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ORIGINAL REPORT

Media attention and the influence on the reporting odds ratio in disproportionality analysis: an example of patient reporting of statins†

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SUMMARY

Aim To study the influence of media attention about statins and ADRs on the level of disproportionality, expressed as the reporting odds ratio (ROR) for statins in the Lareb database, based on patients' reports.

Methods Patient reports about statins, before and after the broadcast of a consumer programme about statins, were compared. In order to calculate the correlation between the ROR for patient-statin reports between the period before and after the broadcast a Pearson correlation-coefficient (r) was calculated. The type of reported ADRs associated with statins before and after the broadcast was compared both on the level of system organ class (SOC) and preferred terms (PT).

Results Pearson's Correlation-coefficient for the comparison of RORs before and after the broadcast was 0.83. In respect to specific ADRs, no differences were found in reporting on SOC level before and after the broadcast, except for the SOC *Musculoskeletal and connective tissue disorders*. For ADRs that were specifically mentioned during the broadcast, no differences were found except for an increased number of myalgia and arthralgia reports.

Conclusion Our study demonstrates that media attention does not necessarily influence the relative reporting by patients expressed as RORs in the national ADR database. On SOC level only in *Musculoskeletal and connective tissue disorders* the relative reporting increased. For myalgia and arthralgia, there was a proportional increase of reporting within the statin class but not for the other ADRs that were explicitly mentioned in the TV programme about statins. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug reactions; media attention; notoriety bias; pharmacovigilance; statins

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INTRODUCTION

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction (ADR) reporting database in the Netherlands. The main objective of a spontaneous reporting system is to signal new ADRs, that have not been recognised prior to marketing, as soon as possible[1,2]. In the Netherlands physicians, pharmacists and patients are able to report suspected ADRs to the pharmacovigilance centre. Patients are allowed to submit reports of possible ADRs directly to Lareb since 2003[3,4].

Reporting to a spontaneous reporting database could increase after a safety alert because of increased reporting of the event of interest, a so-called notoriety bias[2,5]. Similarly, attention in the media could also lead to increased or selective reporting of certain ADRs[6]. The potential behavioural influence of media on both health professionals and consumers can be extensive[7,8].

In England, adverse media publicity about paroxetin led to an increase in the reporting of ADRs to the Medicines and Healthcare products Regulatory Agency (MHRA) through the yellow-card system. Analysis of the yellow-card data showed short-term peaks in

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reporting of ADRs of paroxetin[9]. The effects of these reporting peaks on measures of disproportionality like the proportional reporting ratio (PRR) or the reporting odds ratio (ROR) of certain ADRs in the database of the MHRA were not studied[9].

In March 2007, in the Netherlands, the TV programme *Radar* raised doubts about the safety of prescribing statins to combat high cholesterol[10]. The aim of the television programme was to give attention to the ADRs experienced by some patients and to question the preventive use of statins[10]. This broadcast was watched by approximately 2 022 000 viewers in the Netherlands[11].

In this broadcast, several patients were interviewed who had experienced ADRs like depression, pain in the hands, arms and shoulders, loss of muscle mass and arthralgia. In a second broadcast on March 26th about the same subject, viewers were told that they could report their ADRs about statins to the Netherlands Pharmacovigilance Centre Lareb.

Both broadcasts were followed by concerned reactions from medical bodies in the Netherlands who worried that the programme would encourage patients to stop taking their statins, with or without consulting their general practitioner (GP) first. The Dutch Cardiology Society sent letters to the editors of the TV programme *Radar* and to the Netherlands Health Care Inspectorate[10,12]. Among others, there were also reactions from the Dutch Society of General Practitioners, which draws up standards for cardiovascular risk management, and the Dutch Heart Foundation[10].

The Netherlands Pharmacovigilance Centre Lareb experienced a sharp increase in patient reports about statins in the period after the *Radar* television programme about statins was broadcasted.

AIM

To study the influence of media attention about statins and ADRs on the level of disproportionality, expressed as the reporting odds ratio (ROR) for statins in the database of the Netherlands Pharmacovilance Centre Lareb, based on patients' reports.

METHODS

For this study patient reports about statins from the period April 2003 to February 2007 were compared with patient reports from the period March 2007 to June 2007. The date April 2003 was chosen as the start of the first study period because patients have been allowed to report since that moment[4]. We included the reports from the entire month of March 2007 in the second study period, although the first broadcast occurred on the 5th of March, because we wanted to exclude any effects of early announcements about the programme in the media.

Patients in the two study periods were compared on the basis of age and gender. Report characteristics that were studied included organ classes of the ADRs and seriousness of the reaction. We also analysed a list of individual ADRs that were specifically mentioned during the television programme *Radar*.

The drugs in the Lareb database are coded according to the anatomical therapeutic chemical (ATC) classification of the WHO[13]. For statins as a group the ATC begins with C10AA. ADRs are coded according to the MedDRA-coding system, which refers to a group of MedDRA-terms belonging to a system organ class (SOC). MedDRA is a multi-axial terminology meaning that a preferred term (PT) may be linked to more than one SOC. A MedDRA term may be attributed to multiple SOCs. Each PT is assigned a primary SOC to avoid 'double counting' while retrieving information from all SOCs[14–16]. For this analysis the primary SOC has been used. One report can consist of multiple ADRs in different SOCs.

The seriousness of the reports was categorised in our database according to the criteria formulated by the Council for International Organizations of Medical Sciences (CIOMS), namely death, life-threatening factors, hospitalisation or prolongation of hospitalisation, disability/incapacity, congenital anomaly/birth defect and other ADRs considered serious by the reporter[17].

The Pearson χ^2 test was used to detect differences in gender and seriousness of the reported ADRs between the two study periods. Significance was based on χ^2-test: $p < 0.05$. A *t*-test was used to detect differences in age.

Comparison of reporting odds ratio before and after the broadcast

The strength of the association between the statins and reported ADR in comparison to other drugs in the database is calculated as a reporting odds ratio (ROR), a measure of disproportionality. In our study the ROR provides an estimate for the extent to which ADRs are reported in association with the use of statins as suspected medication relative to the use of other drugs. The ROR is calculated by a division sum; The numerator consists of the number of cases where a statin was used and a specific ADR was reported divided by the number of cases using statins without reporting this ADR. The denominator consists of the number of cases using other suspected drugs and that

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reported the specific ADR divided by the number of cases using other suspected drugs without reporting that specific ADR. The ROR is expressed as a point estimate with corresponding 95% confidence intervals (95% CI).

We calculated the RORs for patient reports received in the period 1 April 2003–28 February 2007 and a second ROR for patient reports received in the period 1 March 2007–30 June 2007.

In a scatterplot the difference for the strength of the association between statin and reported ADRs before and after the broadcast is shown. In order to calculate the correlation between the ROR for patient-statin reports between the period before and after the broadcast a Pearson correlation-coefficient (r) is calculated. A cut-off value of three reports for both periods was taken. The value of r is such that $-1 < r < +1$. If there is a strong positive linear correlation, r is close to $+1$. A correlation greater than 0.7 was seen as *strong* in this study[18].

Comparison of the type of reported ADRs associated with statins before and after the broadcast

To compare the proportion of the type of ADRs before and after the broadcast, we calculated the number of reports of ADRs belonging to a certain SOC that were reported before the broadcast and made a comparison with the type of reported ADRs after the broadcast. Logistic regression analysis was used to get an impression of the increase or decrease of the proportion of ADRs in the various SOCs. First crude odds ratios were calculated. In addition adjusted odds ratios for age and gender were calculated. In contrast to the previously mentioned ROR, where the strength of the association between ADR and suspected drug is compared with all other drugs in the database, these calculations were carried out to compare the proportion of reported ADRs in the various SOCs in the period before and after the broadcast. The same method was used for the number of reports in ADRs belonging to certain MedDRA preferred terms (PT).

In the *Radar* programme certain ADRs were explicitly mentioned (depression, memory impairment, myalgia, muscle weakness, impotence, hepatic and renal disorders). To investigate if these ADRs were reported more often after the broadcast of the programme we screened all preferred terms (PTs) that were coded in the database for patients' statin reports, before and after the broadcast. We then classified these PTs to whether or not they belonged to one of the terms mentioned in the broadcast. Selection was done by FvH and EvP independent of each other and blinded for the period of reporting. Differences were discussed until agreement was reached, however this was only the case for two terms. We were liberal to assign complaints to certain SOC in order to prevent missing data. For example we linked complaints like flank pain and dysuria to the SOC *Renal Disorders*, because patients relate these adverse reactions to renal diseases, although this does not have to be the case from a medical point of view. The same method was used for the other terms.

The matching of PTs to terms mentioned in the *Radar* programme is shown in Table 1.

After the matching of terms, crude odds ratios were calculated, as well as adjusted ORs for age and gender, with logistic regression to compare the relative number of reports before and after the broadcast.

All statistical analyses were performed using SPSS 16.0.

Table 1. Matching of PTs to terms mentioned in the *Radar* programme

Term mentioned in programme	Matching preferred terms
Memory impairment	Amnesia
	Memory impairment
Myalgia	Myalgia
Muscular weakness	Muscular weakness
	Myopathy
	Myopathy toxic
	Rhabdomyolysis
Impotence	Erectile dysfunction
	Libido decreased
Hepatic disorders	Alanine aminotransferase increased
	Hepatic cirrhosis
	Hepatic failure
	Hepatic function abnormal
	Jaundice
	Hepatitis
	Liver disorder
	Liver function test abnormal
Renal Disorders	Blood creatine phosphokinase increased
	Chromaturia
	Flank pain
	Dysuria
	Micturation disorder
	Pollakiuria
	Polyuria
	Renal disorder
	Renal Failure
	Renal pain
	Urge incontinence
	Urinary incontinence
	Urinary tract infection
	Urine analysis abnormal
Arthralgia	Arthralgia
	Back pain
	Pain in extremities
	Musculoskeletal pain
Depression	Depressed mood
	Depression
	Major depression
	Suicidal ideation

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RESULTS

Number of reports

The total number of patient reports that Lareb received in the period April 2003–February 2007 was 2484. In the period March 2007–June 2007 604 patient reports were received in total. These numbers are shown in Figure 1.

In the period April 2003–February 2007 Lareb received 154 patient reports about statins, concerning 364 ADRs.

In the period March 2007–June 2007 patients submitted 251 reports about statins, concerning 726 ADRs. There is a clear peak in the reporting of statins after the broadcast in March 2007, which can be seen in Figure 1.

In the period March 2007–June 2007 we also received 353 patient reports about drugs *other* than statins. As a comparison; in the 4-month period before (November 2006–February 2007) we received 333 patient reports of which 30 reports were about statins.

Patient characteristics

There was no statistically significant difference in age between the patients of the reports in both groups, mean age 56.8 years (SD 10.0 years) for the period after the broadcast *vs*. mean age 55.9 years (SD 5.7 years) for the previous period (*t*-test $p > 0.05$). In the patient reports in the period from March 2007 to June 2007 63.7% were male, compared to 51.9% in the reports from patients reporting earlier (χ^2-test: $p < 0.05$).

Seriousness

In the period March 2007 until June 2007 patients reported 42 serious ADRs compared to 34 in the period April 2003 until February 2007 (16.7% of the cases *vs*. 22.1%), this difference was not statistically significant.

Correlation between the reporting odds ratios in the period before and after the TV programme about statins

In the scatterplot the difference for the strength of the association between statin and reported ADRs before and after the broadcast is shown. The Pearson Correlation-coefficient was 0.83, implying that there is a fairly strong linear correlation between the RORs of the drug-PT combinations in both periods.

The association rosuvastatin—myalgia is an outlier; this association was reported more in the period before the broadcast.

Results are shown in Figure 2.

Comparison of the type of reported ADRs associated with statins before and after the broadcast

System organ class. We analysed if the relative amount of reports of an ADR in a specific SOC changed after the broadcast of the programme *Radar*.

No statistic differences in the reporting about specific SOCs were found, except for the SOC Musculoskeletal and connective tissue disorders; after the broadcast the relative reporting in this SOC significantly increased. Results are shown in Table 2.

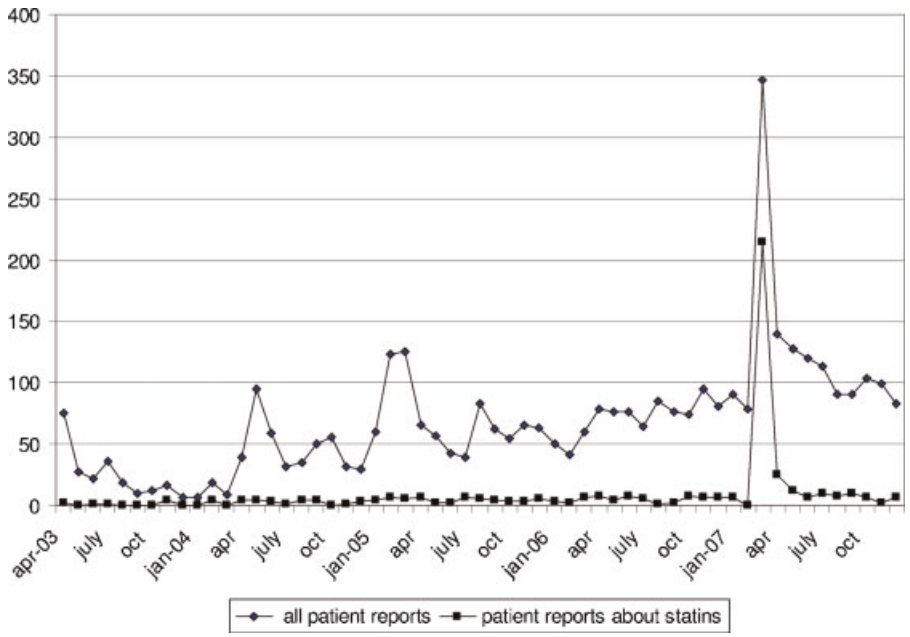

Figure 1. Patient reports of suspected adverse drug reactions received in the Lareb pharmacovigilance database from 1 April 2003 to 31 December 2007

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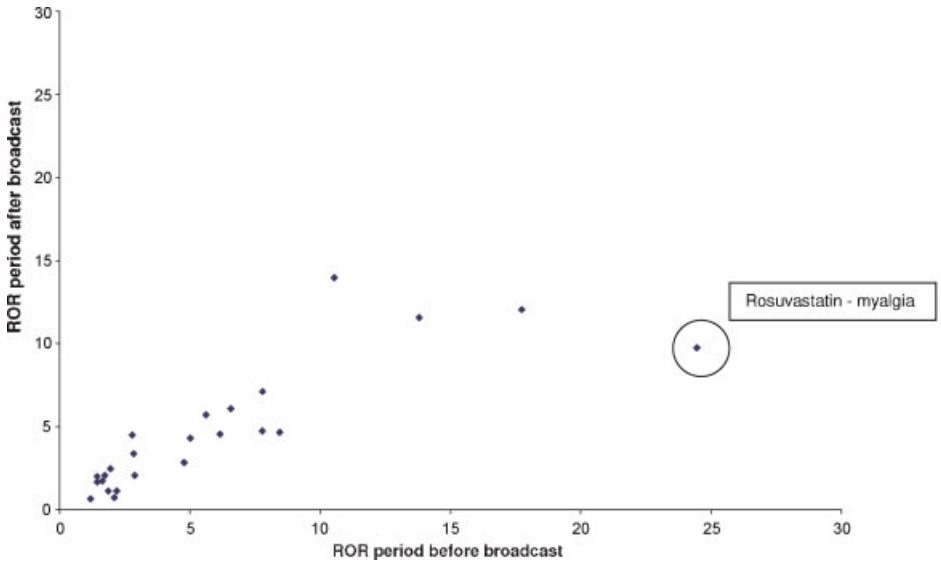

Figure 2. Comparison between reporting odds ratios in the period before and after the broadcasting of the *Radar* TV programme about statins. Period *before* referring to period 1 April 2003–28 February 2007. Period *after* referring to period 1 March 2007–30 June 2007

Specific ADRs. For the individual ADRs that were specifically mentioned during the TV programme *Radar*, no differences were found in the relative reporting of memory impairment, muscle weakness, impotence, hepatic disorders, renal disorders and depression.

After the broadcast the relative reporting of myalgia and arthralgia increased significantly. Results are shown in Table 3.

DISCUSSION

Findings

Our study demonstrates that media attention does not necessarily influence the relative reporting by patients expressed as reporting odds ratios in the national ADR database. As a result of a TV programme about statins we see a peak in the reporting of statins' ADRs by

Table 2. Comparison of patients' reports of ADRs associated with statins in a specific SOC, before and after the broadcast of a TV programme about statins

System Organ Class	Before broadcast		After broadcast		Crude OR (95% CI)	Adjusted for age and gender OR (95% CI)
	Reports with SOC	Reports with other SOCs	Reports with SOC	Reports with other SOCs		
Blood	4	150	0	251	—	—
Cardiac Disorders	7	147	6	245	0.51 (0.17–1.56)	0.53 (0.17–1.64)
Ear disorders Ear	3	151	1	250	0.20 (0.02–1.95)	0.18 (0.02–1.79)
Endocrine disorders Endocr	0	154	1	250	—	—
Eye disorders	9	145	12	239	0.81 (0.33–1.97)	0.82 (0.33–2.00)
Gastrointestinal disorders	27	127	41	210	0.92 (0.54–1.57)	0.94 (0.55–1.62)
General disorders and administration site conditions	37	117	64	187	1.08 (0.68–1.72)	1.10 (0.69–1.77)
Hepatic and biliary disorders	4	150	6	245	0.92 (0.25–3.31)	0.88 (0.24–3.20)
Immune system disorders	2	152	2	249	0.61 (0.09–4.38)	0.60 (0.08–4.39)
Infections and infestations	2	152	2	249	0.61(0.09–4.38)	0.66 (0.09–4.81)
Investigations	6	148	9	242	0.92 (0.32–2.63)	1.22 (0.39–3.74)
Metabolism and nutrition disorders	4	150	4	247	0.61 (0.15- 2.46)	0.57 (0.14–2.35)
Musculoskeletal and connective tissue disorders	82	72	186	65	2.51 (1.64–3.84)	2.57 (1.67–3.95)
Nervous system disorders	28	126	64	187	1.54 (0,95–2.54)	1.55 (0.94–2.58)
Psychiatric disorders	25	129	42	209	1.04 (0.60–1.78)	1.12 (0.64–1.94)
Renal and urinary disorders	8	146	7	244	0.52 (0.19–1.47)	0.59 (0.20–1.72)
Reproductive system and breast disorders	3	151	12	239	2.53 (0.70–9.10)	2.13 (0.58–7.84)
Respiratory, thoracic and mediastinal disorders	9	145	10	241	0.67(0.27–1.68)	0.79 (0.30–2.05)
Skin and subcutaneous tissue disorders	22	132	29	222	0.78 (0.43–1.42)	0.79 (0.43–1.46)
Vascular disorders	3	151	7	244	1.44 (0.37) –5.67	2.11 (0.43–10.40)

Note: Because one report can contain multiple ADRs in several SOCs, the total number in the table is higher than the number of reports.

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Table 3. The Number of patient reports of ADRs associated with statins, before and after the broadcast of a TV programme about statins where these ADRs were explicitly mentioned

Term mentioned in programme	Before broadcast		After broadcast		Crude OR (95% CI)	Adjusted for age and gender OR (95% CI)
	Reports with SOC	Reports with other SOCs	Reports with SOC	Reports with other SOCs		
Memory impairment	4	150	16	235	2.55 (0.84–7.78)	2.77 (0.90–8.5)
Myalgia	52	102	110	141	1.53 (1.01–2.32)	1.59 (1.04–2.43)
Muscular weakness	15	139	33	218	1.40 (0.73–2.68)	1.28 (0.67–2.50)
Impotence	4	150	14	237	2.22 (0.72–6.86)	2.04 (0.65–6.40)
Hepatic disorders	6	148	6	245	0.60 (0.19–1.91)	0.72 (0.21–2.41)
Renal Disorders	10	144	9	242	0.54 (0.21–1.35)	0.61 (0.24–1.58)
Arthralgia	16	138	48	203	2.04 (1.11–3.74)	2.00 (1.09–3.67)
Depression	8	146	22	229	1.75 (0.76–4.04)	1.93 (0.83–5.00)

patients. However, the spectrum of ADRs reported by patients to the Netherlands Pharmacovigilance Centre Lareb seems relatively consistent before and after the broadcast. This means that patient reported more about all classes of ADRs. Only in the SOC Musculoskeletal and CTD patients report relatively more.

The great amount of 'non-serious' and 'well-known' ADRs reported by patients that were sent to the database could cause a diluting effect, which makes signal detection more difficult.

Media attention might increase the reporting rate of a specific drug. In a pharmacovigilance database this can lead to the situation that the problem of general under reporting is more severe for some drugs than for others. Since a non-selective reporting bias has a similar effect on both numerator and denomitor in the 2×2 contingency table this does not necessarily influence the ROR. Non-selective under-reporting ,i.e. pertaining to specific drugs or specific ADR instead of drug-ADR combinations, does not influence the height of the ROR as van der Heijden *et al*. showed[19].

To our knowledge this paper is the first study to investigate the influence of media attention on the ROR for reports by patients. We did not include reports by health professionals in this study. In a previous paper we compared some characteristics of the patients' and health-professionals reports received after the broadcasting of the *Radar* programme[20]. The number of health professionals' reports did not show the same peak after the broadcast as the patient reports[20].

There are more male patients reporting ADRs in the period after the broadcast then in the period before. Statins are prescribed more to male patients in the Netherlands[21] but this does not explain why more male patients started reporting after the broadcast. In a previous study of 3 years of patient-reporting in the Netherlands, in the period April 2004–April 2007 we found that reports referred more often to female patients than to men[3].

When we studied the correlation between the drug-ADR combinations before and after the TV programme, the association rosuvastatin—myalgia was an outlier; this association was reported relatively more in the period before the broadcast. This drug was approved on the Dutch market on 9 June 2004 and more reporting about this drug could be due to something like the *Weber*-effect. The Weber effect refers to an increase in the number of reports of ADRs in the second year after marketing of the drug, followed by a gradual decrease despite continued use of the product[22].

Limitations of the study

This study only addresses patient's reports and one class of drug. Media attention was focussed on statins in particular and not on other drugs.

In an earlier study we also investigated the influence of media attention on the reporting of statins by health professionals[20].

Other studies about the influence of media attention on reporting

An earlier example of reporting as a result of media attention was seen when the effects of non-sedating antihistamines on the risk for inducing arrhythmias were studied using the Lareb database[6]. The findings from this study suggested that the identified increased risk could at least partly be explained by reporting bias as a result of publications about and mass media attention for antihistamine induced arrhythmias. After stratification for time before or after regulatory action the adjusted ADR reporting odds ratios changed notably. In this study period no reports by patients were included.

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KEY POINTS

- Media attention about a specific drug and its adverse reactions can lead to more reporting by patients.
- Media attention does not necessarily influence reporting odds ratios in disproportionality analysis.

CONCLUSION

Media attention about a specific drug and its adverse reactions can lead to increased reporting by patients. As demonstrated in the Dutch ADR database; when the reporting bias is mostly non-differential this does not influence the reporting odds ratio. On SOC level only in *Musculoskeletal and connective tissue disorders* the relative reporting increased. For myalgia and arthralgia, there was a proportional increase of reporting within the statin class but not for the other ADRs that were explicitly mentioned in the TV programme about statins. Media attention did not influence the spectrum of patients' reports of ADRs of statins to a great extent in the Dutch pharmacovigilance database.

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