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Long Term Follow-Up Studies of Users of Nonprescription Medicines Purchased from Community Pharmacies

Some Methodological Issues

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Abstract

Background: Despite the wider availability of medicines to the general public, little is known about their safety when supplied without prescription. Pilot work has already tested 4 methods of recruiting users of ibuprofen purchased from community pharmacies. This paper describes the piloting of a fifth method (a shortened questionnaire), long term follow-up rates of all methods, consistency of reporting of ibuprofen use, and issues relating to possible comparison groups in pharmacovigilance studies.

Methods: A shortened version of a previously tested recruitment questionnaire was used. Eligible study participants were all users, aged over 17 years, purchasing ibuprofen from a research network of community pharmacies (n = 61) in Grampian, Scotland. Postal questionnaires were sent at 1 week and 2, 6 and 12 months irrespective of the method of recruitment. The follow-up questionnaires collected information about ibuprofen and other drug usage, symptoms and associated health service utilisation.

Results: The shortened form recruited 67% of people issued with a questionnaire. The overall 12-month follow-up rate was 67%, although there were important differences in the rates by method of recruitment. There was reasonable consistency in the reporting of use or non-use of ibuprofen at different follow-up times. In the 12 months after the index purchase, 17% of participants never used any ibuprofen (non-users) and 28% used it for more than 8 weeks in total (long term users). At 12 months, long term users were significantly more likely than short term users (≤8 weeks total use) or non-users to have experienced dizziness, skin rash, itchy skin and wheeziness in the previous week.

Conclusions: Our pilot work has confirmed the feasibility of recruiting, and following-up over prolonged periods, users of nonprescription medicines. Evidence of long term use of ibuprofen confirms the need for pharmacovigilance studies of this drug, although further work is required to identify a suitable comparison group in order to inform the interpretation of such investigations.

Background

Self-care and self-medication are increasingly encouraged by governments for the management of minor ailments. Despite the increasing range of potent medicines previously restricted to prescription-only use and the ensuing growth in the nonprescription medicine market,[1,2] self-care remains an under researched area.[3-6] As with all drugs, the safety of nonprescribed medicines is dependent on appropriate use (correctly indicated, not contraindicated and no drug interactions) and appropriate dosage. However, there are methodological issues associated with conducting research into why and how people use nonprescribed medicines. Particular issues include study participant recruitment, the feasibility of long term follow-up, consistency of patient self-reporting and the identification of an appropriate comparison group in order to inform the interpretation of pharmacovigilance studies. Site of purchase is also important; individuals purchasing nonprescription medicines from community pharmacies probably differ from those purchasing the same products (when available) from other retail outlets such as supermarkets or garages. However, the recruitment of individuals from nonpharmacy sites presents particular challenges, which, arguably, are best left until other methodological issues have been resolved.

We have developed a community pharmacy research network of 61 pharmacies (50% of all those available) in Grampian, Scotland, whose staff have shaped and refined pilot pharmacovigilance work using community pharmacy purchased over-the-counter (OTC) ibuprofen as a model.[7,8] Previous pilot studies assessed different methods for recruiting people buying ibuprofen for their own use:[7]

- method 1: insertion of recruitment questionnaire in the shop bag of eligible customers
- method 2: explanation of study and request to complete a recruitment questionnaire. The questionnaire is taken away from the pharmacy for completion
- method 3: explanation of study and completion of recruitment questionnaire in the pharmacy
- method 4: explanation of study and completion of recruitment questionnaire in the pharmacy plus request to complete a 7-day diary for the following week.[7]

Although no method was particularly time consuming (method 4 being the most time consuming, taking 2 minutes 50 seconds) another pilot study (detailed here) was undertaken to assess a fifth recruitment method – a shortened postcard format of the recruitment questionnaire to be completed by all users. This provided the opportunity to assess the feasibility of recruiting users via proxy sales (i.e. sales when the medicine was purchased on behalf of another person who intended using the drug).

Irrespective of the method of recruitment, each group of participants has been followed up at 1 week and 2, 6 and 12 months, using very similar questionnaires which asked about patterns of medicines used (including OTC ibuprofen) and symptoms experienced at different time points. We have already reported evidence of contraindicated use, and of long term and excessive use of ibuprofen, identified by baseline and 1-week follow-up questionnaires in the earlier pilot studies.[7,8] Information about reported symptoms, however, was of limited value because of the lack of an appropriate comparison group. Some participants stated at recruitment that they had purchased the ibuprofen for future use,[7,8] and on subsequent follow-up did not indicate any use of this medicine. The reported frequency of symptoms amongst this group of apparent nonusers of ibuprofen, therefore, might represent the 'background' level of symptoms in the community.

This paper describes the recruitment rate of method 5; follow-up rates for each recruitment method at 1 week and 2, 6 and 12 months after recruitment; consistency of self-reported ibuprofen use (comparing data given at 6 and 12 months); patterns of ibuprofen use during the 12-month follow-up period; and level of symptoms in the previous week experienced at 12 months among short term and long term users of ibuprofen compared with non-users.

Methods

The study was approved by the Joint Ethical

Committee of Grampian Health Board and the University of Aberdeen.

Individuals eligible for recruitment for this new pilot study were aged over 17 years, able to give informed consent, and who purchased themselves (or had purchased on their behalf) a tablet or capsule form of ibuprofen (excluding compound products). The shortened postcard format questionnaire, shown in figure 1, sought written consent and information about the index purchase: product name and strength, whether the respondent purchased the product themselves, whether the questionnaire was completed in the pharmacy or at home and the respondent's name and address.

In February 1999, the 61 network pharmacies were each sent a recruitment pack. An information sheet highlighted the need for objectivity and consistency in recruitment, and emphasised the importance that all members of staff involved in selling ibuprofen be familiar with recruitment procedures and study documentation before starting the pilot. Pharmacies were asked to recruit all eligible users of OTC ibuprofen, including proxy sales (in which case the actual purchaser of the drug was told about the study and asked to give the information sheet and postcard questionnaire to the person on whose behalf they were purchasing the ibuprofen). The recruitment pack also contained a training card with answers to questions and concerns which had been raised by pharmacy staff during network meetings, a pharmacy logbook, 6 sets of recruitment documentation [patient information sheet and freepost (reply paid) postcard questionnaire] and 6 'Ibuprofen Study' labels which could be attached to the counter, the till or beside the stocks of ibuprofen to remind staff of the project. Pharmacies were asked to commence recruitment on 1 March 1999 and continue recruitment until either all 6 recruitment sets were used or until 7 March 1999 (giving a maximum recruitment period of 7 days). The logbook was used to record all eligible sales of ibuprofen, provide brief details of eligible customers not recruited (gender, reason why not recruited), estimated time involved in recruiting patients, and the person making the sale of OTC ibuprofen (pharmacist or assistant). Pharmacies were asked to return their logbooks and any unused recruitment postcards at the end of the recruitment period.

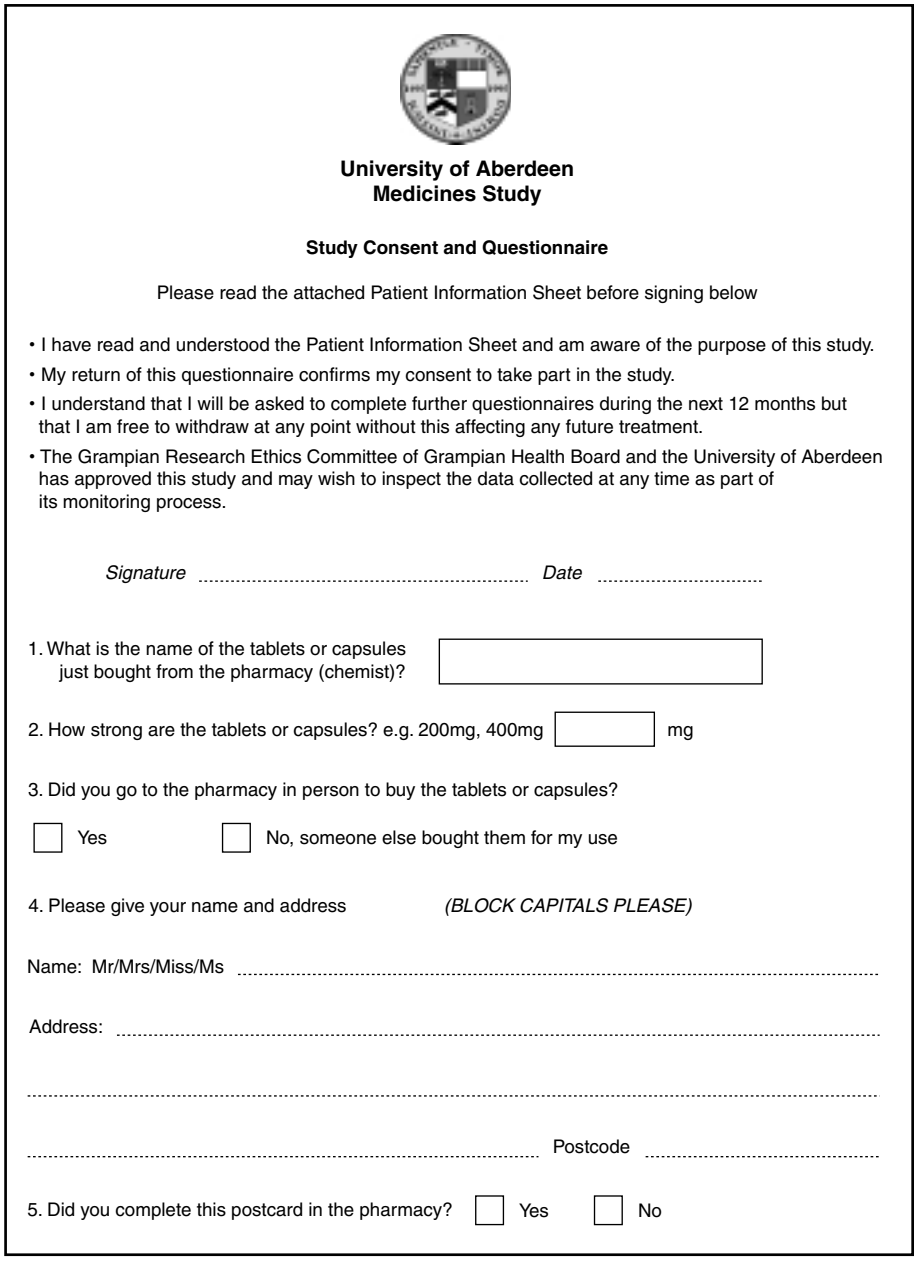
Follow-up postal questionnaires collected demographic data and self-reported information on ibuprofen usage, reason why the drug was purchased, concurrent medication, symptoms experienced and health service utilisation. At each stage, a personalised covering letter, signed by the project coordinator, reminded the participant of their purchase of ibuprofen and their agreement to participate in the study. Nonrespondents were reminded after 2 and 4 weeks with a duplicate questionnaire and reply paid envelope.

SPSS© for Windows[9] was used for data storage, to calculate descriptive statistics and to determine whether there were any important differences between various subgroups. Categorical data were described as percentages and compared using the chi square test. The total number for each variable varied slightly because of missing data. All records and computer data were handled and stored to protect patient confidentiality; no details of individual study participants were released to the pharmacies or any other third party. No pre-study power calculations were carried out because of the pilot nature of the study.

Results

Recruitment Rate for the Shortened Questionnaire

49 of the 61 network pharmacies contributed to this further pilot work. Reasons for not participating included: staff changes, being too busy, forgetting about the study and the pharmacist being on holiday during the recruitment week. From the returned unused recruitment postcards and the logbooks an estimated 276 eligible sales were made, with 227 recruitment postcards given out and 153 completed, a recruitment rate of 55.4% of eligible sales and 67.4% of questionnaires issued. On average, each recruitment took an estimated 1 minute 14 seconds of pharmacy time to complete. The log-



University of Aberdeen
Medicines Study

Study Consent and Questionnaire

Please read the attached Patient Information Sheet before signing below

- I have read and understood the Patient Information Sheet and am aware of the purpose of this study.
- My return of this questionnaire confirms my consent to take part in the study.
- I understand that I will be asked to complete further questionnaires during the next 12 months but that I am free to withdraw at any point without this affecting any future treatment.
- The Grampian Research Ethics Committee of Grampian Health Board and the University of Aberdeen has approved this study and may wish to inspect the data collected at any time as part of its monitoring process.

Signature ..... *Date* .....

1. What is the name of the tablets or capsules just bought from the pharmacy (chemist)? ☐

2. How strong are the tablets or capsules? e.g. 200mg, 400mg ☐ mg

3. Did you go to the pharmacy in person to buy the tablets or capsules?

☐ Yes ☐ No, someone else bought them for my use

4. Please give your name and address *(BLOCK CAPITALS PLEASE)*

Name: Mr/Mrs/Miss/Ms .....

Address: .....

.....

..... Postcode .....

5. Did you complete this postcard in the pharmacy? ☐ Yes ☐ No

Fig. 1. Shortened postcard format recruitment questionnaire.

books showed that the most common reason for pharmacy staff not to issue a recruitment form to an eligible customer was the customer was not interested in the study or declined to participate (n = 21), followed by the pharmacy staff were too busy (n = 8).

Most participants purchased the ibuprofen themselves [91.3%; 137 of 150 (of whom 35 were men and 102 were women)] although 8.7% (13 of 150 of whom 6 were men and 7 were woman) had the medicine purchased for them. Most completed the postcard in the pharmacy, (85.0%; 130 of 153). The most common reason given by customers for not completing the postcard in the pharmacy was a preference to complete it at home (n = 46), followed by being too busy (n = 17).

Study Participant Characteristics

As previously reported, there were no statistical differences in the characteristics (gender, age, smoking habits, alcohol consumption and socioeconomic status) of study participants recruited by the 5 different methods.[8]

Follow-Up Rates of All Methods

A total of 555 individuals were recruited by the different methods tested in the different pilot studies (fig. 2). 33 of the 555 study participants were lost to follow-up during the 12 month period: 11 at 1 week, 3 at 2 months, 10 at 6 months and 9 at 12 months. The overall response rates were 81.4% at 1 week (already reported),[8] 77.8% at 2 months, 70.29% at 6 months and 67.0% at 12 months. However, at each time point, those recruited using method 1 were the most likely to respond while those recruited by method 4 were significantly less likely to respond (fig. 1) ($p < 0.001$ at each time point).

Consistency of Reported Ibuprofen Use

At the 6-month follow-up, 81.0% of the study participants (302 of 373) reported that they had taken some ibuprofen during the previous 6 months. At 12 months, 82.5% of the study participants (288 of 349) reported that they had taken some ibuprofen during the previous 12 months.

A total of 316 study participants provided information at both 6 and 12 months about ibuprofen use since their index purchase. As detailed in figure 3, 76.9% reported at both 6 and 12 months that they had taken ibuprofen and 10.8% that they had not taken any ibuprofen; 7.0% reported they had not taken any ibuprofen by 6 months but had taken it by 12 months. 5.49% of respondents reported at 6 months that they had taken ibuprofen although at 12 months they stated that they had not taken any ibuprofen since their index purchase.

Patterns of Over-the-Counter Ibuprofen Use: 12 Months

Those who reported having used any ibuprofen were asked about the total length of use during the previous 12 months and to indicate whether they used the drug either continuously (i.e. every day), regularly (i.e. a few days each month) or occasionally (e.g. for a few times for a sports injury). A third of respondents (33.7%) had used ibuprofen for less than a week, 29.1% for 1 to 4 weeks, 8.8% for 5 to 8 weeks and 28.4% for more than 8 weeks (table I). Half (51.2%) used ibuprofen occasionally, a third (36.1%) regularly and 12.6% continuously. Those who used ibuprofen for the longest periods (>20 weeks) were more likely than those who had used it for shorter periods to use it regularly or continuously with 11 respondents reporting that they had used it continuously for over 20 weeks during the 12-month study period ($p < 0.001$).

Symptoms Experienced in Different Groups

The 12-month questionnaire respondents were asked 'Please think about the last week. Consider each of the following symptoms. During the last week have you experienced the symptom and if so, sought advice about it?' [Symptoms listed: dyspepsia (acid indigestion), heartburn (acid brash), nausea (feeling sick), vomiting, abdominal pain, diarrhoea (loose motions), constipation, headache, dizziness, palpitations (racing heart), skin rash, itchy skin, malaise (feeling off colour), wheeziness, others – please specify.] The respondents were not asked to differentiate between symptoms from illness or those due to drug adverse effects. Table II compares the symptoms experienced by those who had not used ibuprofen during the 12-month follow-up period since the index purchase (non-users) with those who had used ibuprofen for

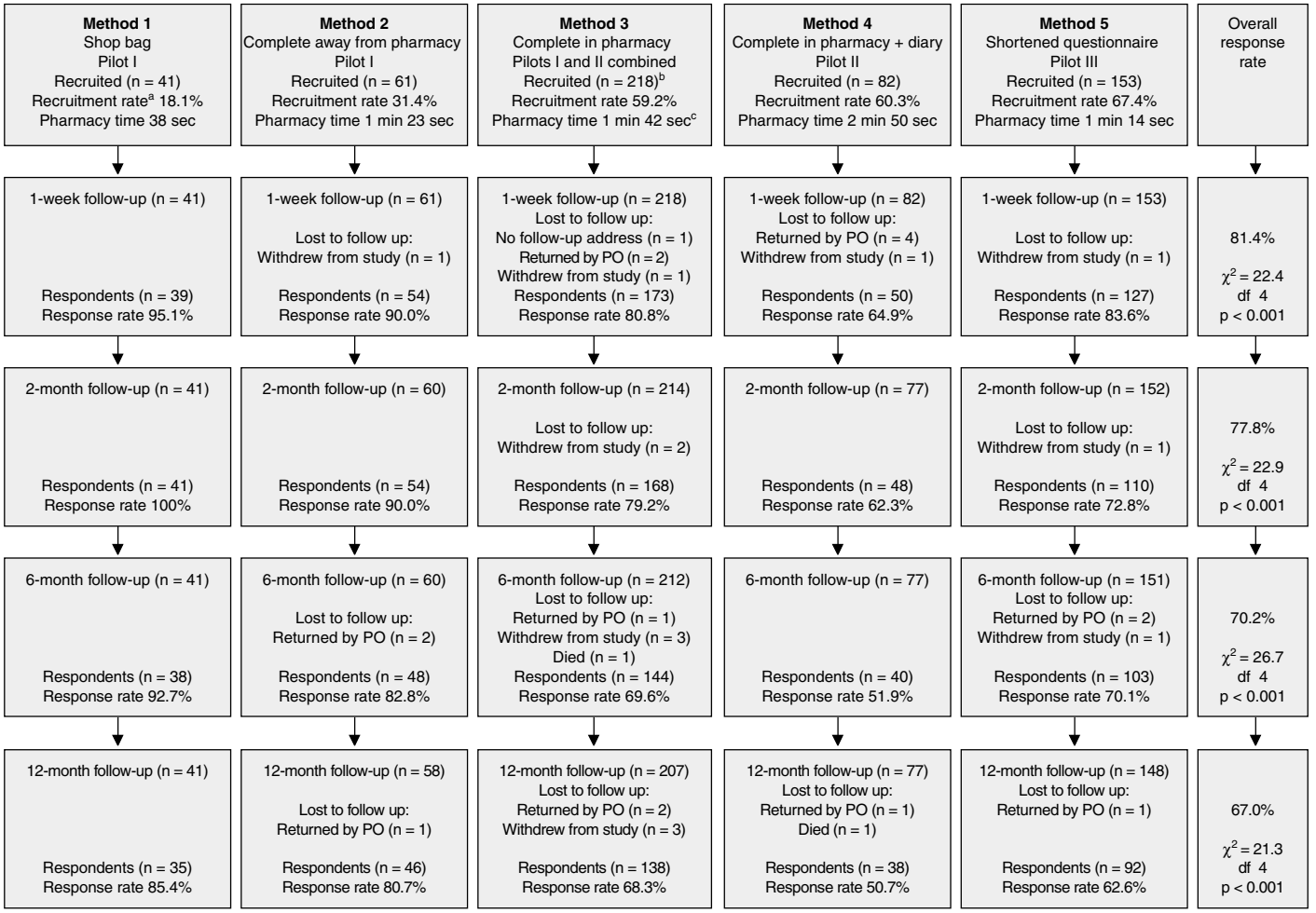


Fig. 2. Postal questionnaire follow-up. a = Recruitment rate based on number of questionnaires issued; b = Recruits had been used in 2 previous pilots and therefore the number of recruits is greater than the number for other methods; c = The average time over 2 previous pilots. **df** = degrees of freedom; **PO** = post office.

a total duration of 8 weeks or less (short term users) and those who had taken it for more than 8 weeks (long term users). Non-users were significantly less likely than short term and long term users to have experienced headaches in the previous week. Long term users were significantly more likely than short term users and non-users to have experienced dizziness, skin rash, itchy skin and wheeziness. Short term users were least likely to have experienced heartburn or wheeziness.

Discussion

Recruitment

Our pilot work aimed to recruit a cohort for follow-up of individuals obtaining ibuprofen by purchases from community pharmacies. We were particularly interested in assessing the feasibility of recruiting, and following up for prolonged periods, such individuals, using a variety of methods of differing complexity. Although this new pilot did not recruit all eligible customers, the shortened postcard format improved on our previous best rates,[7] recruiting 67.4% of individuals given the postcard. The method was also less time consuming.

In our earlier studies, proxy sales were excluded from the sample. In this new pilot, 9% of recruits were from proxy sales and although numbers were small, almost half these were for men. Other community pharmacy studies have shown that men, particularly younger men, are infrequent attenders of pharmacies, so methods to identify and follow-up their proxy use of services are important (if only to avoid sampling bias even if the absolute number of users is low). Many other factors contribute to recruitment problems in the community pharmacy setting. For example, some customers find follow-up potentially threatening;[10] the doctor-patient relationship differs from that of the pharmacist-customer,[11,12] so customers may feel less inclined to accept a pharmacist's invitation to join a study; pharmacies do not have exclusively registered populations; the pharmacist-customer relationship can be commercially sensitive;[10] community pharmacies often lack privacy;[13,14] and time constraints (for both patients and pharmacy personnel) can be a problem.[7]

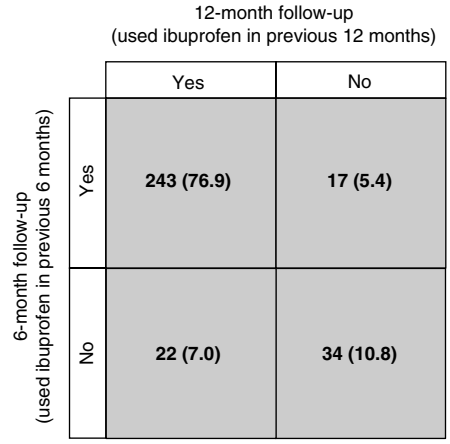


Fig. 3. Consistency of reported ibuprofen use: self-reported use since index purchase at 6- to 12-month follow-up; n (%).

Response Rates

Although Sibbald et al.[15] note the value of postal questionnaires, response rates need to be good since a poor response can render the results worthless.[15,16] There is much debate as to what constitutes an acceptable response rate. Moser and Kalton[17] quote a response rate of 20 or 30% as constituting 'a dangerous failing', while the Pharmacy Practice Research Resource Centre recommend a minimum response rate of 66%.[18]

Factors which influence the response rate include the perceived relevance of the questionnaire, number of reminders, the study participant's perceptions of the research team, and the length of the questionnaire.[7,15,16] Our strategies to maximise response rates included personalised correspondence on university headed paper, use of reply paid envelopes, and the use of 2 reminders to nonrespondents. Although there was a downward trend in response rates over time, two-thirds of all recruited individuals were still responding a year after joining the study. Our strategies therefore were effective, demonstrating that pharmacovigilance studies of nonprescribed medicines are feasible.

Table I. Patterns of ibuprofen use [n (%)][a]

Total use in past 12 months	Overall	Pattern of use			χ^2	df	p-Value
		continuously[b]	regularly[c]	occasionally[d]			
Overall		36 (12.6)	103 (36.1)	146 (51.2)			
<1 week	96 (33.7)	5 (5.2)	20 (20.8)	71 (74.0)			
1-4 weeks	83 (29.1)	10 (12.0)	25 (30.1)	48 (57.8)			
5-8 weeks	25 (8.8)	5 (20.0)	10 (40.0)	10 (40.0)			
>8 weeks	81 (28.4)	16 (19.7)	48 (59.3)	17 (21.0)			
≤20 weeks	238 (83.5)	25 (10.5)	74 (31.1)	139 (58.4)			
>20 weeks	47 (16.5)	11 (23.4)	29 (61.7)	7 (14.9)	29.85	2	<0.001

a Study population = 285 study participants.

b Every day.

c A few days each month.

d For example, for a few times for a sports injury.

df = degress of freedom.

These overall response results however mask significant differences in follow-up between the 5 methods of recruitment tested during our series of pilots. The addition of a 7-day diary in an earlier pilot resulted in significantly more recruitment questionnaires being completed in the pharmacy and more assistance being provided by pharmacy staff.[7] This additional input may have coerced some people into joining the study and may account for the lower follow-up rates.[7] In contrast, participants recruited using the shop bag method (i.e. with the least input from pharmacy staff) had the highest follow-up rates. The shortened postcard format described in this paper achieved the best recruitment rate, while still obtaining an acceptable follow-up rate: 63% at 12 months.

Consistency of Reported Ibuprofen Use

Previous pilot work showed there was agreement between 1-week drug dose data collected prospectively in a diary and that collected retrospectively in a questionnaire.[7] In this paper, we found unaccountable inconsistencies in data supplied at 6 and 12 month follow-up in 5% of individuals. This suggests that self-reported information is a potential source of data for drug safely studies of OTC medicines, at least for recent exposures.

Patterns of Ibuprofen Use

At OTC doses, ibuprofen might be better tolerated than aspirin (acetylsalicylic acid) and as well tolerated as paracetamol (acetaminophen).[19] Nonetheless, a recent meta-analysis of studies examining the effects of long term (≥2 months) use of nonsteroidal anti-inflammatory drugs (NSAIDs) estimated that NSAIDs are the cause of death in about 2000 people each year in the UK through gastric complications.[20] Although the meta-analysis did not differentiate between products, and ibuprofen may be less harmful than other NSAIDs, many would advocate caution in the long term use of all NSAIDs (especially when used in an unregulated environment). We found that 28% of participants in our pilot studies used ibuprofen for more than 8 weeks; with 17% using it for over 20 weeks during the previous 12 months, many regularly or continuously.

Appropriate Comparison Group

Pharmacovigilance studies require data against which the experiences of users of a particular medicine can be compared. In these pilot studies we did not recruit a comparison group because we were testing the feasibility of different recruitment methods. It is impossible, therefore, to say whether the observed frequency of symptoms amongst ibuprofen users is the result of the effects of the drug,

Table 2 to go here

symptoms associated with the condition for which participants bought ibuprofen or were simply symptoms which occur frequently in the community anyway. There are, however, difficulties in determining what might represent an appropriate comparison group. By 12 months, 17% of participants reported that they had not used any ibuprofen since joining the study. Although this maybe an unusual subgroup, and may have a different background frequency of events to the rest of community pharmacy recruited ibuprofen purchasers, their pattern of symptoms may represent the 'background' incidence of symptoms in the community. In contrast, 28% of those who reported having used ibuprofen since joining the study were long term users (i.e. had used it for more than 8 weeks in total). At the 12-month follow-up point, these long term users were more likely than short term users and non-users to have experienced a number of symptoms during the previous week. The comparison between long term users and non-users is presumably comparing ill with well individuals, whereas the comparison between short and long term users presumably compares more seriously ill with less seriously ill individuals. Our finding that non-users were more likely than short term users to have experienced heartburn and wheeziness may reflect careful assessment of OTC purchasers by pharmacists and their staff, or compliance with the product information which warns against use by those with a history of gastrointestinal disease or asthma.

The UK Medicines Control Agency uses proportional reporting ratios to compare proportions of suspected adverse drug reactions among different users of drugs or groups of drugs.[21] Another approach could be to recruit users of different OTC analgesics (e.g. ibuprofen, paracetamol and aspirin) to determine the frequency of symptoms experienced by users of each preparation at different points in time. Provided that the user (e.g. age, gender) and use (e.g. type of condition used for, frequency of use) profiles for different products are similar, it would be reasonable to compare the frequency of symptoms in different groups and so identify differences between products. Ideally,

Table II. Symptoms experienced during previous week at the 12 month follow-up: study participants who reported that they had never used any ibuprofen in the 12 months since joining the study *vs* ≤8 weeks total duration of ibuprofen use *vs* >8 weeks total use

Group	Symptom [no. of patients (%; 95% confidence interval)]													
	dyspepsia	heartburn	nausea	vomiting	adominal pain	diarrhoea	constipation	headache	dizziness	palpitations	skin rash	itchy skin	malaise	wheeziness
Non-users (n = 59)	6 (10.2; 3.8 to 20.8)	9 (15.3; 7.2 to 27.0)	2 (3.4; 0.41 to 11.7)	0 (0.0; 0.00 to 0.06)	5 (8.5; 2.8 to 18.7)	4 (6.8; 1.9 to 16.5)	1 (1.7; 0.04 to 9.1)	11 (18.6; 9.7 to 30.9)	4 (6.8; 1.9 to 16.5)	2 (3.4; 0.41 to 11.7)	1 (1.7; 0.04 to 9.1)	6 (10.2; 3.8 to 20.8)	4 (6.8; 1.9 to 16.5)	5 (8.5; 2.8 to 18.7)
Short term users (n = 201)	23 (11.4; 7.0 to 15.8)	17 (8.5; 5.0 to 13.2)	23 (11.4; 7.0 to 15.8)	3 (1.5; 0.3 to 4.3)	27 (13.5; 8.7 to 18.1)	26 (12.9; 8.3 to 17.6)	20 (10.0; 6.2 to 14.9)	82 (40.8; 34.0 to 47.6)	13 (6.5; 3.5 to 10.8)	5 (2.5; 0.81 to 5.7)	15 (7.5; 4.2 to 12.0)	29 (14.4; 9.6 to 19.3)	25 (12.4; 7.9 to 17.0)	7 (3.5; 1.4 to 7.0)
Long term users (n = 80)	10 (12.5; 6.2 to 21.8)	11 (13.8; 7.1 to 23.3)	12 (15.0; 8.0 to 24.7)	2 (2.5; 0.3 to 8.7)	4 (5.0; 1.4 to 12.3)	11 (13.8; 7.1 to 23.3)	5 (6.3; 2.1 to 14.0)	39 (48.8; 37.4 to 60.2)	13 (16.3; 8.9 to 26.2)	9 (11.3; 5.3 to 20.3)	12 (15.0; 8.0 to 24.7)	20 (25.0; 16.0 to 35.9)	15 (18.8; 10.9 to 29.0)	12 (15.0; 8.0 to 24.7)
χ^2	0.18	3.06	4.88	Not valid	4.70	1.91	4.69	13.86	7.17	Not valid	8.34	6.62	4.43	11.79
df	2	2	2		2	2	2	2	2		2	2	2	2
p-Value	0.91	0.22	0.087		0.096	0.38	0.096	0.001	0.028		0.015	0.037	0.109	0.003

df = degrees of freedom.

such comparisons would involve the recruitment of enough users that subgroups of individuals using products for particular problems (e.g. cold or flu) can be compared directly.

Although ideally a comparison group should be found, we may have to accept that we cannot always find a suitable comparator; therefore new ways of analysis should be developed to advance pharmacoepidemiology research.

Conclusion

Our pilot work has confirmed the feasibility of recruiting, and following-up long term, users of non-prescription medicines. Evidence of long term use of ibuprofen confirms the need for pharmacovigilance studies of this drug, although further work is required to identify a suitable comparison group in order to inform the interpretation of such investigations.

Acknowledgements

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