REVIEW ARTICLE

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Determinants of Under-Reporting of Adverse Drug Reactions

A Systematic Review

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Contents

Abstract

A voluntary reporting system of adverse drug reactions (ADRs) is fundamental to drug safety surveillance but under-reporting is its major limitation. This bibliographic review sought to assess the influence of personal and professional characteristics on ADR reporting and to identify knowledge and attitudes associated with ADR reporting.

A systematic review was conducted using the MEDLINE and EMBASE databases. We included papers that were published in English, French and Spanish, and covered a study population made up of health professionals. In each case, the following data were extracted: study population; workplace; study type; sample size; type of questionnaire; type of scale for measuring knowledge; response rate; personal and professional factors; and knowledge and attitudes (based on Inman's 'seven deadly sins') associated with reporting.

Based on a search of computerized databases, we identified a total of 657 papers in MEDLINE and 973 in EMBASE. In all, the review covered

45 papers that fulfilled the inclusion criteria. Medical specialty was the professional characteristic most closely associated with under-reporting in 76% of studies involving physicians. Other factors associated with under-reporting were ignorance (only severe ADRs need to be reported) in 95%; diffidence (fear of appearing ridiculous for reporting merely suspected ADRs) in 72%; lethargy (an amalgam of procrastination, lack of interest or time to find a report card, and other excuses) in 77%; indifference (the one case that an individual doctor might see could not contribute to medical knowledge) and insecurity (it is nearly impossible to determine whether or not a drug is responsible for a particular adverse reaction) in 67%; and complacency (only safe drugs are allowed on the market) in 47% of studies.

While personal and professional factors display a weak influence, the knowledge and attitudes of health professionals appear to be strongly related with reporting in a high proportion of studies. This result may have important implications in terms of public health, if knowledge and attitudes are viewed as potentially modifiable factors.

Adverse drug reactions (ADRs) are an important public health problem in terms of mortality,[1] morbidity[2,3] and costs.[4] Pharmacovigilance is the public health activity targeted at analysing and managing the risk posed by medications once they have come on to the market. Spontaneous reporting of suspected ADRs by health professionals, followed by evaluation and incorporation into databases, allows for ongoing ascertainment of the benefit-risk ratio of a given medication,[5-7] and constitutes one of the best methods for generating signals about unexpected and uncommon ADRs.[8,9] However, under-reporting is a major limitation of spontaneous reporting systems as it is estimated that only 6% of all adverse reactions are reported.[10] On the one hand, this high rate of under-reporting prevents risk from being quantified, and on the other hand, it leads to excessive delay in triggering alert signals, with the ensuing repercussions on public health.

A theoretical model, known as the 'seven deadly sins', to explain the reasons for under-reporting among physicians has been proposed by Inman.[11-13] Identification of knowledge and attitudes relating to under-reporting would enable educational strategies directly targeted at changing such attitudes to be developed, and the reporting of suspected ADRs to be stimulated. Nevertheless, studies that have attempted to identify factors (personal and professional characteristics, as well as knowledge and attitudes) associated with ADR reporting display widely differing methodology and inconsistent results. This systematic review aims to assess the influence of personal and professional characteristics on the reporting of ADRs and to identify knowledge and attitudes associated with ADR reporting.

1. Literature Search Methodology

This systematic bibliographic review was conducted by searching the scientific MEDLINE and EMBASE databases from January 1986 to December 2006. The 20-year period immediately preceding the review was set as the time limit for our search because the topic is relatively new and because in most European countries pharmacovigilance systems were only introduced in the 1990s.[14] In addition, manual searches of journals, particularly those less likely to be indexed, and of references cited by retrieved articles, were used to locate other articles.

The following search terms and their equivalents were used in MEDLINE and EMBASE: ('attitud*' OR 'factor*' OR 'obstacle*') AND ('adverse drug reaction*' OR 'ADR' OR 'adverse drug event*' OR 'ADE') AND 'reporting'. The search was concluded when all the papers selected

in the databases had been retrieved, and the papers referenced by these had been compiled.

The selection criteria were (i) language, with papers that were not published in English, French or Spanish being ruled out for bibliographic review purposes; and (ii) programme target audience, with all papers that analysed factors or attitudes associated with the reporting of suspected ADRs being included, regardless of the health profession targeted for study. Studies on patients were excluded.

A complementary analysis was conducted in the case of studies with a higher level of evidence, with the following inclusion criteria being established for the purpose: (i) sample size of 200 or more subjects; and (ii) percentage participation of 50% or more.

1.1 Data Extraction

For each study included in this review, a table with the following parameters was drawn up: author (publication year); country; study population; workplace; study type; sample size, with the percentage of reporters among respondents; questionnaire distribution (postal, interviewer, internal hospital mail, directly administered, Internet); and scale (multiple choice, free text, Likert scale, visual analogue scale [VAS]) [table I]. In cases where a study included two or more subpopulations (e.g. reporters vs non-reporters, or physicians and pharmacists), we calculated the weighted mean of the populations covered.

A further table (see table II) was drawn up, using the following data: author (publication year); response rate (%); personal factors associated with reporting (age, sex); professional factors (training, specialty, workplace, workload, qualifications, years since graduation); and excuses given for not reporting (such as government will badger reporter for more data, insufficient space on form, not a professional obligation, reporting is not their responsibility, too bureaucratic/complex). The statements quoted in the results sections of all studies were allocated to Inman's seven deadly sins, as proposed in 1976,[11] subsequently amended in 1986[12] and extended in 1996.[13] Reasons for ADR underreporting, and the following delay in the identification of a drug safety issue, were classified into two groups: (i) failure to recognize an ADR; and (ii) failure to report a recognized ADR. In order to enlighten this last category, and based on doctor's opinions, Inman proposed a list of attitudes described as the 'seven deadly sins':[12]

1. Complacency: the belief that only safe drugs are allowed on to the market.
2. Fear of possible involvement in litigation or investigation of prescribing costs by health departments.
3. Guilt at having administered treatment that may have harmed a patient.
4. Ambition to compile and publish a personal case series.
5. Ignorance of the requirements for reporting.
6. Diffidence at the prospect of appearing ridiculous for reporting merely suspected ADRs.
7. Indifference on the part of an individual doctor to his/her essential role as a clinical researcher who should be contributing to medical knowledge.
8. Lethargy: an amalgam of procrastination, lack of interest or time to find a report card and other excuses.
9. Financial incentives to report.
10. Insecurity: an attitude that was not proposed by Inman, yet appears in many studies,[18,21,40,41,44,56,64] and is associated with the statement, ''It is nearly impossible to determine whether or not a drug is responsible for a particular adverse reaction.''

Our review considered Inman's descriptions of knowledge and attitudes. In addition, we included an open category containing other factors. These allocations were made by one of the authors (ELG), and a random sample of 38% of the papers (17/45) was then assessed by two of the authors (ELG and MTH) to determine whether or not there was a consensus. Lastly, papers in which there were doubts as to statement allocation were jointly reviewed by both authors.

The associations shown in tables I and II were drawn directly from the results sections of the studies. The tables list all the factors (personal, professional, attitudes and other reasons

Table I. Studies that analyse the influence of personal and professional factors, and attitudes of health professionals on reporting of adverse drug reactions: description of methods

Study (publication year)	Country	Study population[c]	Work-place	Sample size (% reporters among respondents)	Questionnaire distribution[d]	Scale
Milstien et al.[15] (1986)	USA	1	A, B	190 (100)	*a*	MC
Walker and Lumley[16] (1986)	UK	1	B	402 (58)	*b* and *d*	MC
Robins et al.[17] (1987)	South Africa	1	B, D	121 (25)	*b*	FT
Rogers et al.[18] (1988)	USA	1	A, B, O	3000 (6.78)	*a*	Likert
Scott et al.[19] (1990)[a]	USA	1	A, B, O	NM	*a*	
Fincham[20] (1990)	USA	2	A, E	302 (NM)	*a*	Likert
Bateman et al.[21] (1992)	UK	1	A, B	1600 (84)	*a*	Likert
Lee et al.[22] (1994)	Hong Kong	2	A, B, C	286 (14.72)	*a*	
Pouget-Zago et al.[26] (1995)	France	1	B	600 (46.6)	*a*	
Belton et al.[24] (1995)	UK	1	A, B, O	500 (63)	*a*	MC
Generali et al.[25] (1995)	USA	2	A, C, O	793 (NM)	*a*	
McGettigan and Feely[28] (1995)	Ireland	1	A, B, O	400 (53)	*a*	MC
Wallace et al.[29] (1995)	Canada	1, 2	A, B, O	2370 (17)	*a*	Likert, MC
Kurz et al.[30] (1996)	Belgium	1	A, B	500 (53)	*a*	
Belton[31] (1997)	Various[e]	1	A, O	NM (9.4 to 74.4)	*a*	
Cosentino et al.[32] (1997)	Italy	1	B	350 (50)	*a*	MC
McGettigan et al.[33] (1997)	Ireland	1	A	190 (45)	*c*	MC
Serrano Cozar et al.[34] (1997)	Spain	1	B	417 (50.4)	*d*	
Ball and Tisocki[35] (1998)[b]	Zimbabwe	1,2	B, C	12 (NM)	*e*	MC
Tubert-Bitter et al.[36] (1998)	France	1	A, B, D	600 (53)	*a*	
Williams and Feely[37] (1999)	Ireland	1	A, B, O	400 (30)	*a*	MC
Eland et al.[38] (1999)	the Netherlands	1	A, B	1984 (62.2)	*a*	MC
Cosentino et al.[39] (1999)	Italy	1	A	162 (67.3)	*b*	MC
Figueiras et al.[40] (1999)	Spain	1	A, B	692 (48.2)	*a*	VAS
Houghton et al.[42] (1999)	UK	1, 2	B, C	500 (18.5)	*a*	
Green et al.[41] (1999)	UK	2	C	40 (3.3)	*b*	MC, FT
Backstrom et al.[44] (2000)	Sweden	1	A, B	1274 (66.3)	*a*	MC
Sweis and Wong[45] (2000)	UK	2	A	548 (17.5)	*a*	Likert
Green et al.[46] (2001)	UK	2	A	600 (25.6)	*a*	Likert
Hasford et al.[48] (2002)	Germany	1	A, B, O	1315 (85.3)	*a*	MC
Perlik et al.[49] (2002)	Czech Republic	1	A, B	500 (NM)	*b*	FT, MC
Van Grootheest et al.[50] (2002)	the Netherlands	2	C	200 (53)	*a*	Likert, FT
Rehan et al.[51] (2002)	India	1, 5	A	224 (NM)	*d*	
Li et al.[52] (2004)	China	1, 3, 4	A	2000 (26.1)	*b*	MC
Kelly et al.[53] (2004)	Australia	1, 2, 3	A	4808 (16)	*e*	MC
Milojevic et al.[54] (2004)	France	1	A	100 (35)	*e*	MC
Herdeiro et al.[56] (2005)	Portugal	1	A, B	859 (19.4)	*a*	VAS
Vallano et al.[57] (2005)	Spain	1,6	A	208 (NM)	*d*	FT

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Table I. Contd

Study (publication year)	Country	Study population[c]	Work-place	Sample size (% reporters among respondents)	Questionnaire distribution[d]	Scale
Nita et al.[58] (2005)	Australia	1, 2	A	2126 (40.9)	*a*	
Bhatia et al.[59] (2005)	India	1	A, B, D	200 (NM)	*d*	MC
Herdeiro et al.[60] (2006)	Portugal	2	A, C	314 (20.5)	*a*	VAS
Aziz et al.[61] (2006)	Malaysia	1	A	415 (18.57)	*b*	MC
Chatterjee et al.[62] (2006)	India	1	A	215 (4.4)	*e*	MC, FT
Granas et al.[63] (2006)[a]	Norway	2	C	412 (7.9)	*b*	
Bawazir[64] (2006)	Saudi Arabia	2	C	240 (4)	*d*	Likert, FT

a Data before drug surveillance intervention.

b Data after drug surveillance intervention.

c Study population: (1) physicians; (2) pharmacists; (3) nurses; (4) administrators; (5) medical undergraduates; (6) medical residents in training.

d Questionnaire distribution: (*a*) postal; (*b*) interviewer; (*c*) internal hospital mail; (*d*) directly administered; (*e*) not mentioned; (*f*) Internet.

e Denmark, France, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, the UK.

A = hospital; **B** = primary care; **C** = retail; **D** = non-hospital specialists; **E** = nursing home; **FT** = free text; **MC** = multiple choice; **NM** = not mentioned; **O** = other; **VAS** = Visual Analogue Scale.

for not reporting) considered by the authors in their studies. (Additional information to tables I and II can be found in the supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com.)

1.2 Results

1.2.1 Selection of Papers

Based on the search of computerized databases, a total of 1630 studies were identified (657 via MEDLINE and 973 via EMBASE). This computerized search was completed with a horizontal review of the chosen literature. Finally, a total of 50 studies were selected.[15-64] Of the studies that met our stated objectives, five were excluded, either because they were not available in English, Spanish or French,[23,27,47] or alternatively because they could not be located.[55] Another paper was also excluded[43] since its principal results had already been published in an earlier paper (figure 1).

A breakdown by geographical distribution showed that 58% of studies had been conducted in the EU (26/45), and that of these, seven had come from the UK[16,21,24,41,42,45,46] and two from the Netherlands.[38,50] There was one study whose population covered nine EU countries.[31] Seven studies came from Asia,[22,51,52,59,61,62,64] five from the US[15,18-20,25] and two from Australia.[53,58] Of the remainder, there were two from African countries[17,35] and one each from the Czech Republic,[49] Norway[63] and Canada.[29]

Tables I and II show papers that fulfilled the inclusion criteria, listed by year of publication. It will be seen that the number of papers published on reporting-related factors has risen over time, with a growing interest in pharmacists in recent years. An increase was also seen in the number of studies that included more than one health profession.

1.2.2 Methods Used in the Selected Studies

Insofar as methodology was concerned, 89% of the studies reviewed (40/45) failed to specify the type of design used. Of the studies reviewed, three claimed to be case-control studies[40,56,60] in which the cases were reporters and the controls a sample of non-reporters, and another study claimed to be qualitative.[57] One paper was identified that reported the results of a pilot study.[35] A total of 40% of studies (18/45) reviewed included a pilot stage to evaluate the

Table II. Studies that analyse the influence of personal and professional factors, and attitudes of health professionals on reporting of adverse drug reactions: main results

Study (publication year)	Response rate (%)	Personal and professional factors associated with reporting[a]	Reasons for not reporting[a]
Milstien et al.[15] (1986)	82	Age, specialty, time spent in teaching, training	
Walker and Lumley[16] (1986)	93		ig, le, uf, fr, fb
Robins et al.[17] (1987)	86	Specialty	ig, le, uf
Rogers et al.[18] (1988)	37	Specialty, workplace, workload	fe, ig, in, le, uf, others
Scott et al.[19] (1990)[b,c]	75.3		ig
Fincham[20] (1990)	62.6	Workplace	ig, le, others
Bateman et al.[21] (1992)	74	Age, qualification, specialty, workload	co, di, fe, ig, in, le, uf, fr, others
Lee et al.[22] (1994)	45.1	Sex, workplace, workload, years in active practice	ig
Pouget-Zago et al.[26] (1995)	39	Pharmacovigilance studied as part of study syllabus	ig, le
Belton et al.[24] (1995)	57	Workload	di, ig, le
Generali et al.[25] (1995)	40	Workplace, workload, years since qualification	di, ig, le, uf
McGettigan and Feely[28] (1995)	53	Workplace	ig, is, le, ua, uf
Wallace et al.[29] (1995)	61.1	Practice location (urban/rural), specialty, workload	di, fe, ig, le, uf, others
Kurz et al.[30] (1996)	66	Sex, workplace	co, ig, is, le, uf
Belton[31] (1997)	From 19 to 77	Specialty	ig, is, le, ua, uf
Cosentino et al.[32] (1997)	59.1		co, if, uf, others
McGettigan et al.[33] (1997)	65	Seniority of position, specialty, workplace	ig, le, uf
Serrano Cozar et al.[34] (1997)	67.4	Specialty, workplace	ig, le, uf
Ball and Tisocki[35] (1998)[c]	92.3		ig, is, le
Tubert-Bitter et al.[36] (1998)	25	Age, graduation university, work setting	
Williams and Feely[37] (1999)	39.5	Specialty	di, ig, le, others
Eland et al.[38] (1999)	72.7	Specialty	ig, is, le, others
Cosentino et al.[39] (1999)	90.7	Specialty, year of graduation	
Figueiras et al.[40] (1999)	63.7	Sex, speciality, specialization, workplace, workload	co, di, in, is
Houghton et al.[42] (1999)	62		di, ig, le, others
Green et al.[41] (1999)	75		di, is, le, fr, others
Backstrom et al.[44] (2000)	58.7		di, ig, le, uf
Sweis and Wong[45] (2000)	63	Training, seniority of position, workload	di, fe, le, others
Green et al.[46] (2001)	51	Training	di, ig, is, le, others
Hasford et al.[48] (2002)	46.8	Location	di, ig, le, others
Perlik et al.[49] (2002)	NM		ig
Van Grootheest et al.[50] (2002)	73.5		co, di, le, others
Rehan et al.[51] (2002)	100	Undergraduates	ig
Li et al.[52] (2004)	85		ig, le, ua, uf
Kelly et al.[53] (2004)	23	Profession, seniority of position	ig, is, le, uf, others
Milojevic et al.[54] (2004)	NM		di, ig
Herdeiro et al.[56] (2005)	54.3	Specialty, workplace	co, di, fe, ig, in, is
Vallano et al.[57] (2005)	100	Workload	di, fe, ig, le, uf, fb
Nita et al.[58] (2005)	40	Profession	di, fe, ig, le, uf, others, fr

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Table II. Contd

Study (publication year)	Response rate (%)	Personal and professional factors associated with reporting[a]	Reasons for not reporting[a]
Bhatia et al.[59] (2005)	NM		di, fe, ig, uf, fr, fb, others
Herdeiro et al.[60] (2006)	86.8	Workplace	co, di, ig, le
Aziz et al.[61] (2006)	84.3	Category of position	di, ig
Chatterjee et al.[62] (2006)	64.2		di, ig
Granas et al.[63] (2006)[b]	83		di, ig, le, others
Bawazir[64] (2006)	71.7		co, di, fe, ig, in, is, le, ua, uf, others

a Factors reported to be statistically significant.

b Data before drug surveillance intervention.

c Data after drug surveillance intervention.

co = complacency; **di** = diffidence; **fb** = feedback; **fe** = fear; **fr** = financial reimbursement; **ig** = ignorance; **in** = indifference; **is** = insecurity; **le** = lethargy; **NM** = not mentioned; **ua** = unavailability of reporting address; **uf** = unavailability of forms.

questionnaire. The sample size of studies varied from 12 to 4808 subjects, with a median of 415 (25th percentile = 219; 75th percentile = 742 [figure 2]). There were two studies that made no express mention of the sample size.[19,31]

Postal questionnaires were used in 60% (27/45) and interviews in 20% (9/45) of the total. Percentage participation in the studies analysed ranged from 23% to 100%. There were three studies in which the response percentage was not mentioned[49,54,59] and one study where the percentage participation was specified by country.[31] It was not possible to obtain an overall participation figure.

Four studies failed to mention the data-collection method.[35,53,54,62] The highest participation rates (100%) were recorded for interviews and directly administered questionnaires. Questionnaires sent by post or distributed by internal hospital mail registered lower participation (25–87%). There were also two studies that used more than one type of distribution,[16,63] namely, interview plus directly administered questionnaire, and interview plus Internet-administered questionnaire.

Information on the type of scale used by the authors to study the answers to the questionnaire was lacking in 27% of studies (12/45). In papers in which this information was included (73%, 33/45), multiple-response analysis was the most frequently used type of scale, used in 64% of papers (21/33), followed by the Likert scale in 24% (8/33). A free-text response analysis was used in 7 (21%) of the studies and a VAS in 4 of the 45 studies evaluated (9%): in one of the latter four studies,[39] the VAS-type scale was used to measure perception of risk *vis-à-vis* certain groups of drugs rather than to analyse attitudes associated with ADR reporting.

1.2.3 Personal and Professional Factors

The personal and professional factor most frequently linked to reporting was medical specialty (or training), which appeared in 76% of the studies that included a medical population (13/17). This was followed by age (9/24); sex (4/15); reporters' workplace (11/13); workload (9/11); number of prescriptions issued per day (3/5); type of education received by reporters (6/6); specific training in pharmacovigilance (4/4); and, in one study, involvement in teaching and research activities.

1.2.4 Influence of Attitudes

The attitudes most frequently associated with not reporting ADRs were (i) ignorance in 95% (38/40); (ii) diffidence in 72% (23/32); (iii) lethargy in 77% (27/35); (iv) indifference and insecurity in 67% (16/24); and (v) complacency in 47% (8/17); and finally, (vii) fear in 24% of studies (7/29).

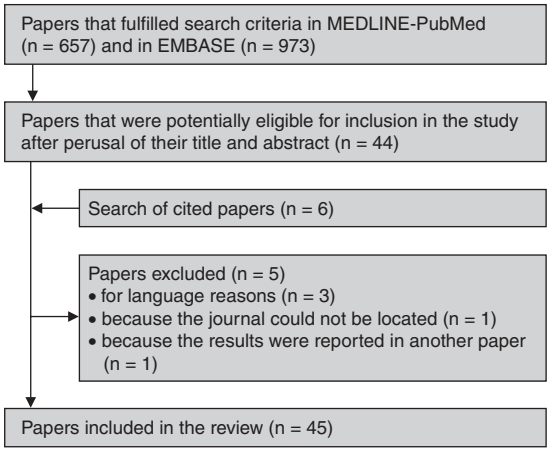

Fig. 1. Identification of studies and inclusion criteria.

1.2.5 Other Factors

Pre-eminent among the other reasons given by reporters as justification for under-reporting was the unavailability of yellow cards or other suitable forms in 76% of studies (19/25). In four[20,29,53,63] of the five[20,29,42,53,63] studies conducted on pharmacists, one of the reasons cited to justify non-reporting was that the pharmacists regarded this task as being the physician's rather than their responsibility. The method developed for reporting suspected ADRs was considered to be too bureaucratic or not easy enough in 35% of studies (6/17).

1.2.6 Results in Studies with a Higher Level of Evidence

Of the 45 studies that fulfilled the study criteria, we analysed those that displayed a higher level of evidence in terms of sample size and percentage participation. There were 25 of the initial 45 that fulfilled the size criteria of 200 or more subjects and a percentage participation of over 50%.

The personal and professional factor most closely associated with reporting was medical specialty, with a figure of 75% (6/8). Of the two studies[21,40] that specified level of education or training, both reported these factors to be associated with reporting. Insofar as attitudes were concerned, ignorance was associated with under-reporting in 92% (22/24), diffidence in 80% (16/20), complacency in 67% (8/12), lethargy in 65% (15/23) and fear in 31% of studies having a higher level of evidence (5/16).

2. Discussion

The results of this review indicate that under-reporting seems to be associated with specific attitudes of health professionals to ADRs and the reporting system. The results also indicate that the 'seven deadly sins' model proposed by Inman appears to be able to account for the factors that influence under-reporting. Personal and professional characteristics, in contrast, seem to be associated with reporting in a low proportion of studies.

2.1 Discussion of Methods

Most studies failed to specify the study design. Only three studies[40,56,60] were found that expressly reported their design, stating it to be case control. We found nine studies[15,17,33,35,39,41,50,54,59] with a sample size of under 200, which could afford low statistical power for detecting an association with reporting.

Percentage participation in studies was generally low, with the highest values being registered by studies that relied on interviews.[16,17,32,46,49,52,57,61,63] A response percentage is an important element for a study's internal validity, in as much as participation bias may be present in accordance with health professionals' motivation in ADR-related

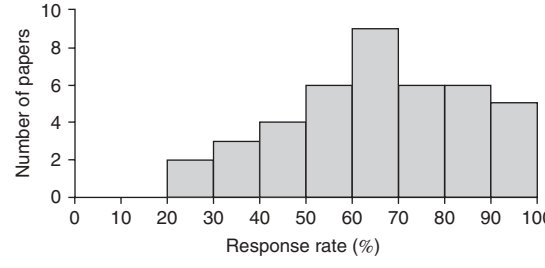

Fig. 2. Distribution of papers by percentage participation. Two papers failed to specify the percentage participation, and one failed to furnish an overall figure.

matters. Indeed, this was evident in the case-control studies, where the response percentage among reporters (cases) was very much higher than that of non-reporters (controls). Most studies used Likert scales. Only three used the VAS,[40,56,60] and it was precisely these that detected a greater number of attitudes associated with reporting.

2.2 Discussion of Results

Few studies report an association between personal and professional characteristics and ADR reporting. Only training and medical specialty seem to be associated with reporting in 76% of papers that analyse this variable, and this may be due to the possibility that the better the training, the better the attitudes towards ADR reporting. Indeed, it is the attitudes and knowledge of health professionals that dictate ADR reporting, as suggested by Inman in his 'seven deadly sins'.[11-13]

The reasons proposed by Inman can be pooled into the following three groups:[65] (i) attitudes relating to professional activity (financial incentives, legal aspects and ambition to publish); (ii) those associated with ADR-related knowledge and attitudes (complacency, insecurity, diffidence, indifference and ignorance); and (iii) excuses made by professionals (lethargy).

In light of the results of our review, Inman's three 'sins' linked to professional activity (financial incentives, fear and ambition to publish) do not seem to be the principal cause of under-reporting. With respect to the first factor (financial incentives), there were just four[16,21,41,59] papers that pointed to financial rewards being used to stimulate ADR reporting.[66,67] Since few studies observed them to be associated with reporting, it also seems that fear (possible involvement in litigation or investigation of prescribing costs by health departments) and personal ambition to publish cases series are not important factors underlying non-reporting.

In contrast, Inman's five knowledge/attitude-related 'sins' show associations with under-reporting in a high proportion of studies. Hence, lack of knowledge on the part of health professionals about the functioning of spontaneous ADR reporting (ignorance) is present in over 90% of studies with a higher level of evidence. Many professionals believe that the ADR spontaneous reporting programme is exclusively designed to detect severe reactions, yet in reality all possible types of undesirable effects associated with a drug are relevant for its safety profile.

Fear of appearing ridiculous (diffidence) is an attitude associated with under-reporting in 72% of the papers reviewed. The majority of professionals eligible to report might well agree with this assertion, perhaps because they are under the impression that only forms that demonstrate a causal relationship are acceptable. Lack of confidence about diagnosing ADRs[25,41,45] could be important in the case of pharmacists because they are more likely to report an ADR when they feel more confident. This attitude may reflect the anxieties of reporters 'not to appear foolish', a sentiment that needs to be dispelled through regulatory agency communications and education.

The conviction that all adverse reactions of a medication are known when it comes on to the market and that only safe medications are marketed (complacency) appears to be associated with reporting in two-thirds of studies displaying a higher level of evidence. This belief serves as an indicator of the poor training received by health professionals in epidemiology and pharmacology. The advantage of complacency is that it is an attitude that is easily modifiable through educational intervention.

Indifference and insecurity are two inter-related reasons that appear to be associated with reporting in over 65% of the studies reviewed. Indifference was proposed by Inman and refers to the essential role of an individual physician as a clinical researcher who should be contributing to the general advancement of medical knowledge. Insecurity, though not proposed by Inman, nevertheless appears in numerous studies[18,21,40,41,44,56,64] as a possible factor for under-reporting, and is based on the impossibility of determining whether or not a drug is responsible for a particular adverse reaction. Viewed from this perspective, insecurity

can also be assumed to be associated with diffidence. Taking McBride[68] and thalidomide as an example, both attitudes can be modified by message-based interventions.

In his 1986 model of reporting factors,[12] Inman proposed lethargy, which could be regarded as a set of factors or excuses that hinder or justify non-reporting. Among these is 'don't have time' to report or think about the diagnosis,[22,24,56] something that may be associated with professionals' burden of care. Lethargy is likewise linked to a lack of yellow cards, in those cases where professionals have neither the interest nor the time to look for them. Nevertheless, the absence or presence of such cards can also be respectively viewed as a barrier to or a facilitating factor for reporting; indeed, it has been shown that when yellow cards are distributed, reporting increases.[69] The perception of the reporting process as extremely bureaucratized and complex[40,56,60] is yet another factor. If potential reporters are unaware of the utility of the information that could be fed into the system and the report cards contain information about the ADR and the patient, then it is comprehensible that, despite any guarantee of confidentiality, those who were unfamiliar with the system would be more reticent to report ADR, due to an aversion to disclosing confidential information. This problem was in fact reported in several studies.[17,20,24,40,45] We feel that the factors included within lethargy could also be modifiable through intervention, by demonstrating that only 5 minutes are needed to complete a yellow card, and that any obstacle posed by its absence could easily be remedied through wider card distribution and/or on-line compliance systems.

2.3 Limitations

In our opinion, the principal limitation of this review lay in the heterogeneity of the study methods used, *vis-á-vis* the respective study populations, data collection methods and scales employed, and in the fact that not all of the studies focused on examining the same features, and when they did so, the definition and classification of the variables, such as 'specialty', varied widely from one study to the next. Thus, the very definition of the 'sins' is not exactly the same in all studies, and the statements used in the studies also exhibit slight differences. We had to allocate statements reported in the results of the studies to one of Inman's deadly sins, and in many cases this proved rather difficult. While it is possible that our choice of allocation to one of Inman's sins did not agree with that of other authors, we feel that this did not alter the principal conclusions of this review.

Furthermore, in the studies reviewed, percentage participation was not only heterogeneous, but in some cases no data were reported. However, if professionals who answer survey questionnaires can be assumed to be more predisposed to report ADRs, and yet most studies nevertheless agree that reporting is influenced by knowledge and attitudes, then one might well conclude that the latter's influence would be greater still if 100% of the sample were to participate.

3. Conclusions and Implications

In this review, personal and professional factors exert little influence on reporting, whereas knowledge and attitudes of health professionals seem to be related to reporting in a high proportion of studies. This result may have important implications, since knowledge and attitudes are potentially modifiable factors. Indeed, recent studies have shown that if an educational intervention is designed on the basis of gaps detected in professionals' knowledge and attitudes, the reporting rate can be sharply increased.[70,71] We thus feel that observational studies designed to analyse the association between attitudes and reporting should only be the first stage of a strategy to increase reporting, which should then lead to a second stage, consisting of an educational intervention that focused on under-reporting-related attitudes and so served to increase ADR reporting. This would, in turn, ensure increased capability to trigger early alerts, enable the health authorities to react more swiftly to prevent the greatest possible number of

patients from being affected and thereby enhance patient safety.

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