REVIEW ARTICLE

Drug Safety 2006; 29 (5): 385-396
0114-5916/06/0005-0385/$39.95/0

Under-Reporting of Adverse Drug Reactions

A Systematic Review

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Contents

Abstract

The purpose of this review was to estimate the extent of under-reporting of adverse drug reactions (ADRs) to spontaneous reporting systems and to investigate whether there are differences between different types of ADRs. A systematic literature search was carried out to identify studies providing a numerical estimate of under-reporting. Studies were included regardless of the methodology used or the setting, e.g. hospital versus general practice. Estimates of under-reporting were either extracted directly from the published study or calculated from the study data. These were expressed as the percentage of ADRs detected from intensive data collection that were not reported to the relevant local, regional or national spontaneous reporting systems. The median under-reporting rate was calculated across all studies and within subcategories of studies using different methods or settings.

In total, 37 studies using a wide variety of surveillance methods were identified from 12 countries. These generated 43 numerical estimates of under-reporting. The median under-reporting rate across the 37 studies was 94% (interquartile range 82–98%). There was no significant difference in the median under-reporting rates calculated for general practice and hospital-based studies. Five of the ten

general practice studies provided evidence of a higher median under-reporting rate for all ADRs compared with more serious or severe ADRs (95% and 80%, respectively). In comparison, for five of the eight hospital-based studies the median under-reporting rate for more serious or severe ADRs remained high (95%). The median under-reporting rate was lower for 19 studies investigating specific serious/severe ADR-drug combinations but was still high at 85%.

This systematic review provides evidence of significant and widespread under-reporting of ADRs to spontaneous reporting systems including serious or severe ADRs. Further work is required to assess the impact of under-reporting on public health decisions and the effects of initiatives to improve reporting such as internet reporting, pharmacist/nurse reporting and direct patient reporting as well as improved education and training of healthcare professionals.

Spontaneous reporting systems (SRSs) such as the UK Yellow Card Scheme for reporting suspected adverse drug reactions (ADRs) operate in most developed countries and many developing countries.[1-3] These schemes are usually administered by a central or regional agency, such as a regulatory authority. In some countries, such as Sweden, France and Italy, reporting is compulsory.[2] The SRS receives ADR reports from medical doctors and other health professionals, such as pharmacists and nurses, either directly or via reporting to pharmaceutical companies.[3] In the US and more recently in other countries, patients can also report directly to the SRS.[4]

The main function of the SRS is early detection of signals of new, rare or serious ADRs.[4] These reactions may not have been detected by the relatively small numbers of patients included in premarketing clinical trials or by larger postmarketing surveillance studies.[4-6] The SRS has the advantage of covering a large number of patients, i.e. the entire population, and a wide range of drugs. It is therefore a relatively cost-effective method of monitoring drug safety.[4-7]

The SRS does, however, have a number of limitations. Data from the SRS, when taken alone, do not accurately quantify the risk associated with a drug. Estimation of risk requires adequate denominator information on drug utilisation but this is commonly taken from sales data, which may not accurately reflect prescribing and usage levels.[8,9] The numerator is also inaccurate, as it is subject to reporting bias. Under-reporting does not only affect older drugs and non-serious reactions; new drugs and serious reactions also suffer from under-reporting. Reporting rate may also vary over time and be influenced by factors such as media attention.[10] In addition, it may be difficult to make judgements on the relative risk of one drug compared with another, since the under-reporting rate may differ between the two drugs. This may mask or exaggerate any true difference in toxicity profile.

The quality of spontaneous reports is also very important for the proper evaluation of drug safety signals. Important details enabling causality assessment may be missing from reports with poor quality or limited information. In addition, there may be reports within the SRS that are confounded by concurrent illness, concomitant medication or other factors. This can lead to background 'noise' within the database, which can make signal generation difficult or impossible, or may generate false positive signals.[11]

The purpose of this systematic review is to provide an estimate for the level of under-reporting of ADRs to the SRS and to investigate whether there are differences between the different types of ADRs.

1. Literature Search Methodology

A systematic literature search was carried out using MEDLINE and EMBASE databases and hand searching of textbooks on pharmacovigilance and pharmacoepidemiology in April 2004. The search

terms used were as follows: ('underreporting' OR 'under reporting' OR 'under-reporting') AND ('post-marketing surveillance' OR 'postmarketing surveillance' OR 'post marketing surveillance' OR 'adverse drug reaction reporting systems' OR 'spontaneous reports' OR 'spontaneous report' OR 'spontaneous reporting' OR 'pharmacovigilance'). The textbooks used were *Pharmacovigilance*,[12] *Pharmacoepidemiology*,[13] *Methodological Approaches in Pharmacoepidemiology*[14] and *Stephens' Detection of New Adverse Drug Reactions*.[15]

Reference titles and abstracts were reviewed and assessed to identify studies containing or permitting calculation of a numerical estimate of under-reporting of ADRs. Studies were included regardless of the methodology used or the setting involved, e.g. both hospital and general practice. General articles on under-reporting of ADRs that did not provide a numerical estimate of under-reporting were excluded. Non-English articles were excluded unless it was possible to interpret the data from the published study. Studies were then categorised into subgroups of similar methodologies or settings.

For the purposes of this review, the definition of 'severe' or 'serious' ADRs was taken, where specified, from the published study. Otherwise, seriousness has been defined according to conventional definitions for the purposes of ADR reporting to SRSs.[16] This includes ADRs that are fatal or life-threatening or result in or prolong hospital admissions.

2. Calculation of Under-Reporting Rate and Statistical Analysis

Numerical estimates of under-reporting were either extracted directly as reported in the study or calculated from the published study data. The under-reporting rate was calculated as the percentage of known, suspected or expected ADRs that were not reported to the relevant national, regional or local SRS for a similar population and time period. Estimates of under-reporting for all ADRs and for more serious or severe ADRs, where available, were then tabulated.

Descriptive statistics such as the range, median and interquartile range (IQR) were calculated across all studies. This was repeated within subcategories of studies using different methods or settings to identify any differences in under-reporting as a result of the methods used. To avoid higher weighting of papers providing more than one numerical estimate of under-reporting rate, the average of these estimates was included in the median calculations, although individual estimates are illustrated in the tables.

3. Literature Search Results

In all, 247 articles were identified from the literature search. Of these 210 were excluded, as they did not provide a numerical estimate of under-reporting, were not available in English language or were irrelevant (e.g. studies investigating under-reporting of spontaneous abortions). In total, 37 studies[17-53] from 12 countries were identified, providing 43 numerical estimates of under-reporting. The UK, France, Sweden and the US provided the highest number of studies. Across the 37 studies, the rate of under-reporting ranged from 6% to 100% with a median under-reporting rate of 94% (IQR 82–98%). Figure 1 shows the distribution of under-reporting rates across the 37 studies.

Studies were categorised into two broad groups – those that provided an estimate of under-reporting

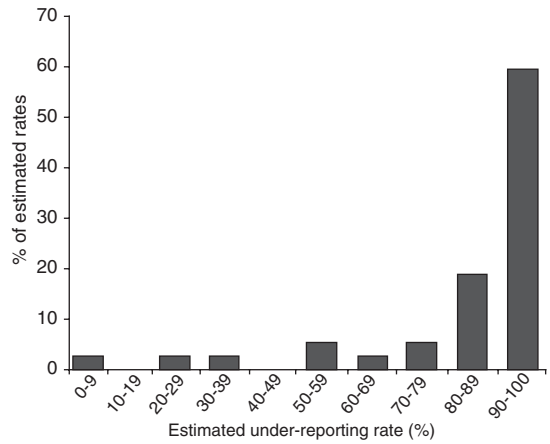

Fig. 1. The distribution of under-reporting rates across 37 studies.

Table I. Estimates of under-reporting by comparing spontaneous reports with data from intensive GP-based monitoring[a]

Study	Country	Study focus	Type of ADR	No. of ADR reports to SRS	No. of ADRs found by GP monitoring	Under-reporting rate (%)
Heeley et al.[17]	UK	PEM data (from 15 newly marketed drugs)	All	376	4211	91
			Serious	27	51	47
Lewis et al.[18]	Germany	Paediatric practices monitoring for 3 months	Majority non-serious	894 per 100 000 patients	1389 per 100 000 patients	36
Lacoste-Roussillon et al.[19]	France	200 GPs monitoring ADRs leading to hospital admission	Serious	328	6236	95
Alvarez et al.[20]	Spain	106 GPs monitoring for 3 days	All	1	1144	>99
			Serious	1	605	>99
Martin et al.[21]	UK	PEM data (from 10 newly marketed drugs)	All	275	3045	91
			Serious	33	145	77
Moride et al.[22]	France	81 GPs monitoring for 3 days	All	1	24 433	>99
			Serious	1	6123	>99
Montastruc et al.[23]	France	3 GPs monitoring for 3 months	All	1	2937	>99
Fletcher[24]	UK	Adverse event data from PMS (7 drugs)	All	202	12 093	98
Lumley et al.[25]	UK	24 GP practices monitoring for 4 weeks	All	35	576	94
			Severe	2	10	80

a Median under-reporting rate for all ADRs: 95% (IQR 91–99%). Median under-reporting rate for serious or severe ADRs: 80% (IQR 77–99%).

ADR = adverse drug reaction; **GP** = general practitioner; **IQR** = interquartile range; **PEM** = prescription event monitoring; **PMS** = postmarketing surveillance; **SRS** = spontaneous reporting system.

for all ADRs and those that provided an estimate of under-reporting for specific ADRs.

3.1 Estimates of Under-Reporting for All Adverse Drug Reactions (ADRs)

For studies providing an estimate of under-reporting for all ADRS, the under-reporting rate was expressed as the percentage of suspected ADRs found during a period of intensive monitoring that were not reported to the relevant SRS for the same or similar time period and population. This group was divided into two subcategories according to the study setting: general practice or hospital setting.

In the nine studies (table I) investigating ADR reporting by general practitioners (GPs), the under-reporting rate ranged from 36% to >99% with a median under-reporting rate of 95% (IQR 91–99%).[17-25] In five of these studies the under-reporting rate for more serious (or 'severe') ADRs was provided and was lower than that for all ADRs, decreasing from 91% to 47%,[17] from 1 in 1144 to 1 in 605 ADRs reported (both >99%),[20] from 91% to 77%,[21] from 1 in 24433 ADRs reported to 1 in 6123 ADRs reported (both >99%)[22] and from 94% to 80%,[25] respectively. In one study,[19] monitoring the reporting of ADRs leading to hospital admission (which are, by definition, serious[16]), the under-reporting rate to the SRS was 95%.

In the eight studies (table II) investigating ADR reporting in the hospital setting the under-reporting rate ranged from 59% to 100% with a median under-reporting rate of 96% (IQR 92–98%).[26,27,29-33,38] Five of these studies[26-29,32] provided a median under-reporting rate (also 95%) for more serious

ADRs by monitoring only serious ADRs in hospitals, by differentiating serious ADRs from all ADRs in hospital or by monitoring ADR-related hospital admissions (which are, by definition, serious[16]).

3.2 Estimates of Under-Reporting for Specific ADRs

Studies that provided an estimate of under-reporting for specific ADRs could be divided into two subcategories. In the first of these, data from SRSs were compared with the number of known or suspected ADRs detected during active or intensive searching of data sources such as drug/disease registries, health insurance claims data, death certificates, laboratory results and hospital discharge notes that were not reported to the relevant SRS. Across the 14 studies included in this category (table III) the under-reporting rate ranged from 6% to 100% with a median under-reporting rate of 83% (IQR 66–95%).[34-47] Thirteen of these studies[34-36,38-47] involved ADRs that were regarded or classified by the author as serious or severe or are serious according to conventional definitions.[16] In the remaining study,[37] investigating drug-induced liver disorders, the under-reporting rate for serious ADRs was calculated as 83% from the published study data.

In the second category, data from SRSs were compared with the expected number of ADRs found in clinical trials, postmarketing studies and other reference studies that were not reported to the relevant SRS for a similar population and time period. Across the six studies included in this category (table IV) the under-reporting rate ranged from 82% to >99% with a median under-reporting rate of 92% (IQR 85–98%). The majority of ADRs involved in these studies were serious or potentially serious, with the exception of one study monitoring ACE inhibitor-induced cough.[50] In all, there were 19 studies investigating the under-reporting of specific serious ADRs (tables III and IV excluding the study on ACE-inhibitor induced cough[50]). The median under-reporting rate for serious ADRs across these 19 studies was 85%.

4. Discussion

4.1 Overall

In this review, the estimated rate of under-reporting of ADRs to the SRS ranged from 6% to

Table II. Estimates of under-reporting by comparing spontaneous reports with data from intensive hospital-based monitoring[a]

Study	Country	Study focus	Type of ADR	No. of ADR reports to SRS	No. of ADRs found by hospital monitoring	Under-reporting rate (%)
Backstrom et al.[26]	Sweden	Serious ADRs in hospitals	Serious	15	107	86
Pouyanne et al.[27]	France	ADR-related hospital admissions	Serious	6371	134 159	95
Imbs et al.[28]	France	ADR-related hospital admissions	Serious	5973	143 624	96
Smith et al.[29]	UK	Hospital ADR monitoring scheme	Vast majority serious	30	477	94
Maistrello et al.[30]	Italy	Hospital ADRs meriting SRS report	All	9	22	59
Chan & Critchley[31]	Hong Kong	Promotion of ADR reporting in hospital setting	All	0	122	100
Hallas et al.[32]	Denmark	ADR-related hospital admissions	Serious	1	157	>99
Classen et al.[33]	US	Computerised/enhanced hospital ADR surveillance	All	9	731	>98

a Median under-reporting rate from all ADRs: 96% (IQR 92–98%). Median under-reporting rate for serious or severe ADRs: 95% (IQR 94–96%).

ADR = adverse drug reaction; **IQR** = interquartile range; **SRS** = spontaneous reporting system.

Table III. Estimates of under-reporting by comparing spontaneous reports with actual number of known or suspected cases for specific ADRs[a]

Study	Country	Study focus	Type of ADR	No. of ADR reports to SRS	No. of known or suspected ADRs	Under-reporting rate (%)
Dugue et al.[34]	France	Drug-induced muscular ADRs	Serious	2	9	78
Mittman et al.[35]	Canada	Drug-induced toxic epidermal necrolysis	Serious	25	674	96
La Grenade et al.[36]	US	Phenyl-propanolamine and stroke	Serious	0	27	100
Bagheri et al.[37]	France	Drug-induced liver disorders	All	1	13	92
			Serious	1	7	83
Skjeldestad et al.[38]	Norway	VTE and oral contraceptives	Serious	3	69	96
Pumphrey & Davis[39]	UK	Fatal drug-induced anaphylaxis	Serious	33	67	50
Kimmel et al.[40]	US	Serious ADRs attributed to protamine	Serious	3	16	81
Samuelsson et al.[41]	Sweden	Thrombosis/PE and hormonal contraception	Serious	0	20	100
Prevots et al.[42]	US	Vaccine-associated paralytic poliomyelitis	Serious	92	98	6
Arneborn & Palmbled[43]	Sweden	Drug-associated neutropenias	Serious	29	84	65
Bottiger et al.[44]	Sweden	Osteitis after BCG vaccination	Serious	89	115	23
Inman[45]	UK	Fatal aplastic anaemia with phenylbutazone/oxyphenbutazone	Serious	5	44	89
Bottiger & Westerholm[46]	Sweden	Drug-induced blood dyscrasias	Serious	Actual no. not provided	Actual no. not provided	~70 (average value)
Inman & Vessey[47]	UK	Fatal thromboembolism and oral contraceptives	Serious	8	53	85

a Median under-reporting rate: 83% (IQR 66–95%).

ADR = adverse drug reaction; **BCG** = Bacillus Calmelte-Guerin; **IQR** = interquartile range; **PE** = pulmonary embolism; **SRS** = spontaneous reporting system. **VTE** = venous thromboembolism.

100%.[17-53] This wide range reflects the considerable variation in study methods used. However, the distribution of under-reporting rates was skewed towards the high end of this range with a median under-reporting rate of 94% across all studies.

In three of the general practice-based intensive monitoring studies the under-reporting rates were particularly high (>99%).[20,22,23] This may have been because the sample of GPs was small, or because monitoring occurred over a short time period. These 'snapshots' may not have been truly representative of the entire population covered by the SRS. In addition, these figures represent under-reporting for all ADRs. This includes the common, non-serious ADRs that are less likely to be reported but which make up the majority of ADRs occurring in general practice.

Only a minority of studies contributed to the lower end of the range of under-reporting rates. Prevots et al.[42] found that only 6% of vaccine-associated paralytic poliomyelitis had not been reported to the SRS, and Bottiger et al.[44] in 1982 found that only 23% of BCG-associated osteitis had not been reported. It is possible that there is an enhanced reporting culture for vaccine-associated adverse reactions, since vaccines are administered to healthy individuals and so the reporting of adverse effects may be regarded as more important, as a public health issue.

It seems that training may improve reporting (at least in the short-term). In the study by Lewis et al.,[18] which included training doctors and involved children, the under-reporting rate was 36%. In the 'spontaneous' reporting component of this study physicians were given individual training on how

and why to report suspected ADRs. However, this relatively low under-reporting rate may reflect, in addition to the effect of training, a greater motivation to report ADRs in this patient group despite the majority of events being classified as mild to moderate in nature.

4.2 General Practice Versus Hospital Reporting

There was no evidence in this review of any significant difference in the under-reporting rates for GPs compared with hospital doctors. The median under-reporting rate for general practice and hospital-based monitoring studies was similarly high at 95% and 96%, respectively. The studies included in these were predominantly from European countries, where surveys of ADR reporting behaviour indicate that higher proportions of GPs report ADRs than hospital specialists.[54-56] Attitudes to ADR reporting may differ, e.g. in the US, where it is possible that hospital doctors may be more likely to report ADRs. Reporting of ADRs may also vary depending on the clinical specialty.

4.3 Selective Reporting Depending on the Type of ADR

Evidence of selective reporting for serious ADRs is provided by the results of several of the intensive general practice monitoring studies. The under-reporting rates were reduced in three studies from 1 in 1144 to 1 in 605 ADRs reported (both >99%),[20] from 1 in 24433 ADRs reported to 1 in 6123 ADRs reported (both >99%)[22] and from 94% to 80%,[25] respectively, for all ADRs compared with serious ADRs.

Further evidence of selective reporting is supported by the results of two studies in the UK[17,21] using data from prescription event monitoring (PEM) studies for a number of newly marketed drugs. Events recorded by GPs as ADRs and also reported to the SRS were identified. Both studies yielded overall under-reporting rates of 91% for all ADRs but this was reduced for serious ADRs to 47%[17] in the 2001 study and 77%[21] in the 1998 study. This would perhaps be expected for older drugs but not for newly marketed drugs, as UK prescribers are asked under a voluntary scheme (the black triangle scheme) to report all ADRs to the regulatory authority. It appears from these studies that reporting for serious ADRs has improved over time. This may have been due to increased promotion of the UK Yellow Card scheme during this period, although other biases may exist; e.g. a different group of drugs was included in each study although the definition of 'serious' used was essentially the same in both studies.

Five studies investigating serious ADRs in a hospital setting or leading to hospital admission (table II) reported consistently high under-reporting rates (86% to >99%; median 95%).[26-29,32] Furthermore, in 19 studies investigating reporting of specific serious ADRs (table III and table IV, excluding the study on ACE inhibitor-induced cough[50]) the median under-reporting rate for serious ADRs was 85%.[34-49,51-53]

It is clear, therefore, that despite some evidence of selective reporting there is also evidence to indicate that there is considerable under-reporting of serious ADRs, including suspected reactions with a fatal outcome.

4.4 Limitations of This Systematic Review

The use of the term under-reporting may have limited the number of relevant studies identified, as this is not a standard search term. This is likely to have had only a minimal effect, since this term appeared to be well accepted in the studies found.

There was considerable variation in the estimates of under-reporting generated in this systematic review. This is not surprising given the range of different study methods identified. The under-reporting rate was calculated in different study settings (general practice vs hospital), using different data sources (e.g. hospital admission data, discharge notes, insurance claims databases, background rate data) and for different drugs (all drugs vs specific drugs). Despite this heterogeneity, however, under-reporting rates were generally high overall.

It is difficult to determine which method may be best for estimations of under-reporting rates. As

discussed previously, intensive monitoring in general practice has its limitations, as these 'snapshots' may not adequately represent the entire population, but they have the advantage of covering a wide variety of drugs and ADRs. Estimations of under-reporting from studies investigating a specific ADR will be biased by the nature of the drug and ADR involved.

For the studies included in table IV, the under-reporting rate was estimated by comparing the number of spontaneous reports received by the SRS with the expected number. However, this expected number is extrapolated from a background incidence rate (e.g. from a previous cross-sectional survey or other pharmacoepidemiology study). It could be argued that these results may be less reliable, as the background incidence rate for the ADR in question may have come from a different country or otherwise be very different for the population or time period covered by the SRS.

This is similar to comparing the number of spontaneous ADR reports with the number of expected reports based on clinical trial data. This may provide a general indication of the degree of under-reporting, but the latter is based on the use of a drug in a controlled population and may not be truly reflective of the 'real-life' incidence of ADRs observed by the SRS.

In addition, geographical differences in spontaneous reporting rates across the 12 countries included may also contribute to the variations in estimates of under-reporting. The most common sources of

Table IV. Estimates of under-reporting by comparing spontaneous reports with expected number of cases extrapolated from reference studies[a,b]

Study	Country	Study focus	Type of ADR	No. of ADR reports to SRS	Expected no. of ADRs	Under-reporting rate (%)
in't Veld et al.[48]	Holland	Drug-induced Stevens-Johnson syndrome	Serious	13 (0.1 per 10^6 prescriptions)	1–6 per 10^6 prescriptions	90–98[c]
		Drug-induced toxic epidermal necrolysis	Serious	14 (0.1 per 10^6 prescriptions)	0.4–1.2 per 10^6 prescriptions	75–90[c]
Farrington et al.[49]	UK	Idiopathic thrombocytopenic purpura with MMR vaccine	Serious	20 (1 in 130 000 doses)	1 in 24 000 doses	82
Begaud et al.[50]	France	Study of ACE inhibitor-induced cough in 60 general practices	Non-serious	3	3915	>99
Torello et al.[51]	Spain	Incidence of ADRs reported to SRS vs data from previous cross-sectional survey	Serious	Per million of Andalusian population	Per million of Andalusian population	97 (average value)
		GI haemorrhage	Serious	1.07	37.4	97
		Anaphylactic shock	Serious	0.34	13.8	97.5
		Bronchospasm	Serious	0.17	30.9	99.5
		Confusion	Serious	0.68	23.6	97
		Hypotension	Serious	0.80	47.1	98
		Liver disorders	Serious	1.8	28.4	94
Rawlins[52]	UK	Admissions due to NSAID-induced bleeding peptic ulcers in >65-year-olds	Serious	364	2000–2500 per year	82–85 83.5 (average value)
Inman & Adelstein[53]	UK	Deaths due to overexposure to bronchodilating aerosols	Serious	12	3500	>99

a Median under-reporting rate: 92% (IQR 85–98%).

b Reference studies include clinical trials and pharmacoepidemiological studies that report the frequency of a specific ADR in a particular population and provide an estimate for the expected number of ADRs occuring in the SRS population.

c The average under-reporting rate for combined analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis was 88.

ADR = adverse drug reaction; **GI** = gastrointestinal; **IQR** = interquartile range; **MMR** = measles-mumps-rubella; **SRS** = spontaneous reporting system.

these studies were from the UK, France, Sweden and the US. These are all countries with well developed SRSs[3] where reporting rates may be expected to be high, but this was not generally borne out by the results from the studies in these countries.

One further limitation of this systematic review is that the definition of seriousness or severity of ADRs was not always clearly defined in the original studies. Although there was some evidence of selective reporting for such ADRs (e.g. in the general practice setting), in the majority of studies where serious or severe ADRs were considered the under-reporting rate remained high.

4.5 Implications of Under-Reporting

Under-reporting is one of the main disadvantages of the SRS, since the absolute number of ADR reports is not truly known. It would be inappropriate to apply a standard 'correction factor' based on the results of this study, since there is inevitably considerable variation in under-reporting for different drugs and types of ADRs, in different populations and at different points in time. For example, it is well accepted that for newly marketed drugs the rate of reporting of ADRs is at its highest in the initial phase after market launch (usually within the first 1 or 2 years).[10] This practice is actively encouraged to ensure that signals of potential ADRs are detected in a timely fashion.

In pharmacovigilance it is often necessary to compare the relative safety profiles of two drugs. It may be possible to use prescription data to estimate drug exposure in the population and allow for a comparison of estimated incidence rates but under-reporting limits the interpretation of these comparisons. It cannot be assumed that the under-reporting rate will be identical for both drugs unless perhaps they are of the same therapeutic class, with similar indications, and are marketed in the same country at the same time.[57] If under-reporting is markedly different, any true difference in toxicity between the drugs may be masked or exaggerated.

In recent years many SRSs have adopted a statistical approach to generate potential signals of ADRs. This includes techniques such as proportional reporting ratios,[58] which essentially compare the proportion of an ADR for a specific drug within an SRS database with the background proportion for that ADR for all drugs in the database. It has the advantage not only of eliminating the need for denominator information but, if the database is large, it can also counteract some of the problems associated with unknown variations in under-reporting. The merits of these techniques in the context of the under-reporting of ADRs are debated elsewhere but remain unclear.[59-61]

4.6 Reasons for Under-Reporting

Many physicians report that they have detected an ADR during their practice but a significant proportion do not report the ADR to a regulatory body.[62,63] Several surveys[54,55,64-66] have investigated the reasons for under-reporting of ADRs. Common reasons for not reporting include a lack of time,[54,66] different care priorities,[66] uncertainty about the drug causing the ADR,[55,64-66] difficulty in accessing reporting forms,[54] lack of awareness of the requirements for reporting[65,66] and lack of understanding of the purpose of SRSs.[54] Well known and trivial ADRs are less likely to be reported.[55,65] In addition, physicians' attitudes towards reporting ADRs contribute to under-reporting. For example, a recent survey has reported that physicians may not report ADRs because they believe that serious reactions will be well documented by the time a drug is marketed or that one case reported by an individual doctor will not contribute to medical knowledge.[67]

4.7 Strategies for Improving Reporting

Various initiatives have been introduced in recent years to encourage and facilitate the reporting of ADRs, such as greater accessibility to the SRS database through electronic and online reporting[68] and the introduction of pharmacist[69] and nurse reporting.[70] Practitioners need to develop a greater understanding as to the purpose of pharmacovigilance in order to improve both the quantity and quality of reports. High quality prescribing includes monitoring ADRs at the clinical level and reporting such ADRs when appropriate. This requires educa-

tion at both the undergraduate and postgraduate level. A recent survey of UK medical and pharmacy schools indicated that fewer than half of the respondents provided undergraduate students with a guide to reporting ADRs.[71] Educational resources are available at the postgraduate level in the form of distance learning modules[72] but these are not compulsory and it is possible that the participants motivated to use these resources are already reliable ADR reporters. Another strategy that has been suggested to help stimulate reporting is to reward practitioners who supply good quality ADR reports with credits points for continuing education as well as feedback information.[73] This has yet to be fully explored.

5. Conclusion

This review provides evidence of significant and widespread under-reporting of ADRs to the SRS, including serious and fatal ADRs. It is not possible to provide an accurate estimate of the level of under-reporting but it is likely to be in excess of 90%. Under-reporting of ADRs has an impact on the benefit/risk evaluation of medicines, particularly when spontaneous reports are the only or the main source used in the assessment of drug safety.[74]

Prescribing medicine is a very important responsibility for the healthcare professional but reporting suspected ADRs and participation in ADR monitoring systems must also be promoted as a fundamental professional duty. Education is the cornerstone for good quality reporting, but both the quantity and quality of reporting for suspected ADRs are important and must become part of continuing medical education and clinical governance. Further studies are required to assess the impact of under-reporting on public health decisions and to evaluate recent initiatives to improve reporting such as online reporting, pharmacist and nurse reporting, greater feedback to reporters and potential links with continuing education and training.

Acknowledgements

The Drug Safety Research Unit (DSRU) is a registered independent charity (No. 327206) associated with the University of Portsmouth. The DSRU receives donations and grants from pharmaceutical companies; however, the companies have no control on the conduct or publication of its studies.

This systematic review was not externally funded. Lorna Hazell has no conflicts of interest with regard to this review. Dr Shakir has provided consultancies and received lecturing fees from pharmaceutical companies but none of these are related to this review.

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