

Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study

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SCHOLARONE™ Manuscripts Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study

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Abstract

Background: In the period 2003–2008, the regulatory authorities issued several warnings restricting the use of SSRIs in paediatrics, in reaction to safety concerns regarding the risk of suicidality. In this study, the SSRIs and suicidality controversy served as a template to analyse the long-term dissemination dynamics of the benefit/risk profile of medications.

Methods: A systematic review of scientific articles (Embase), and NL and UK newspapers (LexisNexis) was performed between 2000-2010. Categorization was done by 'effect' (related treatment effect), 'type of article' and 'age group'. The articles' positive-to-negative effect ratio was determined. Differences in distribution of 'effect' categories were analysed across sources, 'type of article', and 'age group' using the Mann-Whitney (2 sub-groups) or Kruskal-Wallis test (3 or more).

Findings: In total, 1141 articles were categorized: 352 scientific, 224 Dutch, and 565 British newspaper articles. Scientific articles were predominantly on research and were positive, whereas newspaper articles were negative (ratios=3.50-scientific, 0.69-NL and 0.94-UK; P<0.001). Articles on paediatrics were less positive in scientific journals and more negative in newspapers (ratios=2.29-scientific, 0.26-NL, and 0.20-UK; P<0.001), while articles on adults were positive overall (ratios=10.0-scientific, 1.06-NL, and 1.70-UK; P<0.001). In addition, negative-effect reporting trends were exacerbated following regulatory warnings and were generally opinion articles, both in scientific journals and newspapers (2003/4 and after 2007).

Interpretation: 'Good' news in scientific journals is determined by a positive bias in research reporting, however, based on clinical studies outcomes, whereas 'bad' news is related to opinion. Scientific journals and newspapers coincided in the nature and timing of opinion articles. The increase of negative-effect articles in scientific journals and newspapers following regulatory warnings indicates that the public has been informed in a timely fashion.

Article Summary

Article Focus:

- Coverage of health related issues exemplify the relevance of scientific journals evidence through news media to inform the public, yet information might be distorted or confusing in some cases.
- The coverage of drug safety controversies in newspapers vis-à-vis scientific journals has not been thoroughly studied.

Key Messages:

- A positive publication bias was confirmed in scientific journals, however, based on clinical studies outcomes, whereas 'bad' news in scientific journals and newspapers was related to opinion, not evidence.
- This 'bad' news trend was connected to the regulatory warnings, meaning that the public was informed on time about the SSRIs and suicidality controversy, although the information that reached the public was not uniform.
- An open dialogue between stakeholders will improve communication to the public and will educate them about the benefits and risks of medicines, especially during a drug safety controversy.

Strengths and Limitations:

- The study provides for the first time a head-to-head comparison of the process of the dissemination of knowledge and the interaction between scientific journals and newspapers during a drug safety controversy.
- Our study covers 11% of the total population per country (NL and UK) based on circulation figures.
- Extraction of the articles was performed based on keywords, which might result in that some relevant articles have been omitted.

Introduction

The news media are an important source of information about therapeutic drugs and health.[1] Coverage varies from communicating the benefits and risks of medications, to drug regulation and litigation, among others.[2,3] Scientific journals are a significant source of information for journalists writing about medicine.[4] However, this does not necessarily mean that 'good' or 'bad' news about medicines in the news media is determined by the scientific literature.[4,5] The 'good' news and 'bad' news in both news media and scientific and medical journals may be in agreement, but may also differ dramatically depending on the situation.[6,7]

Health care providers and consumers alike seek medical information from the news media and act on it accordingly, changing their perceptions and behaviour.[8,9] Coverage of medical news exemplifies how information from the news media and scientific journals can have a significant impact, yet be confusing.[7,10,11] Most newspapers' coverage studies of the benefits and risks of medications, although valuable, are short-term and lack a comparative perspective among countries.[2,8,12] Given the media's impact on public perceptions, which in turn might affect public trust in drug governance, health care providers, consumers and regulators should have a better understanding of the distinct process of knowledge dissemination by scientific journals compared to newspapers. The dissemination dynamics of 'bad' and 'good' news might differ when taking into account long-term reporting trends using a comparative perspective and during a drug safety controversy. In this study, the SSRIs and suicidality controversy (see box) serves as an example to study the long-term dissemination dynamics of the benefits and risks of medications. Hence, the

characteristics and dynamics of coverage on SSRIs and suicidality by scientific and medical journals and newspapers in NL and in UK were assessed from 2000 to 2010.

The SSRIs and suicidality controversy

In the period 2003–2008, regulatory authorities (FDA, MHRA and EMA, among others) issued several warnings restricting the use of SSRIs in paediatrics, in reaction to safety concerns regarding suicidal ideation.[13-15] While some scientists adulated the warnings, others expressed their concerns about the implied consequences.[16,17] The safety issue arose following GlaxoSmithKline's (GSK) request for a 6-month market exclusivity extension with the FDA for the use of paroxetine (a SSRI) to treat paediatric depression in response to the Food and Drug Administration Modernization Act (FDAMA). Consequently, GSK submitted the results from unpublished paediatric clinical data to the FDA. Meanwhile, the BBC aired a documentary entitled 'The secrets of Seroxat' on October 13 2002 in which it was alleged that internal documents of GSK showed that the dissemination of trial data on paroxetine in childhood depression was spun 'to minimize any negative commercial impact'.[18] GSK was accused of underplaying the association between SSRIs and suicidality. The ensuing worldwide media exposure played a role in driving the SSRI suicide controversy. In the process, confidence in the pharmaceutical industry and regulatory authorities decreased significantly.[19] To date, the controversy remains unsettled, albeit evidence also suggests that SSRIs are useful first-line treatments for depression and most anxiety disorders but exhaustive monitoring is recommended during the initiating phase.[20]

Methods

Time frame

Content analysis was performed on articles published in the period January 2000 to December 2009, including the period in which the regulatory warnings were repeatedly enforced, i.e., 2003/4 and 2007.

Data sources

Scientific articles were extracted from Embase (compilation of Medline and 2000 extra journals not covered by Medline) using two sets of keywords, i.e., first: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicidal behavior' or 'automutilation' or 'aggression' AND 'depression'; and second: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicide'. The search was limited to 'humans', and 'Dutch' and 'English' language.

Newspapers articles were extracted using the LexisNexis database from a selection of high-circulation newspapers in NL (n=six) and in UK (n=four). The newspapers analysed were: *De Telegraaf, Algemeen Dagblad, De Volkskrant, NRC Handelsblad, Trouw* and *Het Parool* for NL; and *The Sun, Daily Mail, The Daily Telegraph* and *The Times* for UK. The newspapers' circulation figures (per country) covered 11% of each total resident population.[21,22] Search queries were performed in the language of the papers (Dutch and English). Dutch articles were retrieved using the terms 'antidepressiv!' or 'anti-depressiv!' or 'SSRI!' or 'serotonine!' AND 'zelfmoord!' or 'aggressi!' or 'geweld!' or 'kwaad!' or 'suicid!' AND 'depressi!'. British articles were extracted using the terms 'antidepress!' or

'anti-depress!' or 'SSRI!' or 'serotonin!' AND 'suicid!' or 'aggressi!' or 'violen!' or 'harm!' AND 'depressi!'.

Data classification

All articles addressing SSRIs, depression, suicidal thoughts, or suicide as the main topic were eligible for analysis. If that was not the case, such an article was categorized as 'out of context', e.g., articles reporting the use of SSRIs to treat premature ejaculation or neuralgia. All scientific and newspaper articles were analysed on the content of full–text, except for scientific articles where the abstract information was regarded as sufficient for categorization. The 'effect', 'type of article', and 'age group' categories were independently determined for these articles by two researchers.

The 'effect' category was divided into positive, neutral, and negative. Articles reporting on positive therapeutic outcomes with no confirmation of causality between SSRIs and suicidal behaviour were classified as positive. Consequently, articles reporting on the association between SSRI use and suicidality, with little or no mention of positive therapeutic outcomes, were classified as negative. Articles with a balanced message (positive and negative effects) were classified as neutral. The 'type of article' category was defined within scientific journals as: case study (patient report), research (study results, such as RCTs, meta-analyses, observational studies, etc.), opinion (letters, commentaries, replies, etc.), and policy (regulatory-related, etc.). The definition of 'type of article' in newspapers was based on the nature of the news: interview, opinion (author's perspective), news report (informative news or general journalism), science journalism (scientific information or reports), and policy (reimbursement,

change of indication, etc.). Finally, the 'age group' category considered adults (above 18 years old), paediatric (18 years old or younger), both (adult and paediatric) or unspecified.

Scoring discrepancies between the two researchers occurred in approximately 5% of all articles. In a case of discrepancy, the categorization of the article in question was settled by consensus.

Data analysis

The positive–to–negative ratio of the 'effect' category was calculated (per source, 'type of article', and 'age group' categories). For the statistical analyses, the total count of articles per category was used. Differences in distribution of the 'effect' categories (positive, neutral and negative) were analysed across the sources (Embase, Dutch and/or UK newspaper articles); 'type of article', and 'age group' were analysed using the Mann–Whitney (2 sub–groups) or Kruskal–Wallis test (3 or more). Statistical significance was defined as P<0.05. Statistical analyses were performed using SPSS software (release 18.0.3).

To assess the publication dynamics, the number of articles (in scientific journals and/or in newspapers) was plotted per year (2000–2010), and per category ('effect', 'type of article', or 'age group').

Results

A total of 1736 articles were retrieved based on the predefined key word sets. Of these, 1141 articles were fully categorized: 352 scientific, 224 Dutch newspaper articles and 565 British newspaper articles (Figure 1). The characteristics of the articles are listed in Table 1.

Publication patterns of the 'effect' category

Of all 1141 articles (scientific and newspapers), the positive-effect category (39%) was significantly larger than the negative-effect (31%) or the neutral-effect categories (30%; P<0.001). The differentiation of the 'effect' category by source showed that scientific journals were predominantly positive (ratio=3.5), whereas Dutch and British newspapers coverage of 'effect' was mainly negative (ratios=0.69–NL and 0.94–UK, Table 1). Statistically significant differences were observed in 'effect' classification for scientific journals and newspapers (both P<0.001), but not between NL and UK dailies (P=0.116, Table 2).

Although the overall coverage of 'effect' was generally positive in scientific journals, temporal changes were observed in the positive-to-negative 'effect' ratio per year, indicating a less positive-effect trend during 2003/4 and after 2007. Newspaper reporting revealed a similar trend as scientific journals. However, the positive-to-negative 'effect' ratio per year in newspapers shifted to the negative side from 2003 to 2005 and after 2007 (Figure 2B). This specific increase in negative-effect articles in newspapers was characterized by repetitive reports about lawsuits (e.g., lawyers' unsubstantiated claims of a causal association between murder and suicide attempts and the use of SSRIs), whistle-blowers or other media interventions, which fuelled the discussion.

Publication patterns of the 'type of article' category

Scientific journals published generally research articles (60%), carrying a positive-effect message (ratio=8.5, Table 2). To a lesser extent, scientific journals published opinion articles (34%), which conveyed an overall positive-effect message (ratio=1.2, Table 2). However, scientific opinion articles displayed

major temporal changes in the positive–to–negative 'effect' ratio following regulatory warnings, showing more negative–effect articles. The nature of these articles was primarily criticism of methodological issues or the author's perspective on SSRIs. Differences of 'effect' distributions related to 'types of article' were statistically significant (P<0.001, Table 2).

Newspapers published mainly news report articles (50.5%) and carried an overall negative–effect message (ratio=0.5, Table 2). A similar negative–effect trend was measured in scientific journalism articles (ratio=0.7). Newspaper opinion articles also portrayed an overall positive–effect message (ratio=2.1), as observed for opinion articles in scientific journals (ratio=1.2, Table 2). Major temporal changes in the positive–to–negative 'effect' ratio of newspaper articles were visible in the period of regulatory warnings (2002–2005 and 2007–2008, Figure 2B). Differences between 'effect' distributions related to 'types of article' were statistically significant in the accumulated newspaper articles group, UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).

Publication patterns of the 'age group' category

Scientific journals reported more frequently on paediatrics (31%) than on adults (25%; P<0.001). Articles on adults were notably more positive concerning 'effect' compared to paediatric articles (ratio=10 and 2.3, Table 2).

Newspapers paid more attention to adults (56%) than paediatrics (15%, Table 1). Reporting trend for articles on adults was primarily positive about 'effect', whereas those on paediatrics were mainly negative (ratio=1.5 and 0.2). Significant differences were found between 'effect' distributions in newspapers

related to 'age group' (P<0.001). Reporting patterns between NL and UK dailies were comparable in all three categories (P=0.116, Table 2).

Articles on paediatrics in scientific journals and in newspapers displayed similar publication dynamics, i.e., a significant peak in 2004, following the warnings. The publication dynamics of articles on adults in scientific journals and newspapers also showed a similar pattern. Thereafter, newspaper articles on adults continued to increase until 2010, while their scientific counterparts remained more or less stable (Figure 3).

Discussion

This study assessed the characteristics and dynamics of SSRIs and suicidality coverage by scientific and medical journals in general, and newspapers in NL and UK from 2000 to 2010. Scientific journals published predominantly research articles about positive therapeutic outcomes with little mention of causality between SSRIs and suicidality, particularly in adults. Despite different ethnic backgrounds (e.g., tabloid culture in UK, among others) and language, newspaper reporting trends in NL and UK were comparable; and were overall negative regarding the therapeutic effect of SSRIs in paediatrics, while positive–effect reporting prevailed for adults.

The present study has several limitations. It covered 11% of the total population per country based on newspaper circulation figures. Nevertheless, the sample size might be representative (n=789 newspaper articles) since we aimed to understand the type and quantity of information the public receives. Although reporting trends between countries were comparable, these results must be extrapolated carefully to other countries. Notwithstanding several keyword sets

were used to extract the articles, some relevant articles might have been omitted. Our sample is, however, random and therefore provides a representative overview of what has been published on SSRIs and suicidality. Other news media channels (television, radio, magazines, or the Internet) were not explored. It would be interesting to analyse the dynamics of knowledge dissemination by other channels during a drug safety event. However, the systematic analysis of Internet data remains methodologically complicated since web sites, blogs, forums, etc, come and go easily, and yet is a massive source of (mis-) information.

The finding that scientific and medical journals reported mainly positive therapeutic outcomes regarding SSRIs might be the influence of a publication bias in research articles, based on clinical study outcomes. Our results are consistent with previous work, which demonstrated that antidepressant trials with a positive outcome were published more often than those with negative outcomes.[23] However, we differentiated that the positive-effect reporting trend still dominated after the regulatory warnings. Studies questioning these warnings, and the possible disservice they did to public health (e.g., the possible inverse association between SSRIs prescriptions and suicidality, or the decline in treatment of depression in paediatrics) contributed to this post-warning positive-effect trend.[16,17] On the other hand, the newspaper dissemination of scientific-based evidence to the public revealed inconsistencies. For instance, science journalism articles (newspapers) that presented an overall negativeeffect regarding SSRIs (ratio=0.7), could not be related to the overall positiveeffect reporting trend found in scientific and medical journals. These findings indicate that either newspaper journalists may selectively report scientific

outcomes to the public, as also stated in the CHMP assessment report on antidepressants, [24] or that controversial, and sometimes misleading, topics might be selected to increase readership. [4,10,25,26] Such practices might generate confusion, since the translation of evidence–based medicine to the public is not uniform. [2,12,27] However, scientific and medical journals might also do disfavour to the scientific community by favouring positive outcome studies, thus limiting the journalists' sources of accurate and critic information to communicate to the public new scientific and medical evidence.

Alterations in publication trends of scientific and medical journals and newspapers could be the direct result of the controversy. The uncertainties regarding the SSRIs' benefit/risk balance, primarily in paediatrics, have led to the restriction of almost all SSRIs under 18 year olds in 2003 and further restrictions for young adults (18 to 24 years old) in 2007.[13–15,28] In the same periods, our data revealed shifts towards negative-effect reporting trends in scientific and newspaper articles on paediatrics and opinion articles. A causal association between this sudden publication growth and the regulatory warnings was not assessed. However, the timing between the warnings and the observed increase in articles might substantiate the possible influence of warnings on media publication trends. Moreover, this increment in the number of articles might also indicate that newspapers informed the public about this particular drug safety event in a timely fashion. Burns et al. underlined the public's right to be informed about medical news within a suitable time frame.[29] However, their study only focused on two high-ranked scientific journals, whereas we did not discriminate among scientific journals. A balance between timely coverage and high-quality information is fundamental when

reporting on drug safety controversies. Ideally, this balance should be the result of open dialogue between healthcare practitioners, academia, governmental agencies, the pharmaceutical industry, journalists and the lay public. Eventually, the public ought to and will be properly educated about the benefits and the risks of medicines by doing so.[30] And, more importantly, public trust will be maintained during unsettling periods.

The implications of the SSRIs and suicidality debate for mentally ill patients must be more adequately addressed. It has been demonstrated that news media reports (on suicide, or related to suicide) have an influence on suicidal behaviour, and on drug usage.[31,32] Further research in this regard might determine the long-term extent to which scientific journals and newspapers influenced this group of patients by investigating the long-term prescribing behaviour of SSRIs.

Conclusion

Publication trends in scientific journals and newspapers, during a drug safety controversy, appear to be more affected by regulatory actions, opinion or lawsuits, than by a straightforward translation of evidence-based medicine. The apparent positive publication bias, based on clinical study outcomes, does not seem to prevent the dissemination of 'bad' news about medications. Agreements in the nature of opinion reports were found in scientific journals and in NL and UK dailies. The occurrence of 'good' or 'bad' news in scientific journals and newspapers was found to be dependent on the news category or type of article. The increase in the number of articles in scientific journals and in newspapers during regulatory warnings might indicate that prompt news dissemination

through these channels has helped to inform the public about this drug safety controversy in a timely fashion. It also shows that a proactive and transparent risk communication strategy of regulatory offices and the pharmaceutical industry might pay off in the long run for reporting on the benefits and risks of medications.

WHAT IS ALREADY KNOWN ON THE SUBJECT

- Coverage of health related issues exemplify the relevance of scientific journals evidence through news media to inform the public, yet information might be distorted or confusing in some cases.
- The coverage of drug safety controversies in newspapers vis-à-vis scientific journals has not been thoroughly studied.

WHAT THIS STUDY ADDS

- A positive publication bias was confirmed in scientific journals, however,
 based on clinical studies outcomes, whereas 'bad' news in scientific
 journals and newspapers was related to opinion, not evidence.
- This 'bad' news trend was connected to the regulatory warnings, meaning
 that the public was informed on time about the SSRIs and suicidality
 controversy, although the information that reached the public was not
 uniform.
- An open dialogue between stakeholders will improve communication to the public and will educate them about the benefits and risks of medicines, especially during a drug safety controversy.

Table 1. Characteristics of the 1141 articles in NL & UK newspapers and in scientific journals (2000–2009)

Characteristics	Scientific Journals	NL newspapers	UK newspapers	
Characteristics	(n=352)	(n=224)	(n=565)	
Effect*				
Positive	191 (54)	65 (29)	192 (34)	
Neutral	106 (30)	66 (29)	169 (30)	
Negative	55 (16)	93 (42)	204 (36)	
Positive to negative	25	0.60	0.04	
ratio	3.5	0.69	0.94	
Type of article				
Case study	13 (4)	N/A	N/A	
Research	210 (60)	N/A	N/A	
Opinion	121 (34)	25 (11)	107 (19)	
Policy	8 (2)	11 (5)	10 (2)	
Interview	N/A	38 (17)	77 (14)	
News report	N/A	110 (49)	291 (52)	
Science journalism	N/A	40 (18)	80 (14)	
Age group				
Adults	89 (25)	128 (57)	313 (55)	
Paediatric	108 (31)	30 (13)	92 (16)	
Both	80 (23)	32 (14)	66 (12)	
Unspecified	75 (21)	34 (15)	94 (17)	

*Statistically significant differences in effect classification were observed



Table 2. Allocation of effect categories related to types of article and age groups, and differentiated by source (NL & UK newspaper articles combined)

					Positive to	
Categ	ories	Positive	Neutral	Negative	negative	p- value
					ratio	
NL newspapers	S	65	66	93	0.69	0.116
UK newspaper	s	192	169	204	0.94	0.110
Scientific journ	als	191	106	55	3.50	
NL & UK Newspapers		257	235	297	0.86	<0.001
(mixed)						
Type of	article		•			
	Case study	4	4	5	0.80	
Scientific	Research	144	49	17	8.47	0.004
journals	Opinion	39	49	33	1.18	<0.001
	Policy	3	5	0	3.00	
	Interview	69	30	16	4.31	
Newspapers*	News report	88	125	188	0.47	
	Science			52	0.73	
	journalism	38	30			<0.001
	Opinion	60	43	29	2.07	
	Policy	2	7	12	0.17	
Age g	Age group					
Scientific	Adults	70	12	7	10.0	< 0.001

journals	Paediatric	48	39	21	2.29	
	Both	33	29	18	1.83	
	Unspecified	40	26	9	4.44	
Newspapers	Adults	176	145	120	1.47	
	Paediatric	18	20	84	0.21	<0.001
	Both	22	33	43	0.51	10.001
	Unspecified	41	37	50	0.82	

^{*} Statistically significant differences in effect distributions related to types of article were also observed in UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).

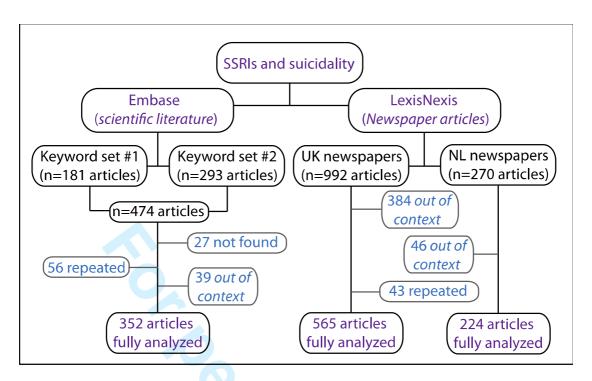


Figure 1. Scheme of the search process performed in the scientific and medical literature and in NL & UK newspapers.

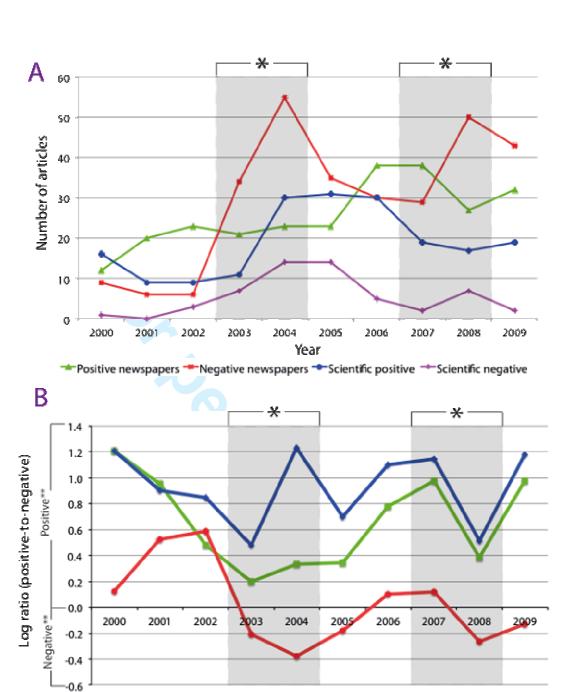


Figure 2. (A) Effect messages (positive and negative) organized along the research period, per year (2000–2009) and according to the source (scientific-medical journals and newspapers). (B) The natural logarithm of the positive-to-negative ratio was calculated and also plotted for the accumulated scientific-medical articles (green line), accumulated newspaper articles (red line), and solely research articles from the scientific-medical literature (dark blue line). *The grey zone illustrates the period where most of the regulatory warnings were issued. **Articles with a positive-

Year

Research (scientfic literature)

Newspapers

Scientific Journals (all)

effect trend are located above zero, whilst articles conveying a negative-effect trend are located underneath zero.



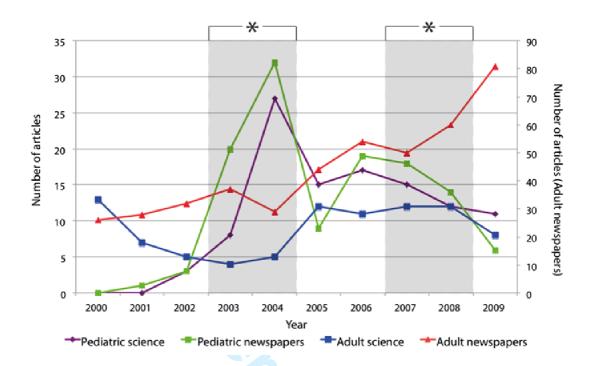


Figure 3. Articles indexed into age groups (paediatric and adult) in scientific-medical journals and in newspapers from 2000 to 2009. The scale of newspaper articles on adults is portrayed on the right y-axis. *The grey zone illustrates the period where most of the regulatory warnings were issued.

Author's contributions: All authors were involved in the design of the study, review of earlier versions of the manuscript, and providing final approval for submission. JFH was responsible for the collection, analysis (also statistical), and interpretation of the data, as well as drafting, and revising the manuscript. TP was responsible for the analysis and interpretation of the data, drafting supervision, and revision. SVB provided support with the statistical analyses, as well.

Competing interests: JAMR is part–time professor at the Utrecht University and vice–president external scientific collaborations for GSK in Europe, and holds stock in GSK. All other authors declare no personal conflict of interest relevant to

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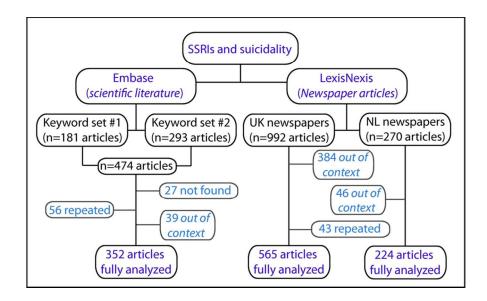
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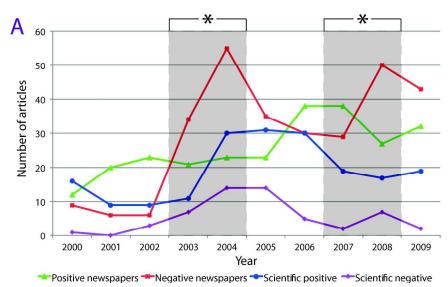
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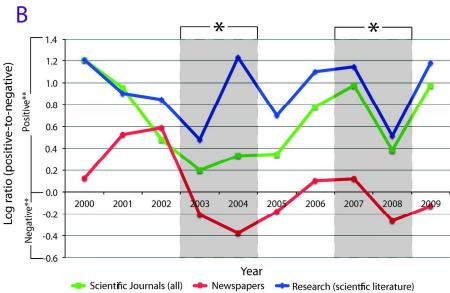
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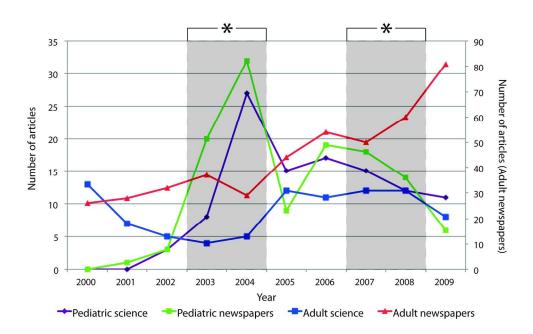


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Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study

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SCHOLARONE™ Manuscripts Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study

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Abstract

Background: In the period 2003–2008, the regulatory authorities issued several warnings restricting the use of SSRIs in paediatrics, in reaction to safety concerns regarding the risk of suicidality. In this study, the SSRIs and suicidality controversy serves, as a template to analyse the long-term <u>publication trends</u> regarding the benefit/risk profile of medications. The <u>aim is to ascertain</u> differences (in terms of numbers, categories and timing) between negative and positive newspaper and journal articles on SSRIs and suicidality, and ascertain correlations between changes in the reports and regulatory warnings.

Methods: A systematic review of scientific articles (Embase), and NL and UK newspapers (LexisNexis) was performed between 2000-2010. Categorization was done by 'effect' (related treatment effect), 'type of article' and 'age group'. The articles' positive-to-negative effect ratio was determined. Differences in distribution of 'effect' categories were analysed across sources, 'type of article', and 'age group' using the Mann-Whitney (2 sub-groups) or Kruskal-Wallis test (3 or more).

Findings: In total, 1141 articles were categorized: 352 scientific, 224 Dutch, and 565 British newspaper articles. Scientific articles were predominantly on research and were positive, whereas newspaper articles were negative (ratios=3.50-scientific, 0.69-NL and 0.94-UK; P<0.001). Articles on paediatrics were less positive in scientific journals and more negative in newspapers (ratios=2.29-scientific, 0.26-NL, and 0.20-UK; P<0.001), while articles on adults were positive overall (ratios=10.0-scientific, 1.06-NL, and 1.70-UK; P<0.001). In addition, negative-effect reporting trends were exacerbated following regulatory

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warnings and were generally opinion articles, both in scientific journals and newspapers (2003/4 and after 2007).

Interpretation: We found a positive publication tendency inherent in journal research articles. This apparent positive publication bias present in scientific journals, however, does not seem to prevent the dissemination of 'bad' news about medications. The negative tendency present in Dutch and British newspapers was perceivable in the paediatrics group and during the warnings, indicating that national news media have informed the public about this international drug safety controversy on time.

Deleted: 'Good' news in scientific journals is determined by a positive bias in research reporting, however, based on clinical studies outcomes, whereas 'bad' news is related to opinion. Scientific journals and newspapers coincided in the nature and timing of opinion articles. The increase of negative-effect articles in scientific journals and newspapers following regulatory warnings indicates that the public has been informed in a timely fashion.

Introduction

The news media are an important source of information about therapeutic drugs and health.[1] Coverage varies from communicating the benefits and risks of medications, to drug regulation and litigation, among others.[2,3] Scientific journals are a significant source of information for journalists writing about medicine.[4] However, this does not necessarily mean that 'good' or 'bad' news about medicines in the news media is determined by the scientific literature.[4,5] The 'good' news and 'bad' news in both news media and scientific and medical journals may be in agreement, but may also differ dramatically depending on the situation.[6,7]

Health care providers and consumers alike seek medical information from the news media and act on it accordingly, changing their perceptions and behaviour.[8,9] Coverage of medical news exemplifies how information from the news media and scientific journals can have a significant impact, yet be confusing.[7,10,11] Most newspapers' coverage studies of the benefits and risks of medications, although valuable, are short-term and lack a comparative perspective among countries.[2,8,12] In this study, we analyzed the long-term publication trends regarding the benefit/risk profile of medications in the context of the SSRIs and suicidality controversy (see box) from 2000 to 2010 in scientific journals and newspapers in the Netherlands (NL) and in the United Kingdom (UK). The aim is to ascertain the differences (in terms of numbers, categories, and timing) between negative and positive newspaper and scientific journal articles on SSRIs and suicidality.

Deleted: Given the media's impact on public perceptions, which in turn might affect public trust in drug governance, health care providers, consumers and regulators should have a better understanding of the distinct process of knowledge dissemination by scientific journals compared to newspapers. The dissemination dynamics of 'bad' and 'good' news might differ when taking into account longterm reporting trends using a comparative perspective and during a drug safety controversy.

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The SSRIs and suicidality controversy

In the period 2003-2008, regulatory authorities (FDA, MHRA and EMA, among others) issued several warnings restricting the use of SSRIs in paediatrics, in reaction to safety concerns regarding suicidal ideation.[13-15] While some scientists adulated the warnings, others expressed their concerns about the implied consequences.[16,17] The safety issue arose following GlaxoSmithKline's (GSK) request for a 6-month market exclusivity extension with the FDA for the use of paroxetine (a SSRI) to treat paediatric depression in response to the Food and Drug Administration Modernization Act (FDAMA). Consequently, GSK submitted the results from unpublished paediatric clinical data to the FDA. Meanwhile, the BBC aired a documentary entitled 'The secrets of Seroxat' on October 13 2002 in which it was alleged that internal documents of GSK showed that the dissemination of trial data on paroxetine in childhood depression was spun 'to minimize any negative commercial impact'.[18] GSK was accused of underplaying the association between SSRIs and suicidality. The ensuing worldwide media exposure played a role in driving the SSRI suicide controversy. In the process, confidence in the pharmaceutical industry and regulatory authorities decreased significantly.[19] To date, the controversy remains unsettled, albeit evidence also suggests that SSRIs are useful first-line treatments for depression and most anxiety disorders but exhaustive monitoring is recommended during the initiating phase.[20]

Methods

Time frame

Content analysis was performed on articles published in the period January 2000 to December 2009, including the period in which the regulatory warnings were repeatedly enforced, i.e., 2003/4 and 2007.

Data sources

Scientific articles were extracted from Embase (compilation of Medline and 2000 extra journals not covered by Medline) using two sets of keywords, i.e., first: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicidal behavior' or 'automutilation' or 'aggression' AND 'depression'; and second: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicide'. The search was limited to 'humans', and 'Dutch' and 'English' language.

Newspapers articles were extracted using the LexisNexis database from a selection of high-circulation newspapers in NL (n=six) and in UK (n=four). The newspapers analysed were: *De Telegraaf, Algemeen Dagblad, De Volkskrant, NRC Handelsblad, Trouw* and *Het Parool* for NL; and *The Sun, Daily Mail, The Daily Telegraph* and *The Times* for UK. The newspapers' circulation figures (per country) covered 11% of each total resident population.[21,22] Search queries were performed in the language of the papers (Dutch and English). Dutch articles were retrieved using the terms 'antidepressiv!' or 'anti-depressiv!' or 'SSRI!' or 'serotonine!' AND 'zelfmoord!' or 'aggressi!' or 'geweld!' or 'kwaad!' or 'suicid!' AND 'depressi!'. British articles were extracted using the terms 'antidepress!' or 'anti-depress!' or 'SSRI!' or 'serotonin!' AND 'suicid!' or 'aggressi!' or 'violen!' or 'harm!' AND 'depressi!'.

Data classification

All articles addressing SSRIs, depression, suicidal thoughts, or suicide as the main topic were eligible for analysis. If that was not the case, such an article was categorized as 'out of context', e.g., articles reporting the use of SSRIs to treat premature ejaculation or neuralgia. All scientific and newspaper articles were analysed on the content of full-text, except for scientific articles where the abstract information was regarded as sufficient for categorization. The 'effect', 'type of article', and 'age group' categories were independently determined for these articles by two researchers.

The 'effect' category was divided into positive, neutral, and negative. Articles reporting on positive therapeutic outcomes with no mention of an association between SSRIs and an increased risk on suicidal behaviour were classified as positive. Consequently, articles affirmatively reporting on the association between SSRI use and suicidality, with no mention of positive therapeutic outcomes, were classified as negative. Articles with a balanced message (positive and negative effects) were classified as neutral. The 'type of article' category was defined within scientific journals as: case study (represents a descriptive and intensive analysis of an individual patient), research (comprehends study results, such as RCTs (randomized clinical trials), meta-analyses, observational studies (multiple patients), etc.), opinion (enclose articles, such as letters to an editor, commentaries, replies, etc.), and policy (comprehends articles discussing regulatory-related topics, etc.). The definition of 'type of article' in newspapers was based on the nature and elaboration of the news conveyed: interview (comprehends articles where the journalist questioned the interviewee to retrieve information), opinion (comprises articles where the author or journalist

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portrayed his/her personal, perspective), news report (covers general articles with informative news or general journalism), science journalism (comprehends articles presenting scientific information or reports), and policy (comprehends articles discussing regulatory—related topics, such as reimbursement, change of indication, etc.). Finally, the 'age group' category considered adults (above 18 years old), paediatric (18 years old or younger), both (adult and paediatric) or unspecified.

Scoring discrepancies between the two researchers occurred in approximately 5% of all articles. In a case of discrepancy, the categorization of the article in question was settled by consensus.

Data analysis

The positive–to–negative ratio of the 'effect' category was calculated (per source, 'type of article', and 'age group' categories). For the statistical analyses, the total count of articles per category was used. Differences in distribution of the 'effect' categories (positive, neutral and negative) were analysed across the sources (Embase, Dutch and/or UK newspaper articles); 'type of article', and 'age group' were analysed using the Mann–Whitney (2 sub–groups) or Kruskal–Wallis test (3 or more). Statistical significance was defined as P<0.05. Statistical analyses were performed using SPSS software (release 18.0.3).

To assess the publication dynamics, the number of articles (in scientific journals and/or in newspapers) was plotted per year (2000–2010), and per category ('effect', 'type of article', or 'age group').

Results

A total of 1736 articles were retrieved based on the predefined key word sets. Of these, 1141 articles were fully categorized: 352 scientific, 224 Dutch newspaper articles and 565 British newspaper articles (Figure 1). The characteristics of the articles are listed in Table 1.

Publication patterns of the 'effect' category

Of all 1141 articles (scientific and newspapers), the positive-effect category (39%) was significantly larger than the negative-effect (31%) or the neutral-effect categories (30%; P<0.001). The differentiation of the 'effect' category by source showed that scientific journals were predominantly positive (ratio=3.5), whereas Dutch and British newspapers coverage of 'effect' was mainly negative (ratios=0.69–NL and 0.94–UK, Table 1). Statistically significant differences were observed in 'effect' classification for scientific journals and newspapers (both P<0.001), but not between NL and UK dailies (P=0.116, Table 2).

Although the overall coverage of 'effect' was generally positive in scientific journals, temporal changes were observed in the positive-to-negative 'effect' ratio per year, indicating a less positive-effect trend during 2003/4 and after 2007. Newspaper reporting revealed a similar trend as scientific journals. However, the positive-to-negative 'effect' ratio per year in newspapers shifted to the negative side from 2003 to 2005 and after 2007 (Figure 2B).

Publication patterns of the 'type of article' category

Scientific journals published generally research articles (60%), carrying a positive-effect message (ratio=8.5, Table 2). To a lesser extent, scientific journals published opinion articles (34%), which conveyed an overall positive-effect message (ratio=1.2, Table 2). However, scientific opinion articles displayed

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major temporal changes in the positive-to-negative 'effect' ratio following regulatory warnings, showing more negative-effect articles. <u>Differences of</u> 'effect' distributions related to 'types of article' were statistically significant (P<0.001, Table 2).

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Newspapers published mainly news report articles (50.5%) and carried an overall negative–effect message (ratio=0.5, Table 2). A similar negative–effect trend was measured in scientific journalism articles (ratio=0.7). Newspaper opinion articles also portrayed an overall positive–effect message (ratio=2.1), as observed for opinion articles in scientific journals (ratio=1.2, Table 2). Major temporal changes in the positive–to–negative 'effect' ratio of newspaper articles were visible in the period of regulatory warnings (2002–2005 and 2007–2008, Figure 2B). Differences between 'effect' distributions related to 'types of article' were statistically significant in the accumulated newspaper articles group, UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).

Publication patterns of the 'age group' category

Scientific journals reported more frequently on paediatrics (31%) than on adults (25%; P<0.001). Articles on adults were notably more positive concerning 'effect' compared to paediatric articles (ratio=10 and 2.3, Table 2).

Newspapers paid more attention to adults (56%) than paediatrics (15%, Table 1). Reporting trend for articles on adults was primarily positive about 'effect', whereas those on paediatrics were mainly negative (ratio=1.5 and 0.2). Significant differences were found between 'effect' distributions in newspapers related to 'age group' (P<0.001). Reporting patterns between NL and UK dailies were comparable in all three categories (P=0.116, Table 2).

Articles on paediatrics in scientific journals and in newspapers displayed similar publication dynamics, i.e., a significant peak in 2004, following the warnings. The publication dynamics of articles on adults in scientific journals and newspapers also showed a similar pattern. Thereafter, newspaper articles on adults continued to increase until 2010, while their scientific counterparts remained more or less stable (Figure 3).

Discussion

This study assessed the characteristics and dynamics of SSRIs and suicidality coverage by scientific and medical journals in general, and newspapers in NL and UK from 2000 to 2010. Scientific journals published predominantly research articles about positive therapeutic outcomes with little mention of an association between SSRIs and suicidality, particularly in adults. Despite different ethnic backgrounds (e.g., tabloid culture in UK, among others) and language, newspaper reporting trends in NL and UK were comparable; and were overall negative regarding the therapeutic effect of SSRIs in paediatrics, while positive–effect reporting prevailed for adults.

The present study has several limitations. It covered 11% of the total population per country based on newspaper circulation figures. Nevertheless, the <u>random</u> sample <u>is</u> representative (n=789 newspaper articles) given the aim to ascertain differences (in terms of numbers, categories, and timing) between negative and positive newspaper and journal articles on SSRIs and suicidality. The categories 'effect' and 'type of article' might be limited by our definition, and their interpretation could differ between readers. We attempted to avoid subjectivity by analysing the data independently by two researchers. We achieved more than

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Deleted: since we aimed to understand the type and quantity of information the public receives. Although reporting trends between countries were comparable, these results must be extrapolated carefully to other countries. Notwithstanding several keyword sets were used to extract the articles, some relevant articles might have been omitted. Our sample is, however, random and therefore provides a representative overview of what has been published on SSRIs and suicidality.

95% agreements during article categorization (effect, type of article, and age

group categories). We did not, however, ascertain the context of the articles in terms of construction of the newspaper and opinion articles from its original source. Neither did we explore other forms of media coverage (television, radio, magazines, or the Internet), The content analysis method used in this study does not allow for these additional more complex queries. Our results showing a positive publication tendency in scientific journals are consistent with previous work, which demonstrated that antidepressant trials with a positive outcome were published more often than those with negative outcomes.[23] This positive publication tendency continued even after the regulatory warnings, and could potentially leave physicians with a biased view of the medications that they are prescribing to patients. Studies questioning these warnings, and the possible disservice they did to public health (e.g., the possible inverse association between SSRIs prescriptions and suicidality, or the decline in treatment of depression in paediatrics) contributed to this post-warning positive-effect trend.[16,17] On the other hand, this positive publication tendency in scientific journals does not seem to prevent the dissemination of 'bad' news about medications. For instance, science journalism articles (newspapers) that presented a <u>negative publication tendency</u> regarding SSRIs (ratio=0.7), could not be related to the positive publication tendency found in scientific journals. These findings indicate that either newspaper journalists may selectively report scientific outcomes to the public, as also stated in the CHMP assessment report on antidepressants, [24] or that controversial topics might be selected to increase readership.[4,10,25,26] Such practices might generate confusion, since the translation of evidence-based medicine to the public is not

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uniform[2,5,12,27], and may have implications for patients compliance with medications, willingness to see physicians, and trust in the doctor-patient relationship. However, scientific and medical journals might also do disfavour to the scientific community by favouring positive outcome studies, thus limiting the journalists' sources of accurate and critic information to communicate to the public new scientific and medical evidence.

The uncertainties regarding the SSRIs' benefit/risk balance, primarily in paediatrics, have led to the restriction of almost all SSRIs under 18 year olds in 2003 and further restrictions for young adults (18 to 24 years old) in 2007.[13-15,28] In the same periods, our data revealed shifts towards negative-effect reporting trends in scientific and newspaper articles on paediatrics and opinion articles. The timing between the warnings and the observed increase in articles substantiate the possible influence of warnings on media publication trends. Moreover, this increment in the number of articles suggests that newspapers informed the public about this particular drug safety event in a timely fashion. Studies have underlined the relevance of informing the public about medical news within a suitable time frame.[6.29] However, these studies only focused on a subset of scientific journals, whereas we did not discriminate among scientific journals. A balance between timely coverage, consistent, and adequate information is fundamental when reporting on drug safety controversies. Ideally, this balance should be the result of an open dialogue between healthcare practitioners, academia, governmental agencies, the pharmaceutical industry, journalists and the public. However difficult, educating the public properly and on time about the benefits and the risks of medicines will help to maintain public trust during unsettling periods.[30]

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Finally, the possible implications of the discovered tendencies in scientific journals and newspapers for patients and doctors have not been addressed in this paper. It has been shown that news media reports (on suicide, or related to suicide) have an influence on suicidal behaviour, and on drug usage.[31,32] It might be valuable in this regard to determine the long-term influence of media coverage and the regulatory warnings on prescription patterns.

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Conclusion

Our study of the SSRIs and suicidality controversy showed several publication tendencies in scientific journals and newspapers. We identified a positive publication tendency inherent in journal research articles, which could potentially affect doctors' assessment of the safety and effectiveness of the medications that they are prescribing to patients. This apparent positive publication bias in scientific journals, however, does not seem to prevent the dissemination of 'bad' news about medications. The occurrence of 'good' or 'bad' news in scientific journals and newspapers was found to be dependent on the news category or type of article. Opinion reports in scientific journals did not differ significantly in the nature and timing of reporting from opinion articles in <u>Dutch and British dailies.</u> Differences between the Dutch and British newspaper reporting patterns were minor. The negative tendency present in Dutch and British newspapers was perceivable in the paediatrics group and during the warnings, indicating that newspapers have informed the public about this drug <u>safety controversy on time</u>. It also shows that a proactive and transparent risk communication strategy of regulatory offices and the pharmaceutical industry

Deleted: Publication trends in scientific journals and newspapers, during a drug safety controversy, appear to be more affected by regulatory actions, opinion or lawsuits, than by a straightforward translation of evidence–based medicine. The apparent positive publication bias, based on clinical study outcomes,

Deleted: Agreements in the nature of opinion reports were found in scientific journals and in NL and UK dailies.

Deleted: The increase in the number of articles in scientific journals and in newspapers during regulatory warnings might indicate that prompt news dissemination through these channels has helped to inform the public about this drug safety controversy in a timely fashion.

might pay off in the long run for reporting on the benefits and risks of medications.

Deleted: WHAT IS ALREADY
KNOWN ON THE SUBJECT¶
<#>Coverage of health related
issues exemplify the relevance of
scientific journals evidence
through news media to inform the
public, yet information might be
distorted or confusing in some
cases.¶
<#>The coverage of drug safety
controversies in newspapers vis-àvis scientific journals has not been
thoroughly studied. [1]

Table 1. Characteristics of the 1141 articles in NL & UK newspapers and in scientific journals (2000–2009)

Ch ave at a vistina	Scientific Journals	NL newspapers	UK newspapers	
Characteristics	(n=352)	(n=224)	(n=565)	
Effect*				
Positive	191 (54)	65 (29)	192 (34)	
Neutral	106 (30)	66 (29)	169 (30)	
Negative	55 (16)	93 (42)	204 (36)	
Positive to negative	3.5	0.69	0.94	
ratio	5.5	0.09	0.54	
Type of article				
Case study	13 (4)	N/A	N/A	
Research	210 (60)	N/A	N/A	
Opinion	121 (34)	25 (11)	107 (19)	
Policy	8 (2)	11 (5)	10 (2)	
Interview	N/A	38 (17)	77 (14)	
News report	N/A	110 (49)	291 (52)	
Science journalism	N/A	40 (18)	80 (14)	
Age group				
Adults	89 (25)	128 (57)	313 (55)	
Paediatric	108 (31)	30 (13)	92 (16)	
Both	80 (23)	32 (14)	66 (12)	
Unspecified	75 (21)	34 (15)	94 (17)	

*Statistically significant differences in effect classification were observed between scientific journals and newspapers (P<0.001), but not between NL and UK dailies (P=0.116). N/A=not applicable.



Table 2. Allocation of effect categories related to types of article and age groups, and differentiated by source (NL & UK newspaper articles combined)

					Positive to	
Categ	ories	Positive	Neutral	Negative	negative	p- value
					ratio	
NL newspapers	5	65	66	93	0.69	0.116
UK newspaper	s	192	169	204	0.94	0.116
Scientific journ	als	191	106	55	3.50	
NL & UK Newspapers (mixed)		257	235	297	0.86	<0.001
Type of	article					
	Case study	4	4	5	0.80	
Scientific	Research	144	49	17	8.47	.0.001
journals	Opinion	39	49	33	1.18	<0.001
	Policy	3	5	0	3.00	
Newspapers*	Interview	69	30	16	4.31	
	News report	88	125	188	0.47	
	Science	38	30	52		
	journalism				0.73	<0.001
	Opinion	60	43	29	2.07	
	Policy	2	7	12	0.17	
Age g	Age group					
Scientific	Adults	70	12	7	10.0	< 0.001

journals	Paediatric	48	39	21	2.29	
	Both	33	29	18	1.83	
	Unspecified	40	26	9	4.44	
Newspapers	Adults	176	145	120	1.47	
	Paediatric	18	20	84	0.21	<0.001
	Both	22	33	43	0.51	
	Unspecified	41	37	50	0.82	

^{*} Statistically significant differences in effect distributions related to types of article were also observed in UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).

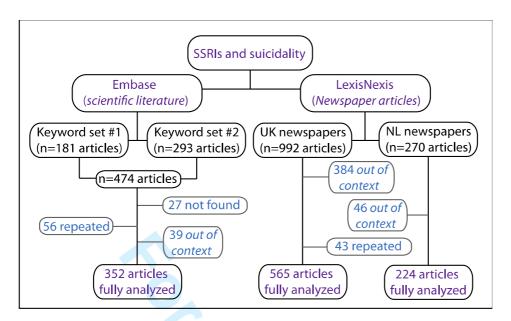


Figure 1. Scheme of the search process performed in the scientific and medical literature and in NL & UK newspapers.

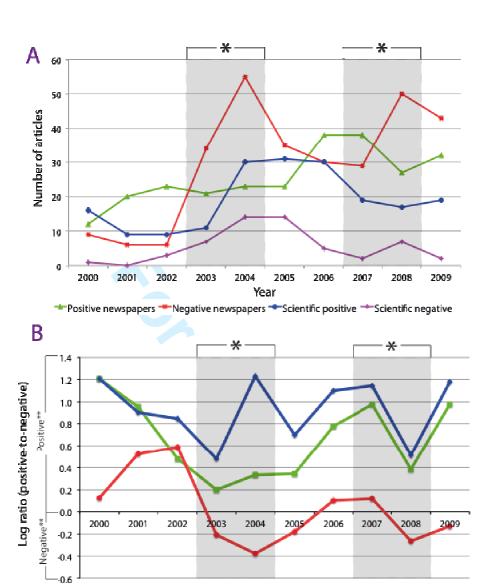


Figure 2. (A) Effect messages (positive and negative) organized along the research period, per year (2000–2009) and according to the source (scientific-medical journals and newspapers). (B) The natural logarithm of the positive-to-negative ratio was calculated and also plotted for the accumulated scientific-medical articles (green line), accumulated newspaper articles (red line), and solely research articles from the scientific-medical literature (dark blue line). *The grey zone illustrates the period where most of the regulatory warnings were issued. **Articles with a positive-

Scientific Journals (all)

Year

Newspapers Research (scientific literature)

effect trend are located above zero, whilst articles conveying a negative-effect trend are located underneath zero.

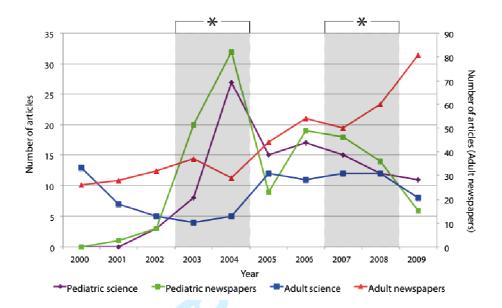


Figure 3. Articles indexed into age groups (paediatric and adult) in scientific-medical journals and in newspapers from 2000 to 2009. The scale of newspaper articles on adults is portrayed on the right y-axis. *The grey zone illustrates the period where most of the regulatory warnings were issued.

Author's contributions: All authors were involved in the design of the study, review of earlier versions of the manuscript, and providing final approval for submission. JFH was responsible for the collection, analysis (also statistical), and interpretation of the data, as well as drafting, and revising the manuscript. TP was responsible for the analysis and interpretation of the data, drafting supervision, and revision. SVB provided support with the statistical analyses, as well.

Data deposited at Dryad: doi:10.5061/dryad.gm2534t7

Competing interests: JAMR is part-time professor at the Utrecht University and vice-president external scientific collaborations for GSK in Europe, and holds

stock in GSK. All other authors declare no personal conflict of interest relevant to the subject matter or materials discussed in the manuscript. This study was performed in the context of the Escher project (T6–202), a project of the Dutch Top Institute Pharma. The Division of Pharmacoepidemiology and Clinical Pharmacology, employing authors JFH, AKM, SVB, JAMR, and TP, has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline (GSK), the private–public funded Top Institute Pharma (www.tipharma.nl, includes co–funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health.

Role of the funding source: None to declare.

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WHAT IS ALREADY KNOWN ON THE SUBJECT

Coverage of health related issues exemplify the relevance of scientific journals evidence through news media to inform the public, yet information might be distorted or confusing in some cases.

The coverage of drug safety controversies in newspapers vis-à-vis scientific journals has not been thoroughly studied.

WHAT THIS STUDY ADDS

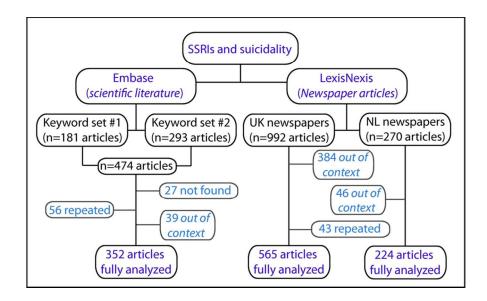
A positive publication bias was confirmed in scientific journals, however, based on clinical studies outcomes, whereas 'bad' news in scientific journals and newspapers was related to opinion, not evidence.

This 'bad' news trend was connected to the regulatory warnings, meaning that the public was informed on time about the SSRIs and suicidality controversy, although the information that reached the public was not uniform.

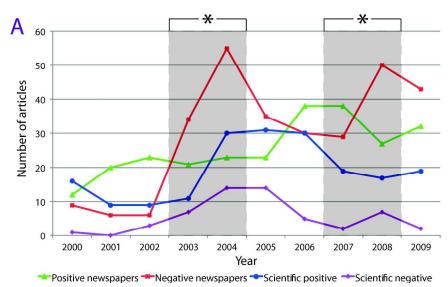
An open dialogue between stakeholders will improve communication to the public and will educate them about the benefits and risks of medicines, especially during a drug safety controversy. **Please note:** BMJ Group requires compliance to the following reporting guidelines, please upload your completed check-list with your submission and label it "Research checklist":

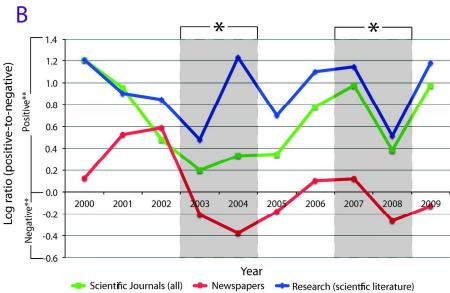
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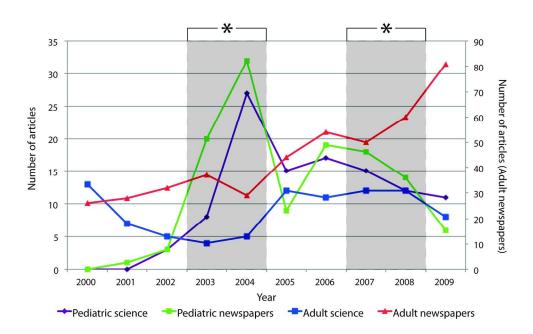


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