Development and preliminary validation of an instrument to enable laypersons to assess suspected side effects from medicines

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Development and preliminary testing of an instrument to facilitate causality assessment of suspected side effects from medicines by lay persons.

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Keywords:	adverse drug reactions, causality assessment, patient experience, side effects

Abstract:	Abstract Purpose: Research into causality assessment tools enabling patients to assess suspected adverse drug reactions (ADRs) is limited. Supporting patients with tools could improve their confidence in discussions with health professionals and encourage reporting of suspected ADRs to regulators. This study describes development and preliminary evaluation of an instrument: Side Effect Patient ASsessment Tool (SE-PAST). Methods: SE-PAST was developed from survey and interview data involving patients experiencing suspected ADRs. It included 10 statements enabling causality assessment, covering timing, additional information sources and experiences, with four options: yes/no/don't know/not applicable. Scoring and weighting resulted in four categories of causal association: highly probable, probable, possible, unlikely. Validation involved obtaining feedback from 31 individuals experiencing an ADR. Evaluation involved on-line distribution through patient support groups and comparison of reported symptoms to known ADRs. Results: Validators found SE-PAST easy to read (31), to understand (27) and complete (29). 294 respondents completed SE-PAST on-line, with 98% completing eight or more causality assessment statements. Symptoms were categorised as: highly probable (46; 16%), probable (80; 62%), possible (44; 15%) and unlikely (21; 7%). 221 identified one suspected medicine, with 95% of these reporting at least one symptom known to be an ADR. Of 227 providing feedback, 139 (61%) found SE-PAST useful, 160 (71%) felt motivated to discuss their experience with a health professional and 136 (60%) were encouraged to report to regulator.

	Conclusion: SE-PAST was easily completed and understood by people experiencing suspected ADRs and could be useful in encouraging patient reporting to health professionals and agencies

Development and preliminary testing of an instrument to facilitate causality assessment of suspected side effects from medicines by lay persons.

Running head: Development of causality assessment instrument for lay persons

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Key words: adverse drug reactions; causality assessment; patient experience; side effects

Key points:

- An instrument – the Side Effect Patient ASsessment Tool (SE-PAST) - was developed to enable lay persons to assess suspected side effects
- The primary purpose of the SE-PAST was to empower patients in their use of medicines and consultations with health professionals
- The SE-PAST was validated amongst people who had experienced a suspected side effect(s) from a medicine
- The majority of participants found the SE-PAST easy to use and a potentially useful healthcare tool
- Further work is required to confirm its reliability/validity and to determine its ability to improve consultations with health professionals

Word count: 3328

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Abstract

Purpose: Research into causality assessment tools enabling patients to assess suspected adverse drug reactions (ADRs) is limited. Supporting patients with tools could improve their confidence in discussions with health professionals and encourage reporting of suspected ADRs to regulators. This study describes development and preliminary evaluation of an instrument: Side Effect Patient ASsessment Tool (SE-PAST).

Methods:

SE-PAST was developed from survey and interview data involving patients experiencing suspected ADRs. It included 10 statements enabling causality assessment, covering timing, additional information sources and experiences, with four options: yes/no/don't know/not applicable. Scoring and weighting resulted in four categories of causal association: highly probable, probable, possible, unlikely.

Validation involved obtaining feedback from 31 individuals experiencing an ADR. Evaluation involved on-line distribution through patient support groups and comparison of reported symptoms to known ADRs.

Results:

Validators found SE-PAST easy to read (31), to understand (27) and complete (29). 294 respondents completed SE-PAST on-line, with 98% completing eight or more causality assessment statements. Symptoms were categorised as: highly probable (46; 16%), probable (80; 62%), possible (44; 15%) and unlikely (21; 7%). 221 identified one suspected medicine, with 95% of these reporting at least one symptom known to be an ADR.

Of 227 providing feedback, 139 (61%) found SE-PAST useful, 160 (71%) felt motivated to discuss their experience with a health professional and 136 (60%) were encouraged to report to regulator.

Conclusion:

SE-PAST was easily completed and understood by people experiencing suspected ADRs and could be useful in encouraging patient reporting to health professionals and agencies.

Development and testing of an instrument to facilitate causality assessment of suspected side effects from medicines by lay persons.

Introduction

Adverse drug reactions (ADRs) are common and can severely impact on peoples' daily lives.[1] ADRs are all types of undesired effects caused by medicine - these unintended effects are sometimes referred to as side effects.[2] While ADRs are always negative, side effects can be predicted and include beneficial as well as harmful effects. The terms ADRs and SE are frequently used interchangeably in patient information. While patient adherence to medicines is essential for positive health outcomes, consistent patient adherence can be difficult to achieve.[3,4] ADRs have been identified as one of the most important barriers to patients' adherence.[3,5] Yet studies suggest that, for some people, suspected adverse effects they raise with health professionals are dismissed.[6,7] Person-centredness in healthcare is increasingly advocated[8,9], which requires exploration and acknowledgement of individuals' personal experiences. Facilitating individuals to describe their experiences of ADRs could enable useful discussions with health professionals about treatments and provide medicine regulators with valuable data to improve public health. Health professionals also need to recognise individuals' ability to identify ADRs for themselves, in order to appreciate the impact these may have on daily life and on future adherence to medicines.

Several studies have illustrated the mechanisms used by lay people to identify ADRs, and proposed a framework for understanding these.[10,11,12] People use five cognitive domains to help identify ADRs, based on the Self-Regulation model of health behaviour: identity; timeline;

cause; consequences and control. Using these, a cognitive schema which facilitates evaluation and identification of symptoms potentially caused by a medicine has been described: identity (symptoms/label); cause; timeline; consequences and cure.[11] This framework provides insight into patient experience and can highlight the impact which ADRs have on their lives.[11,13,14] People use their previous personal health experiences or knowledge of others' experiences[11] and timing of symptoms in relation to medicines use to identify ADRs.[15,16] The majority employ temporal associations to link symptoms to medicines and display knowledge and accuracy in identifying experiences as ADRs. Some use additional information from a range of sources, such as patient information leaflets (PILs), supplied with all dispensed and purchased medicines in the EU, to confirm suspected ADRs.[17] These fundamental processes for assessing causality parallel those employed by healthcare professionals[16] and suggest that a standardised method could be effectively used by lay people to carry out a coherent causality assessment.

Causality assessment is an essential function of pharmacovigilance centres where standardised, highly structured methods are used. Instruments available for assessing causality are however designed for use by professionals working in these centres and were not created for use by general clinicians or patients.[18,19] Few patient-focused instruments exist. One instrument for patient self-assessment of ADRs was developed and tested in Thailand[20] where access to sources of medicines information, such as PILs, is very limited.[21] This novel instrument, which incorporated a previously validated checklist of potential side effects from medicines[22], displayed reliable psychometric properties in preliminary testing and received positive evaluations from patients, but has undergone no further testing. A patient-reported adverse drug event (ADE) questionnaire, also incorporating checklists, was developed and validated in the Netherlands[23], designed for use in clinical trials and post-marketing studies, rather than in clinical practice. An assessment tool designed to help patients decide whether

symptoms they experience are linked to their medicines, the RxISK Report, is available on the Canadian RxISK drug safety website.[24] Generic assessment tools such as these could aid patients in deciding whether to report experiences they suspect to be ADRs to health professionals. They may also increase confidence to initiate such discussions, increasing the patient-centredness of consultations. In addition, it may encourage more reporting to national regulatory agencies, which have increasingly advocated and facilitated direct patient reporting.[25] We therefore set out to develop an instrument for this purpose for use in the UK setting.

Objectives

- To develop an instrument to enable lay persons to assess suspected side effects
- To validate the instrument amongst people experiencing a suspected side effect(s)
- To further validate the instrument in a broader population
- To determine the perceived usefulness of the assessment instrument

Methods

Ethical issues

Study approval was obtained from the [Anonoymised for review (REF xx)]. Comprehensive information describing the purpose of the study was provided and the on-line survey potential participants were required to access this information prior to completing the instrument. Written consent was obtained for interviewees.

Instrument development

The instrument developed was based on the Self-Regulation Model of Health Behaviours [26,27] and the Thai patient causality assessment tool.[20] Findings of two further studies involving patients in England who had experienced an ADR were also utilised: a survey exploring information sources used to find out about ADRs[28] and in-depth interviews exploring in detail the cognitive processes used to identify and confirm ADRs.[28] The term 'side effect(s)' was selected for use in the instrument as inclusive wording that would be more familiar to respondents than ADR and that would encourage reporting of mild/minor effects. For the purpose of this paper the terms 'ADRs' and 'side effects' are used interchangeably.

The instrument, Side Effect Patient ASsessment Tool (SE-PAST), comprised:

Section A – Background information, describing suspected ADR experience, medicines being used, suspected causative medicine, allergies and medical conditions, open/closed questions covering timing, impact on daily life (four-point scale: none, mild, moderate, severe). Basic demographic questions - gender, age group and education level - were included to enable an assessment of the population using the instrument.

Section B – Self-assessment tool with ten statements, with four possible responses ('Yes', 'No', 'Don't know', 'Not applicable'), with a scoring system to calculate a score, which could be categorised using a probability key. Scores were assigned to one of four degrees of causal association: highly probable, probable, possible, unlikely. The format of the tool was similar to the Naranjo algorithm, due to its simplicity. The weighting of the score for each statement was also based on the Naranjo algorithm.[29]

Validation processes

Face validity was assessed by three pharmacist members of the research team, then by members of a public engagement group. The latter were asked to provide feedback on

instrument content and format. Following this, minor format amendments were made and the instrument was validated with adult English residents who had experienced a suspected ADR. These consisted of (i) interviewees from the study which informed the instrument development[28] and (ii) members of the public known to the research team who had experienced an ADR. All completed a paper copy of the instrument, then provided feedback on its' structure, clarity, and usability, their general opinion and any suggestions for improvement. Participants could provide feedback by returning a form by post, or through telephone interview, both covering the same questions. No personal identifiable information was recorded.

An electronic version of the instrument was then developed for online distribution using Qualtrics®. This assigned scores automatically to each response and calculated the score, avoiding the need for respondents to do so. To assess the potential value of the instrument, participants completing the SE-PAST were invited to respond to additional questions covering its usefulness and its potential for encouraging them to report their suspected side effect to the UK regulatory authority or talk to a health professional about it. All responses were anonymous.

Patient support groups/organisations with a record of encouraging patient engagement and supporting health self-management were approached via email to post a recruitment statement with a link to the instrument on their website. The link remained open for five months (April 2016-August 2016).

Data analysis

Data from the online survey were downloaded into SPSS for Windows V23 for analysis. Simple descriptive statistics were used to report patient characteristics. Medicines suspected as

having caused reported suspected ADRs were classified into major therapeutic areas according to the British National Formulary (BNF version 72). To assess external validity, symptoms reported were assessed by review of the Summary of Product Characteristics available on-line for the reported suspect medicine (www.emc.org) and, if not found, in published case reports. The ten causality assessment statements were assessed for internal consistency using Cronbach's alpha, accepting a value of 0.7 as indicating acceptable consistency. Missing statements in the causality assessment tool were assigned a value of 0 (equivalent to don't know/does not apply) to enable calculation of probability levels for all respondents. Chi-squared test was used to assess the relationship between completion of statements and probability level, utilising a statistical significance level of $p \leq 0.05$.

Free-text descriptions of suspected side effect experiences were transferred into Excel and categorised using a simple coding frame covering impacts and methods of identification.

Results

Initial validation

There were 31 individuals who took part in the initial face and content validation of the SE-PAST, 11 were interviewees from a previous study and 20 were members of the public known to the research team. A majority were female (21; 68%) 14 were aged 50 or below, 11 aged 51 to 70 and six were over 70. Just over half were university educated (16; 52%). The time taken to complete the entire instrument ranged from five to forty-five minutes, but 24 (70%) completed it in less than 15 minutes. All 31 judged the instrument easy to read, 87% (27) easy

to understand, 97% thought it was clearly laid out and only one thought it was too long. Following this only changes to the initial instructions were made, to improve clarity.

Online survey - Response rates and demographic details

In total 15 patient support groups/organisations were approached via email and seven agreed to post a recruitment statement with a link to the instrument on their website. The SE-PAST instrument was accessed online a total of 761 times during the five month period, with 563 people (74.0%) consenting to participate. Of these, 312 subsequently accessed the instrument, however 18 then indicated in response to the first question that they had experienced no suspected side effects. Of the remaining 294 respondents, the majority were female (208; 71.5%) a high proportion were aged over 60 (185; 63.3%) and 168 (57.9%) were university educated. (Table 1)

<<TABLE 1>>

Side effect experiences

Details of their suspected side effect experience was provided by 294 respondents as free-text comments. These included 255 (86.7%) who described physical symptoms, 46 (15.6%) describing psychological symptoms and 74 (25.2%) describing social impacts (Table 2).

<<TABLE 2>>

Most (292) gave information about when the experience occurred; almost half (136; 49.6%) experienced the suspected in the past six months, while the remaining respondents indicated experiences more than six months previously. All but one rated the severity of their experience; 115 (39.2%) considered it severe, 112 (38.2%) moderate, 55 (18.5%) mild and only 11 (3.7%) as having no impact.

Causality assessment

Most respondents (283) listed their medicines at the time of the suspected side effect; 85 (30.0%) reported using one medicine, while 198 (70.0%) reported using more than one (Table 1). Despite the majority of respondents using multiple medicines, only 24 (8.2%) were unsure what drug had caused the suspected side effect, and 49 (16.7%) reported combined/multiple medicines either within or across therapeutic areas, whereas 221 (75.2%) respondents identified a single medicine they thought had caused their symptom(s). The proportion who cited multiple possible causative medicines increased with the number of medicines reported as being used (Figure 1).

<<FIGURE 1>>

The therapeutic areas were determined for the causative medicines cited by all 221 who cited a single medicine plus a further 14 who cited two medicines in the same therapeutic area. The most frequently cited therapeutic groups of medicines reported to cause side effects were those acting on the cardiovascular system (74; 31.5%), central nervous system (66; 28.1%), and endocrine system (34; 14.5%). Females identified medicines acting on the central nervous system most frequently (59/167; 35.3%), while males most frequently identified medicines acting on the cardiovascular system (37/66; 56.1%).

All ten questions in the causality assessment section were completed by 184 respondents (62.6%), 80 (27.2%) completed nine and 25 (8.5%) completed eight, thus 98.3% completed at least eight statements (Table 3). Three respondents did not complete any of this section. Responses to the causality statements were supported by free-text comments (Table 2).

For the 184 respondents with fully completed responses, 38 (20.7%) experiences were categorised as highly probable, 119 (64.7%) probable, 18 (9.8%) possible and nine (4.9%) unlikely to be an ADR. Imputing scores of 0 (equating to a response of either do not know/does not apply) for missing responses allows estimation of causal association for 291 respondents. Based on all those completing any causality statements, 46 (15.8%) experiences were categorised as highly probable, 180 (61.9%) probable 44 (15.1%) possible and 21 (7.2%) unlikely to be an ADR. Hence completion of all questions increased the likelihood of a higher score ($p<0.001$), and therefore a higher level of probability.

Internal and external validity

Internal consistency measured using Cronbach's alpha was below the acceptable level, at 0.53. External validation, assessed by comparison of reported symptoms to known ADRs as documented in the current Summary of Product Characteristics found that of the 221 who identified one potentially causative medicine, the majority (194; 95.0%) reported at least one known ADR. For 16 respondents (7.2%) none of the symptoms were listed, and a further two respondents described symptoms indicating potential lack of efficacy. For the symptoms described by the remaining nine respondents a judgement was not possible, due to insufficient information.

Perceived value of the instrument

Following completion of the SE-PAST, 227 respondents agreed to answer additional questions on the instrument's value. Of these, 139 (61.2%) found the SE-PAST useful, 136 (59.9%) were encouraged to report their suspected ADR to the relevant agency and 160 (70.5%) felt motivated to discuss their suspected ADR with a health professional.

Discussion

Main findings

The SE-PAST instrument was found to be easy to use, not onerous in terms of time and seen as potentially valuable by a majority of respondents who had experienced a suspected side effect from a medicine. The background information section of the instrument was designed to facilitate recall of the event and record this, while the causality assessment tool facilitated a simple calculation of a probability level for the association with a medicine. Taken together, these details have the potential to enable those who experience a symptom they consider to be related to a medicine to assess for themselves the likelihood that it could be a side effect. This could lead to the provision of relevant information either to a health professional which might lead to treatment changes to reduce the risk of future ADRs, and improve adherence, or to a regulatory agency, adding to the data used to protect public health from the harms of medicines.

Comparison to literature

Although other instruments designed to facilitate self-assessment of symptom causality exist, they do have limitations. The use of symptom checklists, used in both the Dutch and Thai instruments, while facilitating expression of experiences, can result in over-reporting of adverse events. They can create confusion in respondents unable to distinguish between events potentially related/unrelated to medicines. The Thai instrument[20] was tested to ensure that it was clear, consistent and easy for lay persons to use and facilitated them in calculating a probability level. However it required the recall of a large amount of detailed information about their experience, use of information sources and potentially causative medicines, which, given the dispensing practices and lack of medicine information in Thailand, led to recall

difficulties. No weightings were given to the individual statements used in the causality assessment tool, in contrast to standard methods, such as the Naranjo method, on which it was based. This instrument was validated by comparison to information contained within medical records and probability levels were strongly correlated with respondents' perceived certainty of their experience being an ADR. Completion of the instrument did not increase respondents' degree of certainty in the association of the medicine with the suspected side effect, but over 80% considered it helped them to assess their symptom.

The developers of the Dutch instrument concluded that its reliability for facilitating patients in clinical trials to report ADRs was limited and suggested that it required improvement for this purpose.[23] Both this and the Thai instrument did show satisfactory reliability using the test-re-test method, however internal consistency of the Thai instrument was relatively low (Cronbach's alpha = 0.614), similar to that for SE-PAST, while the Dutch instrument was not subjected to this analysis. In reality all these instruments are designed to gather information on actual experiences, rather than attempting to measure traits or behaviours, hence the need for internal consistency can be questioned. External validity of the Dutch instrument assessed by comparison to the Summary of Product Characteristics found that 73% of symptoms were known ADRs[22], lower than was found for the SE-PAST (95%).

However, the purpose of the instrument was primarily to empower patients in their use of medicines and consultations with health professionals, therefore ease of use and appropriate level of content are probably more relevant. Both the initial and online validation of the SE-PAST indicated good face and content validity, as well as potential usefulness. The SE-PAST is much shorter than the existing instruments as it does not contain a symptom checklist and when used online it also avoids the need for respondents to calculate probability levels themselves. There is of course potential for an instrument such as this to adversely affect

adherence, if it confirms a suspicion that a medicine could be related to an unwanted symptom. Therefore advice is given to users to discuss their experience with a health professional, if the probability level is possible or higher.

Limitations

We were not able to evaluate the individual reported experiences of those completing the SE-PAST to confirm the likely causality of the event using information from medical records. While this is a desirable method of assessing validity, it is not essential for the instrument to be of value in empowering patients to discuss suspected ADRs with health professionals or to trigger a report to a relevant regulatory agency. Reliability testing using test-re-testing was not undertaken. Those involved in initial validation were all known to the team, either directly or as interviewees in a previous study. The sample for the online validation were of necessity self-selected, the majority were university-educated and most were female. Females are known to have higher use of patient support groups and to use groups differently from men, but they also use more medicines and have higher rates of ADRs.[30] A large number of the people who accessed the online instrument failed to complete it. The reasons for this cannot be ascertained and could be many and varied. In addition, not all those who completed the SE-PAST responded to evaluation questions and may have been less likely to consider it useful.

Relevance to practice

A causality assessment instrument specifically developed for lay use may help to facilitate effective discussions between patients and healthcare professionals about suspected ADRs, empowering patients and improving patient-centredness of consultations. While such an instrument could also prompt the discontinuation of medicines, it should be acknowledged that patients frequently discontinue medicines of their own volition, either to test their

suspicions of side effects themselves or to otherwise evaluate its effects.[12,31] The instrument could also contribute to increasing the number of, and enhancing the quality of, reports to regulatory authorities which do not require causation to be proven prior to reporting. They can then perform further causality tests and signal generation to find confirmed ADRs. Incorporation of self-assessment questions such as those used in SE-PAST into direct patient ADR reporting could provide both lay person and pharmacovigilance experts with useful information.

Conclusion

The SE-PAST instrument facilitates lay persons to self-assess causality of suspected ADRs from medicines sufficiently to guide their decisions about whether to discuss these experiences with health professionals or report them to regulatory authorities. It is easy to use but further work is required to confirm its reliability and validity and to determine its ability to lead to improved consultations or direct reporting to regulators.

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Table 1 Characteristics of respondents

Characteristic		**Frequency (%)**
Gender	Female	208(71.5)
(n=291)	Male	83(28.5)
Age (years)	Below 40	27(9.2)
(n=292)	41-50	31(10.6)
	51-60	49(16.8)
	61-70	105(36.0)
	71-80	68 (23.3)
	Over 80	12(4.1)
Education level	School	62(21.4)
(n=290)	Further education	60(20.7)
	University	168(57.9)
No. of medicines	None stated	11(3.7)
(n=294)	One	85(28.9)
	2-4	123(41.8)
	5-9	60(20.4)
	10 or more	15(5.1)

Table 2 Extracts from free-text comments illustrating impacts and methods of identification

Respondent details	Suspected medicine	Description
Male, age 61-70, university-educated, on 2-4 medicines, causality level probable, moderate impact (P138)	simvastatin	Taking simvastatin, I began to experience pains in the low back and hip which affected me during the night. I would go to back with no pain and then around 2 or 3 o clock in the morning I would be woken by the pains in the hips so that I was unable to get back to sleep again. I discussed this with the doctor who didn't believe the statin was the cause. But in the end I stopped taking the drug. After about 9 months the pains had finally disappeared. At that point the doctor persuaded me to re-start the simvastatin, I agreed, and within 2 weeks the nocturnal hip pains had returned.
Female, age 41-50, university-educated, on 2-4 medicines, causality level probable, mild impact (P147)	topiramate	Slower cognitive processing, which manifests itself particularly as sometimes groping for words or having difficulty forming/speaking words. This is worse when speaking a foreign language. I also sometimes find that it is harder for me to begin concentrating on something, like reading or writing (once I am concentrating, and into the flow of the work, the effect is less noticeable).
Female, age 71-80, left school at 16/younger, on 2-4 medicines, causality level probable, moderate impact (P179)	sertraline	A constant feeling of weariness of mental capacity and lack of enthusiasm, somehow encouraging thoughts of a depressive nature. Irritable digestion, difficulty in concentrating.
Male, age 61-70, further education, on 2-4 medicines, causality level probable, severe impact (P196)	bendroflumethiazide	I was prescribed bendroflumethiazide to reduce swelling in my ankles. I developed gout, specifically in my knees and elbows. At one point I was only able to walk with the aid of a crutch. The pains in my arms and elbows was less severe and could be relieved by massage. I put up with the discomfort for some time not realising that it was linked with taking a diuretic. A pharmacist friend made me aware of the links between diuretics and gout. I stopped taking the bendroflumethiazide. The gout symptoms slowly went away and have now completely disappeared.
Female, age 61-70, further education, on 10 or more medicines, causality level probable, severe impact (P259)	cinacalcit	[Cinacalcit] definitely, because I became violently sick whenever I took it and stopped when I stopped taking them. According to my doctor it is already a known side effect.

Table 3 Responses to causality statements

Statement	Number responding				
	Yes	No	Don't know	Does not apply	TOTAL
I experienced this effect(s) for the first time after taking this medicine.	214	63	12	2	291
I have experienced similar effect(s) from this medicine or a related medicine in the past	103	126	17	0	246
When I stopped taking the medicine the effect(s) decreased in severity or disappeared altogether.	176	23	11	0	210
When I took the medicine again the effect(s) reappeared.	16	98	9	167	290
When I increased the dose the effect(s) became more severe.	84	29	15	163	291
When I decreased the dose the effect(s) became less severe.	70	40	21	160	291
I confirmed the effect(s) with some or all of the following information sources – doctors, pharmacists, information leaflets with medicine, the internet or medicine books.	257	20	6	0	283
I think that something else apart from the medicine could have caused the effect(s).	19	206	62	0	287
I think an existing medical condition or conditions could have led to the effect(s).	35	171	76	0	282
I think that other medicine(s) that I was using at the time could have caused the effect(s).	16	216	47	12	291

Figure 1 Number of potentially causative medicines cited in relation to number being used