ORIGINAL RESEARCH ARTICLE

Drug Saf 2009; 32 (11): 1067-1074
0114-5916/09/0011-1067/$49.95/0

Consumer Reporting of Adverse Drug Reactions

A Retrospective Analysis of the Danish Adverse Drug Reaction Database from 2004 to 2006

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Abstract

Background: Reporting adverse drug reactions (ADRs) has traditionally been the sole province of healthcare professionals. Since 2003 in Denmark, consumers have been able to report ADRs directly to the authorities. The objective of this study was to compare ADRs reported by consumers with ADRs reported from other sources, in terms of their type, seriousness and the suspected medicines involved.

Methods: The number of ADRs reported to the Danish ADR database from 2004 to 2006 was analysed in terms of category of reporter, seriousness, category of ADRs by system organ class (SOC) and the suspected medicines on level 1 of the anatomical therapeutic chemical (ATC) classification system. ADR reports from consumers were compared with reports from other sources (physicians, pharmacists, lawyers, pharmaceutical companies and other healthcare professionals). Chi-square and odds ratios (ORs) were calculated to investigate the dependence between type of reporter and reported ADRs (classified by ATC or SOC).

Findings: We analysed 6319 ADR reports corresponding to 15 531 ADRs. Consumers reported 11% of the ADRs. Consumers' share of 'serious' ADRs was comparable to that of physicians (approximately 45%) but lower than that of pharmacists and other healthcare professionals. When consumer reports were compared with reports from other sources, consumers were more likely to report ADRs from the following SOCs: 'nervous system disorders' (OR = 1.27; 95% CI 1.05, 1.53); 'psychiatric disorders' (OR = 1.70; 95% CI 1.31, 2.20) and 'reproductive system and breast disorders' (OR = 2.02; 95% CI 1.13, 3.61) than other sources. Compared with other sources, consumers reported fewer ADRs from the SOCs 'blood and lymphatic system disorders' (OR = 0.22; 95% CI 0.08, 0.59) and 'hepatobiliary system disorders' (OR = 0.14; 95% CI 0.04, 0.57). Consumers were more likely to report ADRs

from the ATC group N (nervous system) [OR = 2.72; 95% CI 2.34, 3.17], ATC group P (antiparasitic products) [OR = 2.41; 95% CI 1.32, 4.52] and ATC group S (sensory organs) [OR = 4.79; 95% CI 2.04, 11.23] than other sources. Consumers reported fewer ADRs from the ATC group B (blood and blood-forming organs) [OR = 0.04; 95% CI 0.006, 0.32] and the ATC groups J (anti-infective for systemic use) [OR = 0.44; 95% CI 0.33, 0.58], L (antioneoplastic and immunomodulating agents) [OR = 0.19; 95% CI 0.12, 0.30] and V (various) [OR = 0.03; 95% CI 0.004, 0.21] than other sources. In the SOC 'nervous system disorders', consumers reported seven categories of ADRs that were not reported by the other sources.

Conclusion: This study showed that compared with other sources, consumers reported different categories of ADRs for different types of medicines. Consumers should be actively included in systematic drug surveillance systems, including clinical settings, and their reports should be taken as seriously as reports from other sources.

Background

Adverse drug reactions (ADRs) have been monitored in many countries and by the WHO since the 1960s in spontaneous reporting systems, also called 'early warning' systems.[1] The primary aim of these systems is to collect new information about possible ADRs in order to acquire new knowledge, in particular about serious, rare and unknown ADRs at an early stage after the drugs are marketed.[1-3] During the first many years of existence of the reporting systems, only doctors and dentists were allowed to submit reports. Since 1995, drug manufacturers have also been placed under obligation to report ADRs, and other healthcare professionals, pharmacists and consumers have been allowed to report ADRs in the hope that this would increase the volume and quality of the reports.[4,5] In Denmark, The Danish Medicines Agency has increased its focus on consumer safety and recognized the role of consumers in drug surveillance since the introduction of consumer reporting in 2003.[6] The decision was fuelled by the case of the anti-obesity drug Letigen® (caffeine/ephedrine). The Danish Medicines Agency suspended marketing of this medication because of reports of serious cardiovascular ADRs and sudden death, presumably caused by Letigen®.[6] In this particular case, the ADR reports had been collected by the Danish Consumer Council and handed over to The Danish Medicines Agency. Besides Denmark, ADR reports from consumers have also been accepted by KILEN (Consumer Association for Medicines and Health) in Sweden since 1978, and by the regulatory authorities in the US (1993), Australia (2003), the Netherlands (2003), Canada (2003) and the UK (2005).[7] Little has been published on consumer reporting of ADRs in the literature. In their review of consumer reporting in 2003, van Grootheest and colleagues[8] concluded that data were insufficient to establish whether patient reporting added value to existing drug surveillance systems. Studies of consumer reports about selective serotonin reuptake inhibitors and benzodiazepines showed that consumers were more likely to report behavioural effects, suicidal tendencies and withdrawal symptoms than healthcare professionals.[9,10] Experiences with consumer reporting in the Netherlands were recently published showing differences in the categories of seriousness and outcome of the reported ADRs between patients and healthcare professionals.[11] The objective of this present study was to compare ADRs reported by consumers with ADRs reported from other sources, in terms of their type, seriousness and the suspected medicines involved.

Methods

Study Setting

The reporting of ADRs has been obligatory in Denmark since 1 May 1968. Initially, only doctors were covered by the obligation; however, in 1972, dentists were also required to report ADRs. Since 1995, drug manufacturers have been obliged to keep registers of suspected and demonstrated ADRs and to make these available to the authorities. Since July 2003, consumers have been able to report ADRs directly to the authorities. The Danish reporting system has been described elsewhere.[12] The Danish ADR system contains all spontaneous reports in Denmark, including those reported directly to the pharmaceutical companies. An ADR report is defined by the following four criteria, which must be included in all reports: (i) information about the patient; (ii) the suspected medicines(s); (iii) the presumed ADR(s); and (iv) information about the person making the report. An ADR report may contain one or more ADR terms. These ADRs are evaluated by the authorities and categorized in the ADR database by degree of seriousness according to CIOMS criteria.[13] The Danish Medicines Agency handles ADR consumer reports the same way it handles reports from other sources.

Classification of Reporters

The Danish ADR database defines the following five categories of persons submitting data to the database:

- Consumers: ADR reports submitted by patients, patients' relatives, other members of the public.
- Lawyers: ADR reports submitted by patient injury insurances and law firms.
- Pharmacists: ADR reports submitted by community or hospital pharmacists.
- Physicians: ADR reports submitted by general practitioners, hospital doctors and dentists.
- Other healthcare professionals: ADR reports submitted by nurses, drug manufacturers, social and healthcare assistants.

ADR reports from consumers keep their initial status as a consumer report even if a physician medically confirms a consumer report at a later stage. This study applies these official designations for the category of persons submitting reports. In the majority of the analyses, we dichotomized reporter categories into consumer reports and reports from other sources.

Study Design

The study comprised all ADR reports submitted to the Danish Medicines Agency from 2004 to 2006. It covers the first 3 years after the introduction of consumer reporting in Denmark. The content of ADR reports made by consumers were compared with ADR reports made by other sources with respect to category of seriousness, category of ADRs classified by system organ class (SOC) and the therapeutic categories anatomical therapeutic chemical (ATC) classification groups reported. We only analysed ADRs classified as 'serious' because the serious ADRs are the primary focus of the spontaneous reporting systems and of particular public health interest. The unit of analysis was ADRs.

Material

Data extraction and statistical data analyses of the raw material were comprehensive and time consuming. ADR information was placed at the disposal of this study in anonymous form with encrypted identification. Information was extracted from the ADR database on the date reports were received; category of persons submitting the reports; and criteria of seriousness and medications for which the ADRs were reported. The reported ADRs were coded according to the Medical Dictionary for Regulatory Activities structure on 'SOC' and 'preferred term' level.[13] ADR reports were classified according to seriousness using CIOMS criteria by academic staff in the Danish Medicines Agency.

Anatomical Therapeutic Chemical (ATC) Classification Groups

The ATC system is a system for classifying medicinal products according to their primary constituent, the organ or system on which they act and

their chemical, pharmacological and therapeutic properties. Medicinal products are classified in groups on five different levels. The medicines are divided into 14 main groups (first level), with one pharmacological/therapeutic subgroup (second level). The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance. The second, third and fourth levels are often used to identify pharmacological subgroups if this is considered more appropriate than therapeutic or chemical subgroups.[14] The extract from the ADR database only provides information according to the trade name of those medicinal products that have been reported as causing ADRs. Therefore, it was necessary to manually translate trade names into generic names on ATC level 5 in The Danish Medicines Agency's medicines register, and then run the generic form of the medicine name against the ADRs reported. In order to present the ADR data in a comprehensible form, they are given at ATC level 1 in this article.

Statistical Analyses

The main thrust of the statistical analysis was the investigation of dependence between the individuals submitting the ADR report and the reported ADRs (classified by ATC code or SOC), which was analysed using a chi-squared test for independence. In the event the test for independence was rejected, the dependence between the reporter and category of ADRs for each category of ATC or SOC were investigated in further detail.[15] Each odds ratio (OR) was calculated using a 2×2 table for the categories of reporters (consumers and other sources) and each ATC group or SOC. Confidence intervals were calculated for all ORs (95% level). The statistical analyses were performed with SAS version 9.1.(SAS Institute Inc., Cary, NC, USA).

Results

Distribution of Reported Adverse Drug Reactions (ADRs)

From 2004 to 2006, 6319 ADR reports corresponding to 15 531 ADRs were made. Consumers reported 136 ADR reports in 2004, 163 ADR reports in 2005 and 245 ADR reports in 2006, encompassing a total of 1700 individual ADRs. As shown in table I, consumer reports contributed to 11% of the total number of reported ADRs. In comparison, lawyers and pharmacists contributed to <2% of the total amount.

Seriousness of Reported ADRs

Table I shows the distribution of reported ADRs according to whether they were classified as serious or category of the person submitting the report ($p < 0.0001$). The chi-squared comparisons of degree of seriousness and category of reporter were 1551.99 ($p < 0.0001$). Table I shows that approximately 45% of the ADRs reported by consumers and physicians were classified as serious. Lawyers and pharmacists reported only rarely; however, almost all reports from pharmacists were classified as serious, whereas only one-third of the reports from lawyers fell in this category. Other healthcare professionals also contributed to a high percentage of serious reports; approximately 85% of their total number of reports.

ADRs by System Organ Class Category and Type of Reporter

Table II shows the distribution of ADRs by category (SOC) and type of reporter. There was a significant difference in the distribution of reports for the various categories of persons submitting the report (chi square = 86.91; $p < 0.0001$). The italicized fields in table II indicate the category of ADRs (SOC) for which consumers and other sources have reported differently. When consumer

Table I. Distribution of adverse drug reactions (ADRs) by reporters, and seriousness according to CIOMS criteria[13]

Reporters	Total ADRs [n (%)]	'Serious' ADRs [n (%)]	Non-serious ADRs [n (%)]
Physician	10 948 (70)	4921 (45)	6027 (55)
Pharmacist	277 (2)	274 (99)	3 (1)
OHCP	2 447 (16)	2065 (84)	382 (16)
Lawyer	159 (1)	47 (30)	112 (70)
Consumer	1 700 (11)	773 (46)	927 (55)

OHCP = other healthcare professionals, including nurses, drug manufacturers, social and healthcare assistants.

Table II. Distribution of 'serious' adverse drug reactions (ADRs) [n] between consumers and other sources by system organ class (SOC).[a] The italicized fields indicate the category of ADRs (SOC) for which consumers and other sources have reported differently

System organ class	Consumers	Other sources	OR (95% CI)	p-Value
Blood and lymphatic system disorders	*4*	*169*	*0.22 (0.08, 0.59)*	*0.0010*
Cardiac disorders	36	292	1.17 (0.83, 1.67)	0.3758
Congenital, familial and genetic disorders	4	56	0.67 (0.24, 1.86)	0.4433
Ear and labyrinth disorders	*9*	*41*	*2.09 (1.01, 4.30)*	*0.0420*
Endocrine disorders	6	28	2.03 (0.84, 4.92)	0.1084
Eye disorders	23	155	1.41 (0.90, 2.20)	0.1239
Gastrointestinal disorders	93	724	1.24 (0.99, 1.56)	0.0627
General disorders and administration site conditions	98	853	1.10 (0.88, 1.37)	0.4100
Hepatobiliary disorders	*2*	*131*	*0.14 (0.04, 0.57)*	*0.0014*
Immune system disorders	8	116	0.65 (0.31, 1.33)	0.2346
Infections and infestations	*9*	*188*	*0.45 (0.23, 0.87)*	*0.0157*
Injury, poisoning and procedural complications	22	175	1.19 (0.76, 1.88)	0.4393
Investigations	*37*	*485*	*0.71 (0.50, 0.99)*	*0.0465*
Metabolism and nutrition disorders	15	206	0.68 (0.40, 1.16)	0.1543
Musculoskeletal and connective tissue disorders	35	368	0.89 (0.63, 1.27)	0.5369
Neoplasms benign, malignant and unspecified	6	84	0.67 (0.29, 1.54)	0.3469
Nervous system disorders	*158*	*1229*	*1.27 (1.05, 1.53)*	*0.0111*
Pregnancy, puerperium and perinatal conditions	3	84	0.33 (0.11, 1.06)	0.0511
Psychiatric disorders	*72*	*416*	*1.70 (1.31, 2.20)*	*<0.0001*
Renal and urinary disorders	12	125	0.91 (0.50, 1.65)	0.7458
Reproductive system and breast disorders	*14*	*66*	*2.02 (1.13, 3.61)*	*0.0153*
Respiratory, thoracic and mediastinal disorders	39	451	0.81 (0.58, 1.13)	0.2119
Skin and subcutaneous tissue disorders	49	604	0.75 (0.56, 1.01)	0.0616
Social circumstances	1	17	0.56 (0.07, 4.18)	0.5624
Surgical and medical procedures	4	39	0.97 (0.35, 2.71)	0.9529
Vascular disorders	14	205	0.64 (0.37, 1.10)	0.1054
Total	773	7303		

a Only 'serious' ADRs according to CIOMS criteria[13] were analysed.

OR = odds ratio.

reports were compared with reports from other sources, consumers were more likely to report ADRs from the SOCs 'ear and labyrinth disorders' (OR = 2.09; 95% CI 1.01, 4.30), 'nervous system disorders' (OR = 1.27; 95% CI 1.05, 1.53), 'psychiatric disorders' (OR = 1.70; 95% CI 1.31, 2.20) and 'reproductive system and breast disorders' (OR = 2.02; 95% CI 1.13, 3.61) than other sources. Compared with other sources, consumers reported fewer ADRs from the SOCs 'blood and lymphatic system disorders' (OR = 0.22; 95% CI 0.08, 0.59), 'hepatobiliary system disorders' (OR = 0.14; 95% CI 0.04, 0.57), 'infections and infestations' (OR = 0.45; 95% CI 0.23, 0.87) and 'investigations' (OR = 0.71; 95% CI 0.50, 0.99).

Serious ADRs by Type of Medicine (ATC Group) and Type of Reporter

Table III shows the distribution of serious ADRs by the type of medicine (ATC groups) and type of reporter. There was a significant difference in the distribution of reports for the various categories of persons submitting the reports (chi square = 301.90; $p < 0.0001$). The italicized fields in table III indicate the type of medicines (ATC groups) for which consumers and other sources reported differently.

Table III. Distribution of 'serious' adverse drug reactions (ADRs) [n] between consumers and other sources by type of medicine (anatomical therapeutic chemical [ATC] classification first level).[a] The italicized fields indicate the type of medicines (ATC groups) for which consumers and other sources have reported differently

ATC group	Consumers	Other sources	OR (95% CI)	p-Values
A (Alimentary tract and metabolism)	45	428	0.98 (0.72, 1.35)	0.9260
B (Blood and blood forming organs)	*1*	*203*	*0.04 (0.006, 0.32)*	*<0.0001*
C (Cardiovascular system)	82	632	1.24 (0.97, 1.58)	0.0793
D (Dermatological)	21	197	1.00 (0.63, 1.58)	0.9988
G (Genito-urinary system and sex hormones)	35	396	0.82 (0.58, 1.17)	0.2730
H (Systemic hormonal preparations)	36	246	1.39 (0.97-1.99)	0.0697
J (Anti-infective for systemic use)	*56*	*1089*	*0.44 (0.33, 0.58)*	*<0.0001*
L (Antioneoplastic and immunomodulating agents)	*21*	*912*	*0.19 (0.12, 0.30)*	*<0.0001*
M (Musculosketal system)	53	586	0.84 (0.62, 1.12)	0.2307
N (Nervous system)	*380*	*1908*	*2.72 (2.34, 3.17)*	*<0.0001*
P (Antiparasitic products)	*13*	*51*	*2.41 (1.32, 4.52)*	*0.0037*
R (Respiratory system)	13	196	0.02 (0.35, 1.10)	0.0899
S (Sensory organs)	*8*	*16*	*4.79 (2.04, 11.23)*	*<0.0001*
V (Various)	*1*	*308*	*0.03 (0.004, 0.21)*	*<0.0001*
Total	765	7168		

a Only 'serious' ADRs according to CIOMS criteria[13] were analysed.

OR = odds ratio.

When consumer reports were compared with reports from other sources, the consumers were more likely to report ADRs from the ATC group N (nervous system) [OR = 2.72; 95% CI 2.34, 3.17], ATC group P (antiparasitic products) [OR = 2.41; 95% CI 1.32, 4.52] and ATC group S (sensory organs) [OR = 4.79; 95% CI 2.04, 11.23] than other sources. Compared with other sources, consumers reported fewer ADRs from the ATC group B (blood and blood-forming organs) [OR = 0.04; 95% CI 0.006, 0.32] and from the ATC groups J (anti-infective for systemic use) [OR = 0.44; 95% CI 0.33, 0.58], L (antioneoplastic and immunomodulating agents) [OR = 0.19; 95% CI 0.12, 0.30] and group V (various) [OR = 0.033; 95% CI 0.004, 0.21] than from other ATC groups.

ADRs Reported by Consumers Exclusively

In table IV it is shown that consumers reported seven different categories of ADRs (preferred term) in the SOC 'nervous system disorders' that were not reported by other sources. Consumers reported serious ADRs such as dysgraphia and parosmia for gabapentin and thromboembolic stroke for rofecoxib.

Discussion

The study showed that in a national ADR reporting system, ADR reporting from consumers and other sources differed with regard to seriousness of ADRs, reported ADRs (SOC) and therapeutic categories. This study retrospectively described the reporting among consumers compared with other reporters. The extent to which the results can be generalized to other countries cannot be determined based on the analysis conducted. The use/implementation of consumer

Table IV. Categories of adverse drug reactions (ADRs) from the system organ class 'nervous system disorders' reported only by consumers

Drug (generic name)	ADRs[a]	Number
Mometasone	Convulsions local	1
Gabapentin	Dysgraphia	2
Gabapentin	Parosmia	2
Nicotine	Dysphasia	1
Tropicamide	Myasthenia gravis	1
Pregabalin	Nerve compression	1
Rofecoxib	Thromboembolic stroke	1
	Total	9

a Preferred term.

data in systematic ADR monitoring in the Danish Medicines Agency was not studied either.

The Magnitude of Consumer Data in the Spontaneous Reporting System

In Denmark, consumer ADR reports contributed 7% of the total number of reported ADRs in 2003,[13] which increased to 11% in 2006. Physicians and other healthcare professionals are the main source for information about ADRs in Denmark. Studies from other countries have shown that consumer ADR reports contribute 7–23% of total reported ADRs.[7,11] The number of ADR reports analysed was comparable to a recent study from the Netherlands, when taking into account the number of inhabitants.[11]

Comparison of Report Characteristics between Consumers and Other Sources

The share of consumer ADR reports classified as serious did not differ from the share of reports from physicians, i.e. about 45% of the total number of reported ADRs. In the Netherlands study, no significant difference in seriousness was detected between consumers and healthcare professionals, although the magnitude was lower than in Denmark (approximately 20%).[11] Pharmacists and other healthcare professionals reported a far greater share of serious ADRs than either consumers or physicians. The high number of serious reports from other healthcare professionals may be due to the inclusion of reports from pharmaceutical companies in this category, which have been classified into serious or non-serious ADRs by the companies and not the Danish Medicines Agency. Consumers primarily reported ADRs for the SOCs 'nervous system disorders' and 'psychiatric disorders' and for medicines in ATC group N (nervous system), which is also in keeping with previous analyses of consumer reports in the Netherlands, Sweden and the UK.[16-18] Our analysis has also shown that consumers contributed different information to the spontaneous reporting system for the SOC 'nervous system disorders' than did the other sources. These consumer reports contained information about diagnoses that lay people are not usually considered able to make. Since consumers and healthcare professionals may have differing ideas of the meaning of ADRs in daily life, analysis of the non-serious ADRs would also provide new information about the seriousness of ADRs. Whether consumers are more or less likely to report ADRs from new medicines compared with older ones would also be of interest. Further analysis of ADR data will be needed to answer this question by precisely identifying which ADRs consumers report differently and how the pharmaceutical companies and regulatory agencies use and act upon this information.

Consumer Reports as a Signal Detection Tool

If introducing consumer reporting in the spontaneous reporting systems is to add new values to the system, ADR reports should detect new signals earlier or find new signals not detected by healthcare professionals.[19-22] Time relationship analyses on the ADR reports are difficult to perform since the relevant information is often missing or incomplete in ADR reports, both from consumers and other sources. Medicines are also marketed at different times in the US and Europe for example, and the first signal of a new ADR can be difficult to identify and recognize because of limited access to other national ADR databases. ADR data sharing and the investigation of new ADR signals in Europe takes place at the central level in the common ADR committee, the Pharmacovigilance Working Party under the European Medicines Agency.

Strengths and Limitations of the Study

van Grootheest and de Jong-van den Berg[18] found that the validity of consumer reports compared with other reports from other sources was high in the Netherlands. In this study, we did not evaluate the validity of the consumer reports since we only had access to the data entered into the Danish ADR database and not the original reports. We analysed differences in the reporting of ADRs and the suspected medicines for those ADRs classified as serious because these data are of special public health interest and concern. An analysis of the remaining non-serious reports could be interesting with regard to the perspectives on

ADRs of consumers versus other sources. Qualitative interview studies with patients could provide valuable information on consumers' experiences with and perspectives on ADRs. Further detailed analysis of the data material, such as comparing the number of ADRs and suspect medicines per patient for each type of reporter could be very interesting, as could a more detailed analysis of the ADRs reported only by consumers.

Conclusions

This study shows that consumers report different categories of ADRs and involving different types of medicines than reports that are made by other sources. This information can give the authorities and researchers access to relevant additional information about the adverse effects of medicines. Consumers should be actively included in systematic drug surveillance systems, including clinical settings, and their reports should be taken as seriously as reports from other sources.

Acknowledgements

The authors would like to thank the Danish Medicines Agency for placing data at their disposal. We also thank the anonymous reviewers in providing guidance, helpful comments and input on earlier versions of the manuscript. This study was conducted as a part of L. Aagaard's PhD project, which was funded by the Danish Medicines Agency. E.H. Hansen and L.H. Nielsen have no conflicts of interest that are directly relevant to the content of this study.

Contributors: L. Aagaard and E. H. Hansen designed the study, analysed data and wrote the first version of the manuscript. L. Aagaard carried out the sampling and L.H. Nielsen the statistical analysis. All authors saw and approved the final version of the manuscript.

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