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Published in:
Drug Safety

DOI:
10.1007/s40264-020-00922-7

Publication date:
2020

Drug Safety
https://doi.org/10.1007/s40264-020-00922-7

ORIGINAL RESEARCH ARTICLE

Drug Safety Issues Covered by Lay Media: A Cohort Study of Direct Healthcare Provider Communications Sent between 2001 and 2015 in The Netherlands

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Abstract

Background Some drug safety issues communicated through direct healthcare professional communications (DHPCs) receive substantial media coverage, while others do not.

Objectives The objective of this study was to assess the extent of coverage of drug safety issues that have been communicated through DHPCs in newspapers and social media. A secondary aim was to explore which determinants may be associated with media coverage.

Methods Newspaper articles covering drug safety issues communicated through 387 DHPCs published between 2001 and 2015 were retrieved from LexisNexis Academic™. Social media postings were retrieved from Coosto™ for drugs included in 220 DHPCs published between 2010 and 2015. Coverage of DHPCs by newspapers and social media was assessed during the 2-month and 14-day time periods following issuance of the DHPC, respectively. Multivariate logistic regression was used to assess potential DHPC- and drug-related determinants of media coverage.

Results 41 (10.6%) DHPC safety issues were covered in newspaper articles. Newspaper coverage was associated with drugs without a specialist indication [adjusted odds ratio 5.32; 95% confidence interval (2.64–10.73)]. Negative associations were seen for time since market approval [3–5 years 0.30; (0.11–0.82), 6–11 years 0.18; (0.06–0.58)] and year of the DHPC [0.88; (0.81–0.96)]. In the social media, 180 (81.8%) drugs mentioned in 220 DHPCs were covered. Social media coverage was associated with drugs without a specialist indication [6.92; (1.56–30.64)], and for DHPCs communicating clinical safety issues [5.46; (2.03–14.66)].

Conclusions Newspapers covered a small proportion of DHPC safety issues only. Most drugs mentioned in DHPCs were covered in social media. Coverage in both media were higher for drugs without a specialist indication.

Key Points

Safety issues described in direct healthcare professional communications (DHPCs) received only limited coverage by newspapers. The drugs concerned were frequently referred to in social media

Coverage of DHPCs by newspapers was declining during the 15-year study period, with older drugs and drugs that did not require a specialist indication being covered more frequently

Social media coverage was associated with drugs not requiring a specialist prescriber and for DHPCs communicating about clinical safety issues

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-020-00922-7) contains supplementary material, which is available to authorized users.

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Published online: 24 March 2020

1 Introduction

Regulators and industry routinely monitor the safety of medicines after their approval. Once an important safety signal is identified and confirmed, healthcare professionals are informed about the new drug safety issue [1–3]. In the European Union, the direct healthcare professional communication (DHPC, also known as the "Dear Doctor Letter") is the most commonly used safety communication tool. In the past decades, its use has increased to around 30 letters annually [4, 5]. European Union pharmacovigilance legislation, enforced in 2012, requires that the impact of a regulatory safety communication is routinely monitored [3, 6–8]. The authors of three systematic reviews of these impact evaluations concluded, however, that it is difficult to disentangle the effect of regulatory safety communications from the effect of concomitant media attention [5, 9, 10].

Some drug safety issues received excessive media attention. An example is suicidality in adolescents using selective serotonin reuptake inhibitors [11, 12]. In consequence, this media attention may affect how the safety issue is perceived by both healthcare professionals and patients, and may amplify the response to regulatory safety communications. An intended decrease in selective serotonin reuptake inhibitor use in children and adolescents was observed in the Netherlands coinciding with a period of extensive media coverage [11]. However, this media attention may also have contributed to an observed unintended decrease of use in adults [11]. While large changes in drug use have been reported for safety issues that were extensively covered by the media [13–18], systematic reviews suggested a more modest, if any, effect for a wide range of studied safety communications that generally may not have received much media attention [5, 9, 10]. It remains, however, largely unknown to what extent media in general pay attention to drug safety issues reviewed by regulatory authorities. It seems that extensive newspaper coverage of safety issues particularly concerned drugs with large numbers of users, e.g. cyproterone acetate/ethinylestradiol (Diane-35) and rofecoxib (Vioxx). Again, not much is known about the association of characteristics of the safety issue communicated through DHPCs and media coverage. Moreover, media attention may already occur before a safety issue is officially communicated through a DHPC. For instance, following publication of a safety issue in a scientific journal [19].

Most research regarding media attention for drug safety issues has focussed on traditional media, such as newspapers [11, 12, 18, 20–24]. As social media use is increasing over time and the public is becoming more and more empowered, it is likely that safety issues will also be mentioned on social media. It is not only used as a meeting place for patients seeking support, but also by people with similar views on the use of certain types of drugs, like 'vaccine refusers' [25–28], and for professionals as well to be in contact with colleagues [29]. A survey study showed that almost half of the responders used social media for advice about acne treatment with only a third of them making treatment changes in line with clinical guidelines [30]. In addition, some work has been performed to mine possible adverse drug reactions from social media postings, albeit with mixed results [31, 32]. One could expect, however, that safety issues for some drug types or drug classes will receive more media coverage than others but as yet this subject has not been studied.

The present study aims to provide a quantitative overview of the newspaper and social media coverage of drug safety issues that have been communicated through DHPCs. Secondary aims are to identify determinants that may be associated with media coverage, and to explore what extent media uptake was seen before and/or after the publication of a DHPC.

2 Methods

2.1 Study Design

In this cohort study, we assessed whether drug safety issues addressed in DHPCs in the Netherlands were covered by newspapers and social media. Direct healthcare professional communications published between 1 January, 2001 and 1 January, 2016 were included in this study. The index date was defined as the date the DHPC was published on the Dutch Medicines Evaluation Board website; www.cbg-meb.nl. This is the same date the healthcare professionals receive the DHPC as a paper-based letter. Direct healthcare professional communications concerning recalls were included when published with supervision of the Medicines Evaluation Board. Media coverage was assessed in the period around the DHPC publication because media may already report on an issue while the regulators are still investigating a safety signal and/or have not yet published the DHPC.

2.2 Outcome Measures

2.2.1 Primary Aim Newspapers

Newspaper coverage was measured as any coverage of the drug safety issue (yes/no) in the 2 months after the DHPC was published (primary outcome).

2.2.2 Secondary Aim Newspapers

For the secondary aim, we assessed: (1) any newspaper coverage of the safety issue in the 2 months before the

publishing of the DHPC; (2) the number of newspaper articles specifically reporting on the safety issue communicated through the DHPC in the 2 months before and in the 2 months after the DHPC was published; and (3) the number of issues covered at least 20 times in the 2 months before or in the 2 months after the DHPC was published.

2.2.3 Primary Aim Social Media

Social media coverage was defined as any coverage of the drug (yes/no) in the 14 days after the DHPC was published (primary outcome).

2.2.4 Secondary Aim Social Media

For the secondary aim, we assessed: (1) any coverage of the drug categorised in the 14 days before the publishing of a DHPC; (2) the number of social media postings about the drug for which a DHPC was published in the 14 days before and in the 14 days after its issuing; and (3) the number of drugs with at least 100 postings in the 14 days before or in the 14 days after the DHPC was published.

2.3 Media Data Sources

2.3.1 Newspapers

Newspaper articles were retrieved from LexisNexis Academic™, a database containing printed newspaper and magazine articles. We searched for articles mentioning the drug name, Dutch and English spelling of the International Nonproprietary Name and/or brand name, as used in DHPCs published between 1 January, 2001 and 1 January, 2016. All articles were read by two researchers, who independently identified those articles that reported on the safety issue. In the case of disagreement, a third researcher was consulted.

2.3.2 Social Media

Web postings were retrieved from Coosto™, a dynamic online repository for social media that contains publicly available messages from platforms such as Facebook and Twitter, but also fora and reactions on news websites. All postings of currently available public accounts are included in this repository. When an account removes a posting or changes from public to private, the posting is no longer included in the repository. The repository of social media could only be searched from 2009 onwards. We limited the search to DHPCs published between 1 January, 2010 and 1 January, 2016. Web postings were retrieved using the drug International Nonproprietary Name and/or brand names within one search. In case the drug International Nonproprietary Name or brand name ended with -ine or -in, both options were used as this was a common misspelling because of differences in the spelling of Dutch and English drug names. Postings in other than the Dutch language were excluded. Given the large volume of relatively short messages, we were not able to reliably identify postings reporting on the safety issue involved. We, therefore, included all postings retrieved regardless of their content. The time period in which web postings were retrieved around the DHPC was shorter than for newspaper articles. We anticipated that if the DHPC would trigger a response, this would be relatively quick after the DHPC and was more likely to concern the safety issue. In addition, we retrieved postings in two reference periods for comparison: (1) a 28-day period preceding the time period around the DHPC and (2) a 28-day period 1 year later corresponding with the time around the DHPC, for a sensitivity analysis.

2.4 Determinants

We identified several drug and DHPC characteristics as potential determinants, based on previous research that examined factors associated with the impact of DHPCs [33]. These included drug class, type of molecule, orphan drug status, drug use, specialist indication, drug age, year and month in which the DHPC was published, type of issue communicated through the DHPC, and whether the DHPC concerned market withdrawal or suspension of the drug.

The following definitions and categorisations were used: drug class defined at the first level of the Anatomical Therapeutic Chemical (ATC) code; type of molecule categorised as biological, small molecule or vaccine; orphan drug status categorised as yes or no; drug use at the time the DHPC was published categorised as low (1 to < 1000 users), moderate (1000–10,000 users), widely used (> 10,000 users) or unknown based on data retrieved from The Drug Information System of the National Health Care Institute (GIP database that contains data on nationwide reimbursed drugs dispensed by public pharmacists; the category unknown covers drugs dispensed over the counter as well as drugs used in the hospital setting only); specialist indication, defined as a medication that according to the Summary of Product Characteristics or national guidelines recommendation should (initially) be prescribed by a specialist (yes/no); drug age, defined as the time between registration (marketing authorisation) and the publishing of the DHPC categorised as ≤ 2 years, 3–5 years, 6–11 years and > 11 years; the year the DHPC was published; type of issue communicated through the DHPC categorised as a new clinical issue or not, a drug shortage and/or a defect/manufacturing problem (more than one type of issue per DHPC possible) as yes or no; and drug withdrawal or suspension categorised as yes or

no. Direct healthcare professional communication and drug characteristics were independently classified by two researchers, and in the case of disagreement, a third researcher was consulted.

2.5 Analyses

Descriptive statistics were used to report whether, how often, and when newspapers and social media covered DHPC-related drug safety issues respectively in the study period. As the data were paired, a McNemar test was performed to analyse coverage before and after the DHPC was published.

Univariate and multivariate logistic regression analyses were used to explore which drug or DHPC characteristics were associated with any newspaper coverage in the 2 months after the DHPC was published, and any social media postings in the 14 days after the publishing of the DHPC. Potential determinants with a p value of less than 0.20 in univariate analyses were entered in the full multivariate regression model. In addition, specialist indication and drug use were entered in the model separately and with an interaction term as it was expected that specialist indication had a more limited use. Subsequently, we performed a backward elimination regression removing determinants with the highest p value until in the final model only, the most likely relevant determinants with a $p \leq 0.05$ remained.

A sensitivity analysis was performed for social media coverage, in which the average 14-days coverage in the two above-defined reference periods was subtracted from the coverage in the 14 days after the publishing of the DHPC. When the DHPC involved a withdrawal or suspension, only the first reference period was used.

All analyses were performed using SPSS Statistics 23 (IBM SPSS Inc., Chicago, IL, USA).

3 Results

Between 1 January, 2001 and 1 January, 2016, 387 DHPCs were published concerning 250 different drugs, of which 220 DHPCs for 164 drugs were published between 1 January, 2010 and 1 January, 2016 (Fig. 1a,b). The number of DHPCs published per year ranged from 12 in 2002 to 48 in 2011 (Fig. 1). A considerable number of DHPCs was published for antineoplastic and immunomodulating agents (ATC code L: 27.4%). The majority of the drugs involved (76.2%) had a specialist indication (Table 1). Most DHPCs concerned a clinical issue (94.6%), occasionally in combination with a delivery issue or defect/recall. Only 22 (5.7%) DHPCs announced a drug withdrawal, of which 18 had a safety issue as an underlying reason.

3.1 Newspapers

In total, 457 newspaper articles reported on the drug safety issue in the 2 months after the DHPC was published (primary outcome), covering 41 (10.6%) of the 387 DHPCs published in the 15-year study period. The median number of articles per covered DHPC was two [interquartile range (IQR) 1.0; 11.5]. The years with the highest percentages of newspaper coverage were 2001 (43.8% of DHPCs), 2004 (25.0%) and 2008 (18.5%) (Fig. 1a). Direct healthcare professional communications for drugs of the ATC classes cardiovascular system (C), alimentary tract and metabolism (A) or nervous system (N) had the highest coverage (20.8%, 20.0% and 17.7%, respectively). Widely used drugs (24.7%), drugs without a specialist indication (26.1%) and older drugs were covered most frequently (18.5%) (Table 1). In the multivariate analysis, the following determinants were included; ATC code, orphan drug, drug use, drug, specialist indication, drug age, DHPC year and drug use*specialist indication. The multivariate analysis showed that safety issues for drugs without a specialist indication were more likely to be covered than safety issues for drugs with a specialist indication [adjusted odds ratio (ORadj) 5.32; 95% confidence interval (2.64–0.73)] (Table 1). Drugs approved between 3–5 years and 6–11 years were less likely to be covered than drugs with a marketing authorisation older than 11 years [respectively, 0.30; (0.11–0.82) and 0.18; (0.06–0.58)], while drugs approved ≤ 2 years were not differently covered [0.45; (0.19–1.10)]. In addition, coverage by newspaper decreased over time [0.88; (0.81–0.96)]. Remaining drug and DHPC characteristics were less likely to be associated with newspaper coverage (Table 1).

3.1.1 Secondary Aim

In the 2 months before DHPCs were published, 326 newspaper articles had already reported on the drug safety issues communicated through these DHPCs. These articles covered 28 (7.2%) of the 387 DHPCs published in the 15-year study period. The median number of postings per covered DHPC was 3.5 (IQR 1; 19.75). Overall, only 55 (14.2%) of the DHPCs were covered both in the 2 months before and/or after the DHPC was published. Drug safety issues were numerically more often covered after (7.0%) than before (3.6%) a DHPC had been published (McNemar's nominal $p = 0.06$).

In the 2 months after the DHPC was published, newspaper articles covered seven safety issues 20 times or more; i.e. cerivastatin (two cases: 76 articles after the

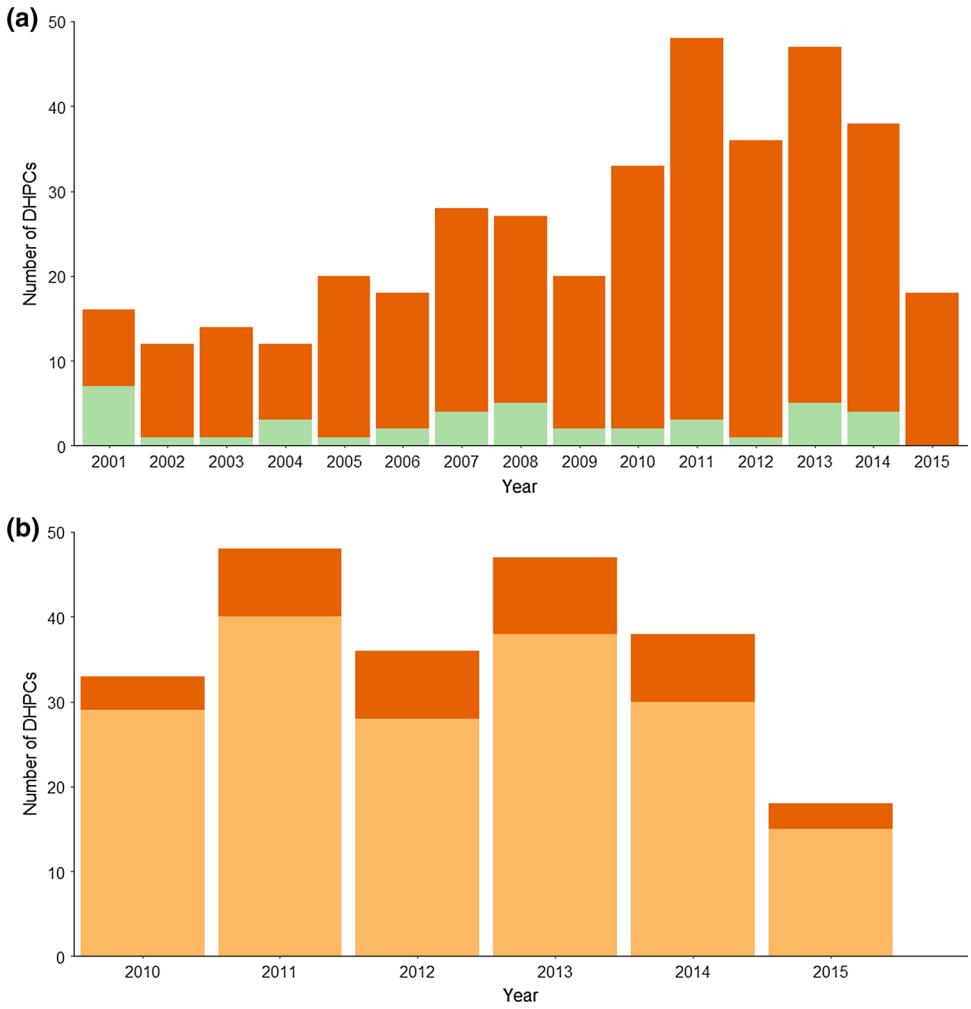

Fig. 1 **a** Newspaper coverage. This figure shows the number of direct healthcare professional communications (DHPCs) published from 1 January, 2001 up to 1 January, 2016. Green bars indicate that drug safety issues addressed in DHPCs were covered in newspaper articles, dark orange bars indicate no coverage. **b** Social media coverage. This figure shows the number of DHPCs published between 1 January, 2010 and 1 January, 2016. Light orange bars indicate that the names of drugs for which DHPCs were published were covered in social media, dark orange bars indicate no coverage. Program used: Rstudio

DHPC on concomitant use with gemfibrozil contraindicated, due to risk of rhabdomyolysis and 95 after the DHPC on temporary discontinuation of cerivastatin), moxifloxacin (38 articles after the DHPC on severe skin and liver reactions) and doxorubicin (two cases: 34 articles after both DHPCs on shortage) [Fig. 2, Table 1 of the Electronic Supplementary Material (ESM)]. Two of these DHPCs were also covered more than 20 times before the DHPC was published: celecoxib (26 articles after and 55 before the DHPC on increased cardiovascular risk) and cyproterone acetate/ethinylestradiol (25 articles after and 43 before the DHPC on restriction of indication, new contra-indication due to venous thromboembolism and arterial thromboembolism risk). In the 2 months before the DHPC was published, five safety issues were covered more than 20 times. These publications concerned rimonabant (two cases: 49 articles before the DHPC on risk of depression and 20 before the DHPC on suspension registration due to severe psychiatric risk), strontium ranelate [24 articles before the DHPC on drug reaction with eosinophilia and systemic symptoms (DRESS)], diclofenac (24 articles before the DHPC on new contra-indication due to cardiovascular risk) and cabazitaxel (23 articles before the DHPC on dosing errors due to preparation errors) (Fig. 2, Table 1 of the ESM).

3.2 Social Media

A total of 5928 social media postings were retrieved mentioning the name of a drug for which a DHPC was published between 1 January, 2010 and 1 January, 2016. Of the 220 DHPCs published, 180 (81.8%) were covered by social media in the 14 days after the DHPC was published (primary outcome). The median number of postings per covered DHPC was eight (IQR 3.25; 19). Highest coverage was seen for moderately (1000–10,000) and widely used (> 10,000) drugs, and for drugs without a specialist indication (89.5%, 92.3% and 95.8%, respectively). Drugs for which a DHPC was published because of a defect, shortage or withdrawal received lower coverage than clinical issues [70.2%, 66.7% and 66.7% vs 84.9%, respectively (Table 2)]. In the multivariate analysis, the following determinants were included:

Table 1 Determinants of newspaper coverage in the 2 months after the publishing of a direct healthcare professional communication (DHPC): univariate, full multivariate and final multivariate analyses

	DHPCs (%)	Covered (%)	Univariate	*p* value	Full multivariate model	*p* value	Final multivariate model	*p* value
	387	41 (10.6)	OR (95% CI)		ORadj (95% CI)		ORadj (95% CI)	
Drug class (ATC code)				0.077		0.794		
A	45 (11.6)	9 (20.0)	Ref		Ref			
B	35 (9.0)	3 (8.6)	0.38 (0.09–1.51)		0.62 (0.13–3.02)			
C	24 (6.2)	5 (20.8)	1.05 (0.31–3.59)		1.14 (0.25–5.31)			
J	43 (11.1)	3 (7.0)	0.30 (0.08–1.20)		0.62 (0.13–2.87)			
L	106 (27.4)	5 (4.7)	0.20 (0.06–0.63)		0.66 (0.16–2.73)			
M	35 (9.0)	3 (8.6)	0.38 (0.09–1.51)		0.37 (0.08–1.81)			
N	45 (11.6)	8 (17.7)	0.87 (0.30–2.49)		0.81 (0.24–2.77)			
Other	54 (14.0)	5 (9.3)	0.41 (0.13–1.32)		0.36 (0.09–1.44)			
Type of molecule				0.765				
Biological	103 (26.6)	9 (8.7)	Ref					
Small molecule	282 (72.9)	32 (11.3)	1.34 (0.62–2.91)					
Vaccine	2 (0.5)	0 (0.0)	0.00 (–)					
Orphan drug				0.086		0.660		
No	342 (88.4)	40 (11.7)	Ref		Ref			
Yes	45 (11.6)	1 (2.2)	0.17 (0.02–1.28)		0.62 (0.07–5.35)			
Drug use				0.001		0.246		
Low (1 to < 1000)	111 (28.7)	9 (8.1)	Ref		Ref			
Moderate (1000–10,000)	80 (20.7)	6 (7.5)	0.92 (0.31–2.69)		0.70 (0.17–2.90)			
Widely used (> 10,000)	73 (18.9)	18 (24.7)	3.71 (1.56–8.81)		3.31 (0.64–17.25)			
Unknown	123 (31.8)	8 (6.5)	0.79 (0.29–2.12)		0.59 (0.15–2.31)			
Specialist indication				*< 0.001*		*0.037*		*< 0.001*
Yes	*295 (76.2)*	*17 (5.8)*	*Ref*		*Ref*		*Ref*	
No	*92 (23.8)*	*24 (26.1)*	*5.77 (2.94–11.34)*		*7.28 (1.13–46.97)*		*5.32 (2.64–10.73)*	
Drug age (in years)				*0.009*		*0.012*		*0.010*
≤2	*92 (23.8)*	*11 (12.0)*	*0.60 (0.27–1.32)*		*0.49 (0.17–1.36)*		*0.45 (0.19–1.10)*	
3–5	*93 (24.0)*	*6 (6.5)*	*0.30 (0.12–0.79)*		*0.32 (0.10–0.97)*		*0.30 (0.11–0.82)*	
6–11	*94 (24.3)*	*4 (4.3)*	*0.20 (0.06–0.60)*		*0.15 (0.04–0.51)*		*0.18 (0.06–0.58)*	
> 11	*108 (27.9)*	*20 (18.5)*	*Ref*		*Ref*		*Ref*	
DHPC year (continuous)	*387 (100)*	*41 (10.6)*	*0.87 (0.82–0.96)*	*0.003*	*0.87 (0.80–0.96)*	*0.003*	*0.88 (0.81–0.96)*	*0.003*
Issue clinical				0.387				
No	21 (5.4)	1 (4.8)	Ref					
Yes	366 (94.6)	40 (10.9)	2.45 (0.32–18.78)					
Issue shortage/delivery				0.590				
No	349 (90.2)	36 (10.3)	Ref					
Yes	38 (9.8)	5 (13.2)	1.32 (0.48–3.59)					
Issue defect/manufacturing				0.517				
No	316 (81.7)	35 (11.1)	Ref					
Yes	71 (18.3)	6 (8.5)	0.74 (0.30–1.84)					
Issue other				0.999				
No	373 (96.4)	41 (11.0)	Ref					
Yes	14 (3.6)	0 (0.0)	0.00 (–)					

Table 1 (continued)

	DHPCs (%)	Covered (%)	Univariate	*p* value	Full multivariate model	*p* value	Final multivariate model	*p* value
	387	41 (10.6)	OR (95% CI)		ORadj (95% CI)		ORadj (95% CI)	
Withdrawal or suspension				0.242				
No	365 (94.3)	37 (10.1)	Ref					
Yes	22 (5.7)	4 (18.2)	1.97 (0.63–6.13)					
Drug use* specialist without indication interaction						0.314		
Low (1 to < 1000)					Ref			
Moderate (1000–10,000)					0.31 (0.02–4.34)			
Widely used (> 10,000)					0.19 (0.02–2.03)			
Unknown					1.35 (0.11–16.94)			

A—alimentary tract and metabolism, B—blood and blood forming organs, C—cardiovascular system, J—Anti infectives for systemic use, L—anti neoplastic and immunomodulating agents, M—musculo-skeletal system, N—nervous system, other: D—dermatologicals, G—genito urinary system and sex hormones, H—systemic hormonal preparations, excl. sex hormones and insulins, R—respiratory system, S—sensory organs, V—various

Values in italics indicates a determinant likely to be associated ($p < 0.05$) with newspaper coverage in the final multivariate regression model

ATC Anatomical Therapeutic Chemical, *CI* confidence interval, *OR* odds ratio, *ORadj* adjusted odds ratio, *Ref* reference

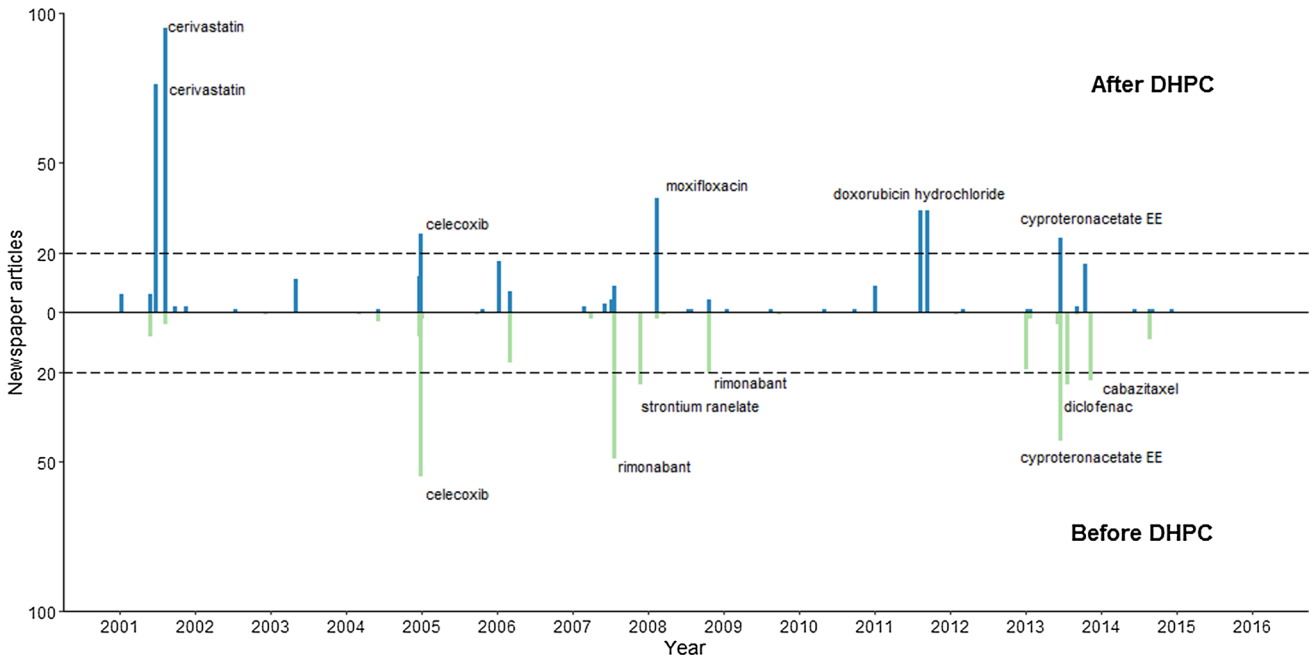

Fig. 2 Newspaper articles before and after the direct healthcare professional communication (DHPC) was published. The *x*-axis represents the index dates of the DHPCs. On the *y*-axis shown in blue are the number of newspaper articles covering the drug safety issue after the DHPC has been published and in green the number of newspaper articles are shown that covered the drug safety issue before the DHPC was published. The dashed line indicates 20 newspaper articles. *EE* ethinylestradiol. Program used: Rstudio

drug use, specialist indication, clinical issue, shortage issue, defect/manufacturing issue, withdrawal and drug use* specialist indication. The multivariate analysis for social media coverage showed that DHPCs concerning drugs without a specialist indication and for which the DHPC was published because of clinical issues were more likely to be covered [ORadj 6.92; 95% CI (1.56–30.64), 5.46; (2.03–14.66) (Table 2)]. The sensitivity analysis, in which the social media coverage was corrected for posting frequency in two reference periods, showed slightly attenuated results, but specialist indication [2.31; (1.00–5.40)] and DHPCs for clinical issue [4.01; (1.57–10.20)] still were more likely to be covered by social media (Table 2 of the ESM).

3.2.1 Secondary Aim

In the 14 days before the DHPC was published, 4162 social media postings were retrieved mentioning the drug for which the DHPC had been published. These postings covered 119 (54.1%) of the 220 DHPCs. The median number of postings per covered DHPC was five (IQR 2; 16). Overall, 186 DHPCs (84.6%) were covered both in the 14 days before and 14 days after the DHPC was published. More drugs for which DHPCs were published received social media posts (30.5%) in the 14 days after the DHPC publication than before (2.7%; McNemar's nominal $p < 0.001$). In comparison, 132 of the drugs mentioned in the 220 DHPCs (60.0%) were covered in the 28-day period preceding the study period, and 116 DHPCs (52.7%) were covered in the reference period during a similar 28-day period 1 year later.

In the 14 days after a DHPC was published, eight drugs received more than 100 postings: cyproterone acetate/ethinylestradiol (251 postings after the DHPC on a restriction to the indication, new contraindication and new safety information on venous thromboembolism and arterial thromboembolism risk), sibutramine (167 postings after the DHPC on suspension registration due to cardiovascular risk), rosiglitazone (129 postings after the DHPC on suspension registration due to cardiovascular risk), isotretinoin (125 postings after the DHPC on severe skin reaction) and domperidone (108 postings after the DHPC on new recommendations to minimalise cardiovascular risk) (Fig. 3, Table 1 of the ESM). Three of these DHPCs also received more than 100 postings in the 14 days before the DHPCs was published. These postings concerned iron-containing products (2332 postings after and 2393 before the DHPC on hypersensitivity reactions in intravenous use), levothyroxine (254 postings after and 157 before the DHPC on change in packaging leads to increased adverse drug events, mostly hyperthyroidism) and diclofenac (231 postings after and 143 before the DHPC on cardiovascular risk and contraindication). Finally, one drug received more than 100 postings only in the 14 days before the DHPC was published: ethinylestradiol and norgestimaat (128 postings before the DHPC on recall) (Fig. 3, Table 1 of the ESM).

4 Discussion

This paper provides an overview of 15 years of newspaper and 6 years of social media coverage of drug safety issues that were communicated through DHPCs. Newspaper articles covered around one out of ten safety issues published in DHPCs. Social media paid attention to around eight out of ten drugs for which a DHPC had been published. Newspapers were more likely to cover safety issues concerning drugs without a specialist indication as well as older drugs. This coverage, however, declined over the years. Social media coverage was associated with drugs mentioned in published DHPCs reporting on drugs without a specialist indication as well as new clinical safety issues.

Coverage of safety issues and drugs in newspapers (trend), respectively, social media (significant) for which a DHPC had been published, even if discussed at times already earlier, increased once the DHPC was published.

The low coverage of DHPCs in newspapers implies that only a selective group of safety issues receives attention in the traditional media. This may not come as a surprise because a Canadian study showed that although 65% of newspaper articles are health related, less than 5% were related to healthcare treatment/management [20]. This might be explained by a study on health news reports, which states: "the value of health information relies on whether people can use it" [34]. Therefore, one may suggest that for newspapers, in most cases, reporting drug safety issues is not seen as valuable for their readers. This low coverage contrasts strongly with the high social media coverage. Postings, however, were not limited to the specific safety issues communicated through DHPCs, and such postings may be related to other health matters as well. Coverage was, however, clearly higher (82%) in the period after the DHPC was published than in the reference periods (55–60%), or the 14-day period immediately preceding the DHPC (54.1%). These data suggest that social media attention for drug safety issues truly exceeds newspaper attention. This difference may be caused by newspapers weighting the value of reporting, or not, on drug safety issues. For example, newspaper editors may consider the potential readers' interest, perceived relevance of the safety issue, possible societal impact and concomitant/competing news. Social media, in contrast, is mostly unregulated and anyone can post a story. Some drugs generated constant activity on social media, particularly issues regarding the use of diclofenac, iron products and levothyroxine. Many safety issues in the newspapers were covered both before and after the DHPC was published. This may be the result of the time between the identification of a safety

Table 2 Determinants of social media coverage in the 14 days after the publishing of a direct healthcare professional communication (DHPC): univariate, full multivariate and final multivariate analyses

	DHPCs (%)	Covered (%)	Univariate	*p* value	Full multivariate model	*p* value	Final multivariate model	*p* value
	220	180 (81.8)	OR (95% CI)		ORadj (95% CI)		ORadj (95% CI)	
Drug class (ATC code)				0.847				
A	20 (9.1)	20 (100.0)	Ref					
B	22 (10.0)	18 (81.8)	0 (–)					
C	19 (8.6)	16 (84.2)	0 (–)					
J	18 (8.2)	14 (77.8)	0 (–)					
L	71 (32.3)	59 (83.1)	0 (–)					
M	15 (6.8)	11 (73.3)	0 (–)					
N	21 (9.5)	18 (85.7)	0 (–)					
Other	34 (15.5)	24 (70.5)	0 (–)					
Type of molecule				0.516				
Biological	61 (27.7)	49 (80.3)	Ref					
Small molecule	157 (71.4)	130 (82.8)	1.18 (0.55–2.51)					
Vaccine	2 (0.9)	1 (50.0)	0.25 (0.01–4.20)					
Orphan drug				0.221				
No	190 (86.4)	153 (80.5)	Ref					
Yes	30 (13.6)	27 (90.0)	2.18 (0.63–7.56)					
Drug use				0.029		0.365		
Low (1 to < 1000)	74 (33.6)	61 (82.4)	Ref		Ref			
Moderate (1000–10,000)	38 (17.3)	34 (89.5)	1.81 (0.55–5.99)		1.23 (0.34–4.46)			
Widely used (> 10,000)	39 (17.7)	36 (92.3)	2.56 (0.68–9.59)		0.91 (0.16–5.10)			
Unknown	69 (31.4)	49 (71.0)	0.52 (0.24–1.15)		0.51 (0.21–1.24)			
Specialist indication				*0.012*		*0.562*		*0.011*
Yes	*172 (78.2)*	*134 (77.9)*	*Ref*		*Ref*		*Ref*	
No	*48 (21.8)*	*46 (95.8)*	*6.52 (1.51–28.11)*		*2.02 (0.19–21.81)*		*6.92 (1.56–30.64)*	
Drug age (in years)				0.370				
≤ 2	44 (20.0)	35 (79.5)	1.20 (0.48–2.99)					
3–5	56 (25.5)	49 (87.5)	2.16 (0.83–5.66)					
6–11	48 (21.8)	41 (85.4)	1.81 (0.69–4.77)					
> 11	72 (32.7)	55 (76.4)	Ref					
DHPC year (continuous)	220 (100)	180 (81.8)	0.92 (0.74–1.15)	0.459				
Issue clinical				*0.001*		*0.020*		*0.001*
No	*21 (9.5)*	*11 (52.4)*	*Ref*		*Ref*		*Ref*	
Yes	*199 (90.5)*	*169 (84.9)*	*5.12 (2.00–13.11)*		*3.93 (1.24–12.50)*		*5.46 (2.03–14.66)*	
Issue shortage/delivery				0.024		0.769		
No	190 (86.4)	160 (84.2)	Ref		Ref			
Yes	30 (13.6)	20 (66.7)	0.38 (0.16–0.88)		0.84 (0.27–2.67)			
Issue defect/manufacturing				0.010		0.330		
No	163 (74.1)	140 (85.9)	Ref		Ref			
Yes	57 (25.9)	40 (70.2)	0.39 (0.19–0.79)		0.61 (0.23–1.64)			
Issue other				0.223				
No	215 (97.7)	177 (82.3)	Ref					
Yes	5 (2.3)	3 (60.0)	0.32 (0.05–1.99)					

Table 2 (continued)

	DHPCs (%)	Covered (%)	Univariate	*p* value	Full multivariate model	*p* value	Final multivariate model	*p* value
	220	180 (81.8)	OR (95% CI)		ORadj (95% CI)		ORadj (95% CI)	
Withdrawal or suspension				0.173		0.172		
No	208 (94.5)	172 (82.7)	Ref		Ref			
Yes	12 (5.5)	8 (66.7)	0.42 (0.12–1.47)		0.30 (0.05–1.70)			
Drug use* specialist without indication interaction						0.976		
Low (1 to < 1000)					Ref			
Moderate (1000–10,000)					143,504,726.60 (–)			
Widely used (> 10,000)					2.26 (0.07–74.80)			
Unknown					1,537,630,006.00 (–)			

A—alimentary tract and metabolism, B—blood and blood forming organs, C—cardiovascular system, J—anti infectives for systemic use, L—anti neoplastic and immunomodulating agents, M—musculo-skeletal system, N—nervous system, other: D—dermatologicals, G—genito urinary system and sex hormones, H—systemic hormonal preparations, excl. sex hormones and insulins, R—respiratory system, S—sensory organs, V—various

Values in italics indicates a determinant likely to be associated ($p < 0.05$) with newspaper coverage in the final multivariate regression model

ATC Anatomical Therapeutic Chemical, *CI* confidence interval, *OR* odds ratio, *ORadj* adjusted odds ratio, *Ref* reference

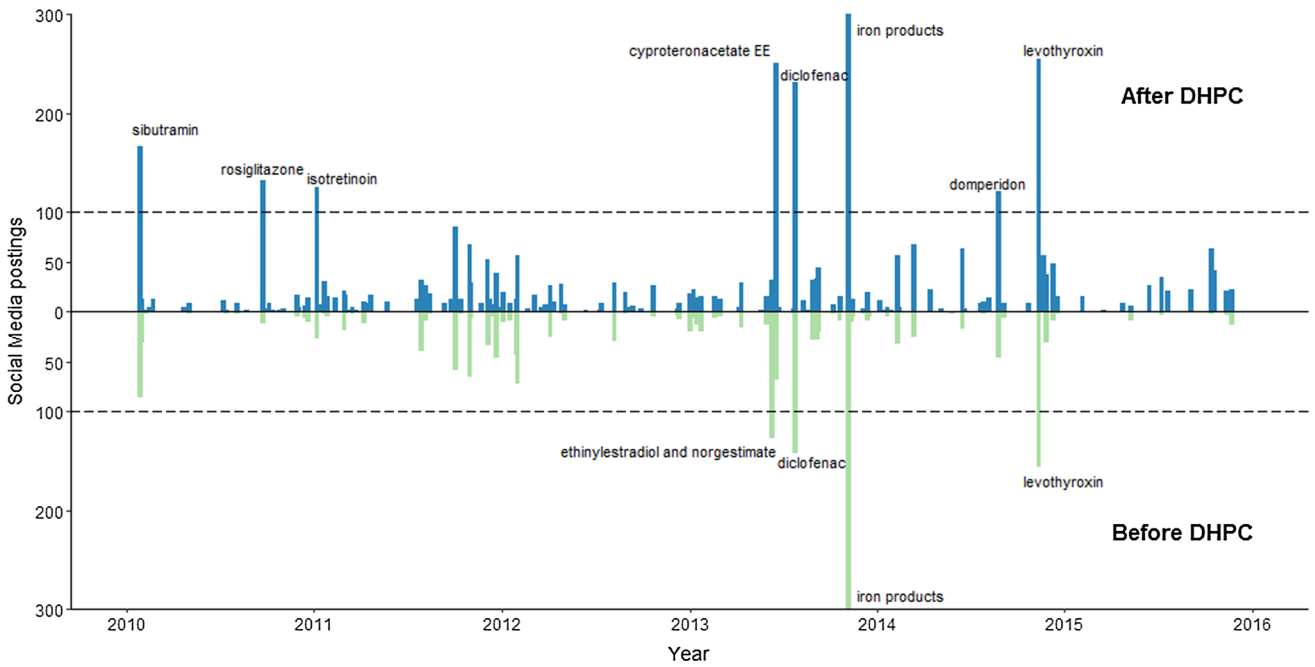

Fig. 3 Social media postings before and after the direct healthcare professional communication (DHPC) was published. The *x*-axis represents the index dates of the DHPCs. On the *y*-axis shown in blue are the number of social media postings covering the drug mentioned in the DHPC in the 14 days after the DHPC has been published and in green the number of social media postings are shown that covered the drug mentioned in the DHPC in the 14 days before the DHPC was published. The numbers of postings of iron products before and after the DHPCs was published were beyond the maximal value of the *y*-axis (before 2393 and after 2332). *EE* ethinylestradiol. Program used: Rstudio

signal and its confirmation after regulatory review and the subsequent decision to issue a DHPC. In this time period, the safety issue may have already been derived from scientific publications, marketing authorisation holder press releases or regulatory agency websites announcing that they are investigating a particular safety signal [1]. Social media appeared more reactive, showing more activity for the drug in question after a DHPC was published than before.

Our finding that DHPCs related to drugs without a specialist indication were covered more often seems to be in line with earlier studies showing a high newspaper coverage of non-specialist drugs, such as cyproterone acetate/ethinylestradiol (Diane-35) and rofecoxib [Vioxx (selective serotonin reuptake inhibitor)] [13, 35]. With regard to social media, one might also expect more postings by laypeople on common non-specialist drugs because such drugs are more widely used. Drugs already with older marketing authorisations were associated with more newspaper coverage then recently authorised drugs. The reason for this is not clear but it could be that newspaper journalists prefer to focus on safety issues regarding well-known drugs and are less interested in similar information about relatively new, less familiar drugs. Somewhat to our surprise is that safety issues were covered less frequently over time by newspapers. This finding does not indicate journalists may become more averse of drug risks, but could just reflect that the number of newspapers is declining [36].

In our study, coverage by newspapers and social media are not directly comparable, owing to the different methods of coverage measured; i.e. discussion of safety issues in the newspaper articles respectively mentioning of the drug names in social media posts. In addition, the time periods were different as well as the reach of newspaper articles and individual posts. We noted, however, differences in drugs with safety issues that received large interest from newspapers and social media. Both media covered cyproterone acetate/ethinylestradiol and diclofenac, but surprisingly sibutramine and rosiglitazone were only covered by social media. These products, indicated for obesity and diabetes mellitus, respectively, were both withdrawn from the market as a result of their cardiovascular risk (Table 2 of the ESM). In view of the seriousness of their safety issues with both drugs not having a specialist indication, newspapers surprisingly did not cover these cases. In contrast, in the period before social media were included, rimonabant, also indicated for obesity, and celecoxib, a non-steroidal anti-inflammatory drug, were extensively covered by newspapers. For both drugs, most of the coverage preceded the issuing of the DHPC reflecting that in these cases the safety issue had already been derived from marketing authorisation holders' press releases or scientific papers. In the case of celecoxib before the DHPC was published, the marketing authorisation holder communicated about its increased cardiovascular risk as observed in two separate clinical trials [37, 38]. In the month before a DHPC was published regarding psychiatric side effects associated with rimonabant, the US Food and Drug Administration had announced that they would not approve this weight reduction drug because of their concerns with this particular safety issue [39]. In addition, just a few days before a third DHPC was published for rimonabant, the European Medicines Agency announced online its withdrawal, which is reflected in the coverage in Dutch newspapers that preceded this third DHPC (Fig. 2) [40]. In the case of cyproterone acetate/ethinylestradiol 3 weeks before the DHPC, the Pharmacovigilance Risk Assessment Committee finished its assessment and immediately published its report [41]. These European Medicines Agency announcements rather than the DHPC seem therefore responsible for the newspaper coverage that preceded the publishing of the respective DHPCs.

4.1 Implication

Coverage of drug safety issues is not always as balanced as one would like it to be [24, 42]. A study examining media attention in the USA with regard to next-day drowsiness as the result of zolpidem intake showed that media coverage was not always complete and therefore sometimes only provided a partial view of the message the DHPC intended to convey [24]. Our study showed that drug safety issues are most likely to be covered when they involve non-specialist older drugs. As coverage of these drug safety issues in the newspapers and the drug names in social media was also observed before the DHPC was published, regulators could benefit from screening the media immediately prior to publishing a DHPC. At this stage, DHPCs are usually still fine-tuned between regulatory agencies and marketing authorisation holders. Concerns and uncertainties about the safety issue as identified in the media could be addressed and the message towards healthcare professionals in the DHPCs adjusted accordingly.

In The Netherlands, drug safety issues addressed in DHPCs are often shared by professional organisations on social media. Although these social media postings are directed toward healthcare professionals, it should be noted that patients use these platforms extensively to share experiences about drugs and use it as a source for medical information [43–45]. Although patients are not targeted by DHPCs, the information will reach them when it is gleaned by the media [46, 47]. When communicating about drug safety issues, regulators and professional organisations should keep this in mind and possibly provide lay versions of these communications as well.

4.2 Strengths/Limitations

The present study provided a unique and comprehensive review of newspaper and social media coverage of DHPCs over 15- and 6-year study periods, respectively. Some limitations should, however, be mentioned. We only looked at newspaper and social media coverage, but television or radio coverage of a drug may also have been important as this could have influenced subsequent newspaper and social media coverage [14, 16]. In addition, people could have learned from a drug safety issue through other means than the DHPC, e.g. they could have been triggered by other social media postings and have posted a response or new thread on the drug that is not necessarily based on actual awareness of the DHPC itself. We did not assess the severity of safety issues, which may have been a determinant for the media to cover a DHPC. All safety issues were, however, considered of sufficient importance for the regulator to issue an urgent safety communication, i.e. a DHPC. We did not make statistical adjustments for multiple comparisons. Our assessment of determinants is therefore explorative of nature, and can be used as a starting point to focus the monitoring of the public's response to drug safety issues by national regulatory agencies. For cerivastatin and doxorubicin, two DHPCs were published within 2 months and may have resulted in a double count of newspaper articles for these drugs. We discuss the more salient issues using an arbitrary cut-off of 20 newspaper articles and 100 social media postings covering DHPCs. Other cut-offs could have identified safety issues and some newspapers or social media posts may have a larger impact, but this is beyond the scope of this paper. With regard to social media, the most important limitation was that postings were not screened for their content. We performed a sensitivity analysis, using two reference periods as a correction, with the assumption that social media postings in the reference periods should not have been affected by the safety issue addressed in the DHPCs. This analysis suggested that social media coverage was still increased after the DHPC. Finally, we used a short observation period for the social media (14 days), assuming that posts shortly after a related DHPC had been published were more likely associated with the communicated safety issue.

5 Conclusions

The present study provides an overview of how often new information about drug safety issues communicated through DHPCs was covered in newspaper articles and circulates on social media during 15 respectively 6-year study periods in The Netherlands. Newspapers covered only 10% of the safety issues mentioned in DHPCs. Social media covered 82% of the drugs mentioned in the DHPCs in the period shortly after they were published. Overall, DHPCs concerning drugs without a specialist indication were more likely to receive coverage by both media types. Newspaper coverage was associated with older drugs and coverage became less frequent towards the end of our study period.

Acknowledgements The authors thank J.V. Koomen, MSc for assistance with the R graphs and all the students involved in the data collection.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by EV, STV, TBMM, JGH and PGMM. The first draft of the manuscript was written by EV and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding No specific funding for this study was obtained. Esther de Vries is performing a part-time PhD study programme that is supported by the Dutch Medicines Evaluation Board.

Compliance with Ethical Standards

Conflict of Interest Petra Denig, Sieta T. de Vries and Jacqueline G. Hugtenburg have no conflicts of interest that are directly relevant to the content of this study. Esther de Vries, Taco B.M Monster and Peter G.M. Mol are (part-time) employees of the Dutch Medicines Evaluation Board. Any opinions, conclusions and proposals in the text are those of the authors and do not necessarily represent the views of the Dutch Medicines Evaluation Board.

Data Sharing The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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