients. However, there may be a practical hurdle to doing so. Medicines mostly have many

more than four known side effects, so including numerical information on each individual side effect might result in unmanageable amounts of information for patients.

Implications and Suggestions for Future Research

There are four main implications from this study. First, it has confirmed previous findings that people overestimate the risk of side effects, irrespective of the manner in which information is presented. Presenting this information numerically as absolute frequencies[18] or percentages[15] increases the accuracy of risk perceptions compared with verbal descriptors, but we still have some way to go in terms of informing patients about side effects in a way that enables them to make accurate estimates of risk.

Second, this study has added to growing evidence that people are less accurate at estimating side effects that are less frequent. Since individuals' intentions to take medicines are at least partly determined by their perceptions of consequent side effects,[4-6] it is important that we understand this phenomenon further. This is potentially important, since a patient's decision about whether or not to take a medicine that is based on inaccurate or incomplete understanding of benefits and risks could not be said to be 'informed'. It would be useful for research to understand the link that people make between perceived frequency of side effects and the effect they have on health. The link between side effect perception and medicine-taking behaviour should also be explored.

Third, the findings confirm those of previous studies that have demonstrated the inadequacy of verbal descriptors when presenting risk information (however, it should be noted that a 2006 revision of the 1998 EU Readability Guideline, which first suggested the use of such descriptors, no longer makes reference to the use of verbal descriptors).[11]

Finally, this study suggests that the MHRA[12] recommendation to use combined verbal-plus-numerical descriptors when describing the likelihood of medicine side effects requires further validation.

The 'combined' descriptors may perform poorly because the verbal descriptors they contain are themselves flawed. Improving the verbal descriptors employed to describe medicine side effects is still, therefore, a fruitful avenue. Verbal descriptors may have a place in the presentation of side effect risk as they can break up long lists of side effects into more manageable sections based on frequency of occurrence; this possibility should be researched. Furthermore, verbal descriptors can convey the inherent uncertainty of risk descriptors and the variations in incidence rates across clinical trials. Finally, some people are more comfortable with verbal descriptors than numerical information, which can be seen as complex and difficult.

Limitations

One limitation of this study is that it used a hypothetical scenario, rather than recruiting patients who were actually taking tamoxifen. However, the CancerHelp UK website is aimed at individuals looking for information about cancer and cancer treatment. Many individuals accessing the site currently have cancer and are receiving treatment, and would be motivated to find and understand the information. Figures from a recent survey of CancerHelp UK users in 2007 showed that 21% of visitors to the website were diagnosed cancer patients, 53% were relatives or friends and 7% were the 'worried well' (E. Woolf, personal communication). Visitors to the site may be considering tamoxifen as a future treatment option. Forty percent of the participants in this study reported experiencing at least one side effect, suggesting that for these people the scenario was not entirely hypothetical.

The extent to which the scenario was imaginable is important, not least because of the difference between cancer and other conditions. Patients attach such high value (or utility) to the positive outcome of cancer treatment that a high incidence of side effects might impact less on their decision about taking the medicine than would be the case for many non-cancer treatments. Certainly, the experience of treatment and/or side effects might be expected to impact on ratings of satisfaction with information about medicines, including risk

communication. However, MANCOVA analysis showed no effects of personal experience in this study (although no prior power analysis was conducted to ensure that there were sufficient participants to detect a significant effect).

The characteristics of the sample (i.e. predominantly female; having access to the internet; mostly comprised of people with experience of cancer) mean that the study results might not apply elsewhere. Risk perception by patients for more commonplace medicines and about less life-threatening conditions might be different, although two studies[14,19] in different settings report similar risk perceptions associated with the verbal descriptors tested in this study. However, the study's findings are limited to information provided in a written form – it would be useful for research to evaluate different methods of providing risk information in a spoken form, since patients' priority is for spoken information from health professionals.[3]

Tamoxifen is a medicine used to treat breast cancer and so it is not surprising that study participants were almost all female. Women are also more likely than men to view websites containing health information; for example a recent meta-analysis reports that, among Internet users in the US, three-fifths of women reported looking for such information, while the rate among men was two-fifths.[24]

The study showed no effect of the format of risk communication on perceptions of the benefit of treatment. This warrants further investigation, given the complex nature of risk-benefit decisions taken by patients about treatment.

Finally, the study included only four side effects of tamoxifen, whereas the medicine has at least 25 side effects attributed to it.[25] It is unknown what effect this had on risk or benefit estimates, although it is likely to have contributed to a sense that participants were taking part in a hypothetical or unreal study.

Conclusions

Patients are currently encouraged to play an active and involved role in their healthcare and make informed choices about treatment. Providing patients with information about these medicines is a crucial part of this process. Information about side effects is a significant contributor to influences on decisions regarding whether or not to take a medicine. Previous research has demonstrated the deficiencies in presenting risks as percentages or in verbal terms, and the weakness of verbal terms alone is further supported by this study. The solution of using combined descriptors instead of verbal descriptors alone, as suggested by the MHRA,[12] was not supported unequivocally in this study. There was no evidence that combined descriptors led to an appreciably better understanding of risk than absolute frequencies alone, and combined descriptors were viewed less positively than frequencies alone. However, presentation by frequencies alone will be difficult when there are more than a few side effects to present. The study also showed that, in this context, participants' perceived personal susceptibility to side effects was not different to their perception of the average person's susceptibility. Furthermore, participants who had personal experience of a side effect with this medicine made higher estimates of other side effects occurring, regardless of how risk information was presented. Lastly, as in previous work in this area, this study reported large variation in risk estimates.

Further work is needed to ascertain how we might improve the accuracy of patients' side effect risk estimates, thus improving their ability to make informed decisions about treatment. Improving the manner in which side effect risk is presented is vital if we are to achieve this aim.

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