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Media coverage of drug regulatory agencies' safety advisories: a case study of citalopram and denosumab

Short running title (max 40 characters): Media coverage of medicine safety advisories

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Abstract

Aims: Drug regulators issue safety advisories to warn clinicians and the public about new evidence of harmful effects of medicines. It is unclear how often these messages are covered by the media. Our aim was to analyse the extent of media coverage of two medicines that were subject to safety advisories from 2007 to 2016 in Australia, Canada, United Kingdom and United States.

Methods: Two widely-used medicines to treat mental health or physical conditions were selected: citalopram and denosumab. Media reports were identified by searching LexisNexis and Factiva. Reports were included if they stated at least one health benefit or harm. A content analysis of the reports was conducted.

Results: In total, 195 media reports on citalopram and 239 on denosumab were included. For citalopram, 43.1% (84/195) of the reports mentioned benefits, 85.6% (167/195) mentioned harms and 9.7% (19/195) mentioned the harm described in the advisories (cardiac arrhythmia). For denosumab, 94.1% (225/239) of the reports mentioned benefits and 39.7% (95/239) mentioned harms. The harms described in the advisories were rarely mentioned: 10.9% (26/239) of the reports mentioned osteonecrosis and ≤5% mentioned any of the other harms (atypical fractures, hypocalcemia, serious infections, and dermatologic reactions).

Conclusions: We found limited media coverage of the harms highlighted in safety advisories. Almost two-thirds of the media stories on denosumab did not include any information about harms, despite the many advisories during this time frame. Citalopram coverage covered harms more often but rarely mentioned cardiac arrhythmias. These findings raise questions about how to better ensure that regulatory risk communications reach the general public.

What is already known about this subject:

- Drug regulators issue safety advisories to warn about emergent risks of medicines. The effectiveness of these warnings can vary, with one key determinant whether they reach the intended audience.

- Media reports could influence awareness of harms reported in safety advisories and subsequent shifts in health care utilisation. However, it is unclear how often drug regulators' messages on safety concerns of medicines are transmitted through media coverage.

- Previous research has shown significant shortcomings in media coverage of medicines, including overstating of benefits and downplaying of harms.

What this study adds:

- There was limited media coverage of the safety concerns highlighted in advisories released by drug regulators on citalopram and denosumab.

- While citalopram coverage often covered harms, almost two-thirds of the media stories on denosumab did not include any information about harms, despite the many advisories released during this time frame.

- The media can be an important conduit for medicine safety communication and its role in the context of drug regulators' messaging could be improved.

Background

Drug regulatory agencies regularly issue safety advisories to warn clinicians and the public about new evidence of harmful effects of medicines, with the aim of guiding safer prescribing and use. The effectiveness of these warnings can vary, and one key determinant of this is whether they reach the intended audience.[1]

The general media is an important channel for public health communication and for raising awareness about threats to human health.[2] This avenue may be particularly important when drug safety concerns emerge. For example, in the early 1980s the media were an important channel for the diffusion of information about the relationship between use of aspirin and Reye's syndrome.[3] Media coverage coincided with a sudden decline in Reye's syndrome incidence in the United States.[3] Similarly, in 2002-2003 a decline in hormone replacement therapy use was observed following the extensive media coverage generated by the publication of the Women's Health Initiative, a trial that demonstrated the risks of hormone therapy.[4]

Due to their potential to affect clinical practice and health care utilisation, media reports could also influence uptake of safety advisories. However, it is unclear how often regulators' drug safety messages are transmitted through media coverage around the time that the advisory is disseminated. Previous research has shown significant shortcomings in media coverage of medicines, including overstating of benefits and downplaying of harms.[5, 6] For example, an analysis of Canadian newspaper coverage about five prescription medicines found that beneficial effects were mentioned 4.7 times more often than harms.[5] Concerns have also been raised about the failure to include information on funding sources and financial ties of investigators when scientific research is reported in the media.[6, 7]

The objective of this study was to analyse the extent and patterns of media coverage of two medicines that were subject to safety advisories in four countries -Australia, Canada, United Kingdom (UK) and United States (US). A secondary objective was to assess whether funding source and financial ties of investigators of the scientific studies cited in the media were available to journalists and whether they were reported in the media stories.

Methods

We used a case study approach in order to conduct an in-depth exploration of media coverage of safety advisories.[8] We intentionally chose as illustrative case studies two different types of medicines used by different subsets of patients under different circumstances. The four countries were selected for their similar medical traditions, population size and demographics (Australia and Canada), for their strong influence on drug regulation internationally (UK and US), and for the possibility to analyse media reports without need for translation.

Identification of the case studies

Our team previously compiled all of the post-market safety advisories issued by drug regulatory agencies in Australia, Canada, UK and US from 01 January 2007 to 31 December 2016.[9] Safety advisories were defined as communications to prescribers and/or the public about real or potential safety concerns intrinsic to the medicines' effects. We excluded communications about manufacturing problems, drug shortages, misuse and overdose. Over this 10-year period, 1441 advisories were identified in the four countries after excluding duplicate advisories by the same regulator and on the same medicine and safety issue within a 30 day period. Based on discussion among co-investigators, we selected two widely-used medicines using the following criteria:

- medicines that may be prescribed by general practitioners as well as specialists;
- one medicine used to treat mental health conditions and one medicine used to treat physical conditions;
- medicines that were subject to serious safety concerns and for which at least one of the four regulators had issued an alert or a Direct Healthcare Professional Communication (DHPC) as these are the main communication interventions used by drug regulators to deliver important information directly to healthcare professionals.[10, 11] However, it should be noted that in Australia DHPCs are not publicly available,[12] therefore our list of Australian safety advisories could be incomplete.

Based on these criteria, we selected citalopram, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, and denosumab, a monoclonal antibody that inhibits the activity of osteoclasts. Denosumab is frequently used for the treatment of osteoporosis, but a higher dose formulation is also used to prevent complications caused by bone malignancies

and to treat giant cell tumor of the bone.[13] The final decision about which medicines to include was made before analysing any media coverage. Table 1 lists the safety concerns highlighted in the advisories that were issued on citalopram and denosumab during the study period. Citalopram was subject to advisories on risks of QT prolongation and cardiac arrhythmia, and denosumab was the focus of advisories on the risks of atypical fractures, hypocalcemia, osteonecrosis, serious infections, and dermatologic reactions.

Database search

We identified English-language media coverage in Australia, Canada, UK and US by searching Lexis Nexis and Factiva, two electronic databases of global news. In order to assess whether there was an increase in media reporting after advisories, we identified media reports about citalopram and denosumab from one year before the first advisory to one year after the last advisory in any included country. Searches were carried out using the generic and the originator brand names of citalopram and denosumab in Australia, Canada, UK and US (Citalopram search: *citalopram OR escitalopram OR cipramil OR celexa OR lexapro OR cipralex***;** Denosumab search: *denosumab OR Xgeva OR Prolia*). We included general media such as print and online journalism (daily, weekly and monthly newspapers and magazines, news blogs, radio/television journalism). Broadcast transcripts were also included from Factiva, but not from Lexis Nexis where most broadcast transcripts were 'unclassified' with regard to the geographical provenance.

Eligibility criteria

Two investigators independently screened the full texts of all the retrieved media reports for inclusion, applying the following criteria:

- at least one health benefit or harm (including a lack of effect) of the selected medicines was stated. This could have been any health outcome. We included reports on non-approved as well as approved indications, and reports about claims of cost-effectiveness;
- the media report was from Australia, Canada, UK or US.

We excluded the following types of media reports:

- those only mentioning the drug indication without any other information on beneficial or harmful effects, for example "citalopram is a treatment for depression";
- those only mentioning market share, profitability, and other business issues;

- press releases (these were excluded because their intended audience is media outlets and journalists, and we were only interested in the final media reports that are read by the public);
- reports in the medical press (journals with a health professional audience).

Discrepancies between coders on inclusion/exclusion were resolved by consensus. If agreement could not be reached, a third assessor adjudicated. Media reports were often syndicated and made available via multiple news outlets. For the included media reports, we kept track of the number of syndicated reports but coded only the first one which appeared.

Data collection

We conducted a content analysis of the identified media reports examining:

- the type of benefits and harms mentioned;
- whether the harms listed in the advisories were mentioned and whether the media report portrayed an increased risk of harm or minimised the risk of harm (e.g. stating that no cases were found or that the cases were not serious);
- who was cited;
- whether identifiable research studies (primary empirical research and systematic reviews, but not editorial or opinion pieces) were cited, and if so, whether funding source and financial ties of investigators were reported;
- the coders' assessment of the overall emphasis of the media reports (mainly on harms of the medicine, mainly on benefits, neutral, unclear).

We created a structured coding questionnaire to assess the above (see Supplementary File 1) that was pilot tested with 25 media reports in order to address ambiguities identified through coding disagreements. A written manual with instructions was developed and a training session for the coders was conducted before starting the data collection. From each included record, four assessors (working in pairs) independently extracted the above mentioned information using Redcap, a secure web-based application for data collection and management.[14] Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a third assessor adjudicated.

For the media reports mentioning the safety concerns described in the advisories, we also conducted an additional analysis looking at the type of news source (e.g. newspaper, magazine, blogs) and coverage (e.g. local or national).

Concordance between reporting of financial ties in media reports and related scientific articles

If specific scientific studies were reported in news articles, we determined whether information on funding source and investigators' financial conflicts of interest was available to journalists from the published study report. We recorded the study name, author, journal, and date (when available). We then searched PubMed and Google for the scientific journal articles that were mentioned in the media reports. Two investigators independently examined these articles for research funding and authors' financial conflict of interest disclosures. We then compared this information with the disclosures in the media.

Statistical analysis

We graphed monthly media coverage counts for the entire study period. Descriptive statistics were used to summarise extracted data. Analyses were performed using Excel and SPSS (Version 22).

Results

In total, 3452 media reports were screened, 1603 on citalopram/escitalopram and 1849 on denosumab.(Figure 1 and 2) For 24 reports (0.7%), screeners' judgments were resolved via adjudication.

Citalopram/escitalopram

In total, 195 articles on citalopram/escitalopram were included. (Figure 1) As Table 2 shows, 5.1% of the reports (10/195) mentioned the brand name in the title and 65.6% (128/195) specified the treatment indication. In total, 13.8% (27/195) only mentioned benefits, 28.7% (56/195) cited both benefits and harms, and 56.9% (11/195) only mentioned harms. The harm mentioned in the advisories (i.e. cardiac arrhythmia) was described in 9.7% (19/195) of the reports.

The overall emphasis of 69.7% (136/195) media reports was found to be mainly on harms of citalopram, and 20.0% (39/195) on benefits. The emphasis was found to be unclear in 8.2% (16/195) of reports and neutral (presenting both benefits and harms equally) in 2.1% (4/195) of reports.

Reporting benefits and harms

Among media reports mentioning benefits, these most frequently related to improvements in depression (16.4%, 32/195) or anxiety (7.2%, 14/195), or general statements about effectiveness (6.7%, 13/195). In 12.8% (25/195) of the reports the benefits were described through the positive experience of a patient with statements such as *"it was miraculous", "it was brilliant", "after about six weeks I was just back to myself".* Benefits were quantified in 8.2% (16/195) of the reports.

The number of media reports per month before and after the release of the safety advisories are shown in Figures 3 and 4 for citalopram, and citalopram and cardiac arrhythmias respectively. All media reports including information on cardiac arrhythmia (9.7%, 19/195) were published after the first safety advisory and portrayed an increased risk of harm with statements such as:

- *"Health Canada says consumers should avoid taking a daily dose of the antidepressant Celexa in excess of 40 milligrams. The drug's Canadian distributor, Lundbeck Canada, says doses higher than that can cause abnormal heart rhythms." [15]*
- *"In Britain, meanwhile, doctors have been told to lower the maximum dose of the UK's most widely prescribed antidepressant, Cipramil, after a study last month revealed that the drugs increase the risk of heart problems which can cause sudden death".* [16]

There was an increase in citalopram coverage when the first US advisory was published in August 2011. Out of the 21 US media reports on citalopram published that month, six focused on cardiac arrhythmia. The second US advisory in March 2012 received less coverage. The Canadian advisories released in October 2011 and January 2012 were both covered in three media reports, and there was no coverage of the advisory released in May 2012. An additional Canadian media report was published in February 2013, prompted by a new study on cardiac risks of antidepressants. In the UK we identified three media reports on

the cardiac risks of citalopram. They were published several months after the release of the advisories by the Medicines and Healthcare products Regulatory Agency and were prompted by new scientific studies. As Table 3 shows, most of the media outlets mentioning cardiac arrhythmia were press services with national coverage (12/19).

Other safety concerns were described in 77.9% (152/195) media reports.(Table 2) The most frequently reported adverse effects were: suicidal thoughts or behaviours (19.5%, 38/195), homicidal thoughts and violence (17.9%, 35/195, of which 27 were related to homicide trials), withdrawal symptoms (10.8%, 21/195), lack of effectiveness in treating depression (9.2%, 18/195) and sexual side effects (8.7%, 17/195).

The top three types of people cited in the media reports were scientists/academics (31.8%, 62/197) followed by patient/consumers (29.7%, 58/195) and legal professionals or coroners (24.1%, 47/195).

Reporting funding source and conflicts of interest

Specific studies on citalopram/escitalopram or the SSRI class were cited in 31% (60/195) of media reports and in less than half of these (n=28) sufficient information was included to identify the published study. Some studies were reported in multiple media stories; in total we identified 21 published scientific articles that were mentioned 36 times in the 28 media reports. As Table 4 shows, while information on funding source and investigators' conflicts of interest was readily available in the scientific articles, there was little reporting of this information in media reports.

Denosumab

In total, 239 reports on denosumab were included.(Figure 2) As Table 5 shows, 41.8% of the reports (100/239) mentioned the brand name in the title and 96.2% (230/239) specified the treatment indication. In total, 60.3% (144/239) only mentioned benefits, 34.0% (81/239) stated both benefits and harms, and 5.9% (14/239) only mentioned harms. The harms mentioned in the advisories were rarely reported.

Accordingly, the overall emphasis of 81.6% (195/239) of the media reports was considered to be mainly on benefits of denosumab, 12.6% (30/239) mainly on harms, in 3.3% (8/239) the emphasis was neutral (namely, presenting both benefits and harms equally), and 2.5% (6/239) were unclear.

Reporting benefits and harms

Figure 5 shows the number of media reports on denosumab per month. There was a surge in media coverage in 2011 and 2012, especially in the US where the majority of the reports were related to the publication of results of clinical trials, and to successes or failures in getting regulatory approval for new indications.

Among the media reports mentioning benefits, the most frequent reported effects were prevention or delay of bone metastases (36.8%, 88/239), benefits for osteoporosis (e.g. increase bone mass) (29.3%, 70/239), and a potential new use of denosumab for prevention of breast cancer (9.2, 22/239). Benefits were quantified in 26.4% (63/239) of the reports.

The harms mentioned in the advisories were infrequently reported (Figures 6-10):

- The risk of atypical fracture was mentioned in 4.6% (11/239) of the media reports; nine reports portrayed an increased risk of atypical fractures, and two minimised the risk. Three reports were published in Canada immediately after the first advisory in November 2012. None of the other articles were related in time to the advisories nor did they mention the advisory or drug regulators.
- The risk of hypocalcemia was mentioned in 3.8% (9/239) of the media reports; seven of which stated that there was an increased risk of hypocalcemia, and two minimised the risk. Only two reports were stimulated by the release of a safety advisory in Australia in August 2016. Although safety advisories were also released in Canada, UK and US, there was no coverage of the advisories.
- The risk of osteonecrosis was described in 10.9% (26/239) of the media reports; 23 reports portrayed an increased risk, two minimised the risk and one was unclear. Most reports (n=19) were published before the first safety advisory in US and were related to the publication of preliminary results of clinical trials, and to successes or failures in getting marketing authorisation for new indications. None of the six advisories on osteonecrosis generated an increase in media coverage.
- Only 1.7% (4/239) and 0.8% (2/239) of the media reports covered serious infections and dermatologic reactions, respectively. Based on the timing and content of these reports, none appeared to have been stimulated by the release of three safety advisories in the US.

Most of the articles mentioning the harms described in the advisories were published in media outlets with national coverage.(Table 3) As stated above, while some media reports stated that there was an increased risk of the harms mentioned in the advisories, other minimised the risk. Below we report two illustrative quotes from two articles that increased and minimised the risk of harm, respectively:

- *"...it can occasionally lead to osteonecrosis of the jaw and atypical fractures. And, for people with kidney disease, it can lead to drops in calcium levels that can cause muscle spasms and abnormal heart rhythms. Finally, because Prolia is injected into the skin and may affect immune function, it may slightly increase the risk of skin infections at the site of the injection.[17]*
- *"Rates of adverse events, serious adverse events, and fatal adverse events were similar in the treatment groups, and there were no cases of hypocalcemia, jaw osteonecrosis, complications of fracture healing, or atypical femoral fractures during the study". [18]*

Other safety concerns were described in 31.8% (76/239) media reports. The most frequently reported were: unspecified side effects (13.4%, 32/239) and lack of effect such as failure to meet the study endpoint in a clinical trial (7.1, 17/239).

The top three types of actors cited in the media reports were the drug industry (38.5%, 92/239), followed by scientists/academics (20.9%, 50/239) and drug regulators (11.7%, 28/239).

Reporting funding source and conflicts of interest

In 31 media reports sufficient information was provided to identify the specific published study that was cited. We identified 13 published scientific articles that were mentioned in these 31 reports. As Table 4 shows, while information on funding source and investigators' conflicts of interest were usually readily available in the scientific articles, the reporting of this information in the media was very limited.

Moreover, a higher proportion of research articles cited in media reports for denosumab (75.0%) were funded by industry compared with citalopram (10.5%).

Discussion

In this study, we aimed to characterise media coverage of two medicines that were subject to serious safety concerns. We found limited media coverage of the safety concerns highlighted in advisories released by drug regulators. For citalopram, the risk of cardiac arrhythmia was mentioned only in 10% of the media reports. For denosumab, the risk of osteonecrosis was mentioned in just 11% of media reports, while the other safety concerns mentioned in the advisories were reported in ≤5% of the reports. Despite the limited media coverage in all four countries, in the citalopram case study we observed an interesting pattern in the US and Canada: the coverage of subsequent advisories tended to decline, in comparison with coverage after the initial advisory. 'Media fatigue' could explain this pattern as journalists may not be interested in covering the same issue again.[19] We did not find any association between the amount of media coverage and the type of communication used (e.g. safety alert, DHPC, bulletin article) but our ability to assess any differential effect by communication tool was limited by the small number of media reports per advisory.

We found an asymmetry between citalopram and denosumab in the proportion of media coverage about harm compared to benefit. While most citalopram media coverage mentioned harms (86%), most of the media reports on denosumab cited benefits (94%) and almost two thirds of the stories did not mention a single potential harmful effect. For both medicines, most of the reports lacked quantitative information on benefits and harms that could help the readers to understand the likelihood of these effects. A possible explanation for the difference in media coverage of the two medicines is that antidepressants in general are an established and often controversial topic in the media. Previous analyses of Danish, Dutch and British newspapers have reported negative media coverage on antidepressants.[20, 21] Another possible explanation might be the "drug age". While citalopram is an older and off-patent medicine that has been on the market for longer (e.g. since 1998 in US), denosumab is still on-patent [22] and a relatively recent medicine (e.g. on the market from 2010 in US) and this could have stimulated an overly enthusiastic media coverage. An overall positive bias in the presentation of information on new medicines was found in previous studies in Canada and US.[5, 6] Several hypotheses have been developed to explain this phenomenon such as journalists' reliance on industry-sponsored materials [23] or on press releases about scientific research that have been found to often exaggerate the importance of findings.[24]

We also found that when making reference to scientific studies, only a few media reports mentioned the funding source and whether the study authors had any financial links to pharmaceutical companies, despite this information being readily available in most of the cited scientific articles. Evidence across several fields has shown that industry funding and authors' conflicts of interest related to commercial companies can influence the research process.[25, 26] For example, examinations of pharmaceutical industry-sponsored research show that such funding produces studies with outcomes that are favourable to the sponsor more often compared with non industry-funded studies.[27] Public disclosure of research funding and authors' conflicts of interest is now routinely required by medical journals [28] and we urge journalists to incorporate this information to allow the readers to critically assess the reported research.

Interestingly, in both case studies, we found that scientists and academics were among the most cited actors in the media reports while regulators were less frequently cited or mentioned. This suggests that journalists value academic researchers as an information source and may be interviewing researchers in order to convey the relevant research evidence. We did not measure whether the cited researchers accurately conveyed the research evidence. However, the infrequent quantification of either benefit or harm and the many articles mentioning only benefits or only harms suggests a need for improvement. Contacts between journalists and experts have been described as a *"meeting between two professional cultures"* and calls have been made to improve the communication skills of both sectors in order to improve the quality of the interaction and of the outcome.[29]

Our study has some limitations. First, the patterns seen with these two illustrative cases may not reflect those seen with other medications. Similarly, the trends in the four included countries may differ from those in other countries or other time periods. Second, we excluded press releases because we were interested only in the final media reports that are read by the public. Third, although we excluded media reports that did not have any mention of beneficial or harmful effects of the drugs, we did not control for the overall focus of the reports. For example, in media reports where the health effects of the drug were only mentioned in passing, some information might have been appropriately omitted. Fourth, we did not examine the accuracy of the claims about the included drugs as this was beyond the scope of our study. Finally, the analysis of funding and conflict of interest disclosures was conducted only for the subset of media reports that provided sufficient information to identify

the published scientific study.

This study builds on previous work looking at media and pharmacovigilance. For example, Woloshin et al. analysed the amount and content of media coverage of safety advisories on zolpidem released by the Food and Drug Administration and found high variability, with only some messages broadly reported.[19] The media play an important role in communicating about medicine safety issues and their role in extending the reach of drug regulators' messaging could be improved. Unfortunately our data does not allow us to explain why these important messages were not broadly picked up by the media and we do not know to what extent regulators deliberately target media channels to help communicate safety messages. Careful consideration needs to be given to the duration and amount of media coverage that may be of most benefit to the public. Whilst media coverage tends to be short-lived, information on medicine safety needs to be consistently available to the public.[30] Medicine regulators may therefore need to consider a multi-faceted strategy to disseminate pharmacovigilance messages to the public, taking advantage also of the increasing use of social media.

Journalists clearly face challenges in producing good quality media reports due to lack of time, and pressure to write stories that are concise as well as interesting.[29] Although it would be impractical for journalists to cover every potential beneficial and harmful effect, media reports should allow readers to develop a balanced assessment of medicines and health interventions. In this regard, there have been several calls and attempts to improve the quality of media reports on health and medicine through the development of principles of good media coverage.[31]

Conclusion

We found limited media coverage of the safety concerns highlighted in advisories released by drug regulators. Almost two-thirds of the media stories on denosumab did not include any information about harms, despite the many advisories relating to five different safety concerns during this time frame. Citalopram coverage covered harm more often, but rarely mentioned cardiac arrhythmias, the subject of the safety advisories. These findings raise

questions about how to better ensure that regulatory risk communications reach the general public, including users of the medicine in question, so that they are able to make informed decisions. Outcomes from these case studies should be compared with media uptake of other regulators' messages to help regulators expand dissemination of these important messages to the public and ensure the greatest public health impact.

Our findings also raise concerns about the quality and completeness of media coverage of medicines. Many media reports included an unbalanced reporting of expected benefits and potential harms of drug use; drug effects were also rarely quantified. Given their potential to affect clinical practice and health care utilisation, media should allow readers to develop a balanced assessment of medicines and health interventions so that they can make informed decisions.[5] Finally when media reports referred to specific scientific studies, reporting of funding source and conflicts of interest was limited. We urge journalists to more regularly report this information in order to allow the readers to critically assess the reported research.[7]

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Authors contribution: All the authors contributed to the design of the study. AF, MOK and RM screened the retrieved media reports. AF, MOK, AM, and BM coded the media reports. AF and AM analysed the data. AF drafted the manuscript. All the authors interpreted the data and contributed to the writing of the manuscript.

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Table 1. Safety advisories released on citalopram and denosumab within the study period

Safety concerns	Safety advisories (country, month/year, and category of safety advisories)[a]							
	Australia		**Canada**		**UK**		**US**	
Citalopram/ Escitalopram								
QT prolongation/ Cardiac arrhythmias	02/12	Bulletin	10/11	Investig.	10/11	DHPC	08/11	Alert
			01/12	DHPC	12/11	DHPC	03/12	Alert
			05/12	Alert				
Denosumab[b]								
Atypical fracture	c		11/12	DHPC, Public Comm.	02/13	DHPC, Alert	06/14	REMS
							02/15	REMS
							05/15	REMS
Hypocalcemia	04/13	Bulletin	05/12	DHPC	09/12	DHPC	06/14	REMS
	08/16	Bulletin			10/12	Alert	02/15	REMS
					08/14	DHPC	05/15	REMS
Osteonecrosis	04/16	Bulletin			08/14	DHPC	06/14	REMS
					06/15	DHPC	02/15	REMS
							05/15	REMS
Serious infections							06/14	REMS
							02/15	REMS
							05/15	REMS
Dermatologic reactions							06/14	REMS
							02/15	REMS
							05/15	REMS

a) Categories of safety advisories: Direct Healthcare Professional Communication (DHPC), Alert, Investigation, Bulletin Article, Public Communication, Risk Evaluation and Mitigation Strategy (REMS).

b) Also neoplasm, hearing loss, cardiovascular disorders – Canadian Summary Safety reviews with no findings of risk/not enough evidence to suggest an association.

c) In April 2013 the Therapeutic Goods Administration (TGA) published an article on "Denosumab and severe hypocalcemia" in the Medicines Safety Update, the medicines safety bulletin of the TGA. The article briefly mentioned that the Product information *"was also updated to specify that atypical femoral fractures have been reported in patients being treated with Prolia".*

Table 2. Characteristics of the media reports on citalopram

	n (%)
Media reports	195 (100)
Brand name in the headline	10 (5.1)
Treatment indication specified	128 (65.6)
Any benefit mentioned	84 (43.1)
Type of benefit[a]	
• Improve depression	32 (16.4)
• Improve anxiety	14 (7.2)
• Effective	13 (6.7)
• Reduce hot flashes	11 (5.6)
• Safe/well tolerated	11 (5.6)
• Life-saving drug	5 (2.6)
• Reduce suicides	2 (1.0)
Any harm mentioned	167 (85.6)
Harm listed in safety advisory:	19 (9.7)
• QT prolongation/Cardiac Arrhythmia	
Other harms[a]	152 (77.9)
• Suicidal thoughts	38 (19.5)
• Homicidal thoughts	35 (17.9)
• Withdrawal symptoms	21 (10.8)
• Lack effect in depression	18 (9.2)
• Sexual side effects	17 (8.7)
• Side effects (not specified)	9 (4.6)
• Stroke/Heart attack	8 (4.1)
• Birth defect	7 (3.6)
• Seizure	6 (3.1)
Benefit quantified	16 (8.2)
Harms quantified	20 (10.3)
Contraindication	40(20.5)
Actors represented[a]	
• Scientists/academics	62 (31.8)
• Patient/consumers	58 (29.7)
• Legal professionals	47 (24.1)
• Health professionals	43 (22.1)
• Drug regulator	24 (12.3)
• Drug industry	15 (7.7)
• Medical societies	2 (1.0)
• Patient groups	1 (0.5)
Coders' assessment of overall emphasis of the media reports	
• Harms	136 (69.7)
• Benefits	39 (20.0)
• Unclear	16 (8.2)
• Neutral	4 (2.1)

a) We report only the most frequently mentioned ones.

Table 3. Types of media mentioning the safety concerns described in the advisories

	Total	Coverage	Type of news sources*
Citalopram	**19**		
Australia	0	-	-
Canada	8	National (n=5)	Press service
		Local Urban (n=1)	Newspaper
		Local Rural (n=2)	Newspaper
United Kingdom	3	National (n=3)	Newspaper
United States	8	National (n=7)	Press service
		Local Urban (n=1)	Newspaper
Denosumab	**36**		
Australia	4	National (n=4)	Blog/websites (n=2) Press service (n=1) Newspaper (n=1)
Canada	5	National (n=2)	Press service
		Local Urban (n=3)	Newspaper
United Kingdom	1	National (n=1)	Newspaper
United States	26	National (n=24)	Press service (n=11) Blogs/websites (n=10) Magazine (n=2) Unclear (n=1)
		Local Urban (n=2)	Newspaper

*Newspapers included both online and print versions. Some press services have a coverage that is broader than national but we followed how the databases indexed the geographical provenance of the media outlets.

Table 4. Disclosure of funding source and investigators' conflicts of interest in the media reports and in the cited scientific articles.

	Media reports	**Scientific articles**
Citalopram	(n of mentions=36)	(n=21)
Disclosure of the funding source • Pharmaceutical industry funding • Public or non-profit funding • States that no specific funding was received for the study	8/36 (22.2) 0/8 (0) 8/8 (100) 0/8 (0)	19/21 (90.5) 2/19 (10.5) 14/19 (73.7) 3/19 (15.8)
Disclosure of conflict of interests • researchers with ties with pharmaceutical industry • researchers with no ties with pharmaceutical industry	2/36 (5.5) 2/2 (100) 0/2 (0)	21/21 (100) 11/21 (52.4) 10/21 (47.6)
Denosumab	(n of mentions=31)	(n=13)
Disclosure of the funding source • Pharmaceutical industry funding • Public or non-profit funding	7/31 (22.6) 6/7 (85.7) 1/7 (14.3)	12/13 (92.3) 9/12 (75.0) 3/12 (25.0)
Disclosure of conflict of interests • researchers with ties with pharmaceutical industry • researchers with no ties with pharmaceutical industry	3/31 (9.7) 3/3 (100) 0/3 (0)	13/13 (100) 10/13 (76.9) 3/13 (23.1)

Table 5. Characteristics of the media reports on denosumab

	n (%)
Media reports	239 (100)
Brand name in the headline	100 (41.8)
Treatment indication specified	230 (96.2)
Any benefit mentioned	225(94.1)
Type of benefits[a]	
- Bone metastases	88(36.8)
- Osteoporosis	70 (29.3)
- Prevention of breast cancer	22 (9.2)
- Medication-induced osteoporosis	15 (6.3)
- Giant-cell tumor of the bone	10 (4.2)
- Survival rates	9 (3.8)
- Tolerability	5 (2.1)
-Cost-effectiveness	4 (1.7)
-Convenience of administration	4 (1.7)
Any harm mentioned	95 (39.7)
Harms listed in the safety advisories:	
-Osteonecrosis	26 (10.9)
-Atypical fractures	11 (4.6)
-Hypocalcemia	9 (3.8)
-Serious infections	4 (1.7)
-Dermatologic reactions	2 (0.8)
Other harms[a]	76 (31.8)
-Side effects (not specified)	32(13.4)
-Lack of effect	17 (7.1)
-Diarrhea and/or nausea	12 (5.0)
-Renal side effects	4 (1.7)
-Not cost-effective	4 (1.7)
Contraindication	14 (5.9)
Benefit quantified	63 (26.4)
Harms quantified	24 (10.0)
Actors represented[a]	
- Drug industry	92 (38.5)
- Scientists/academics	50 (20.9)
- Drug regulator	28 (11.7)
-Patient/consumers	21 (8.8)
-Health Professionals	21 (8.8)
-Market analysts	11 (4.6)
- Patient groups	9 (3.8)
-Medical societies	1 (0.4)
Coders' assessment of overall emphasis of the media reports	
-Benefits	195 (81.6)
-Harms	30 (12.6)
-Neutral	8 (3.3)
-Unclear	6 (2.5)

a) We report only the most frequently mentioned ones.

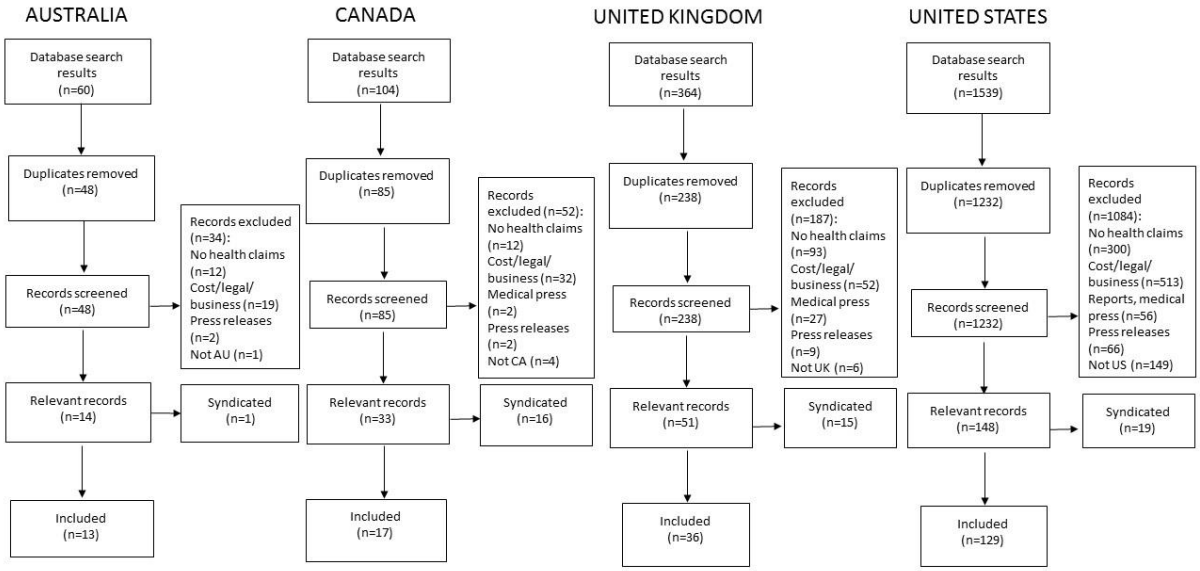

Figure 1. Study flow diagram - Citalopram

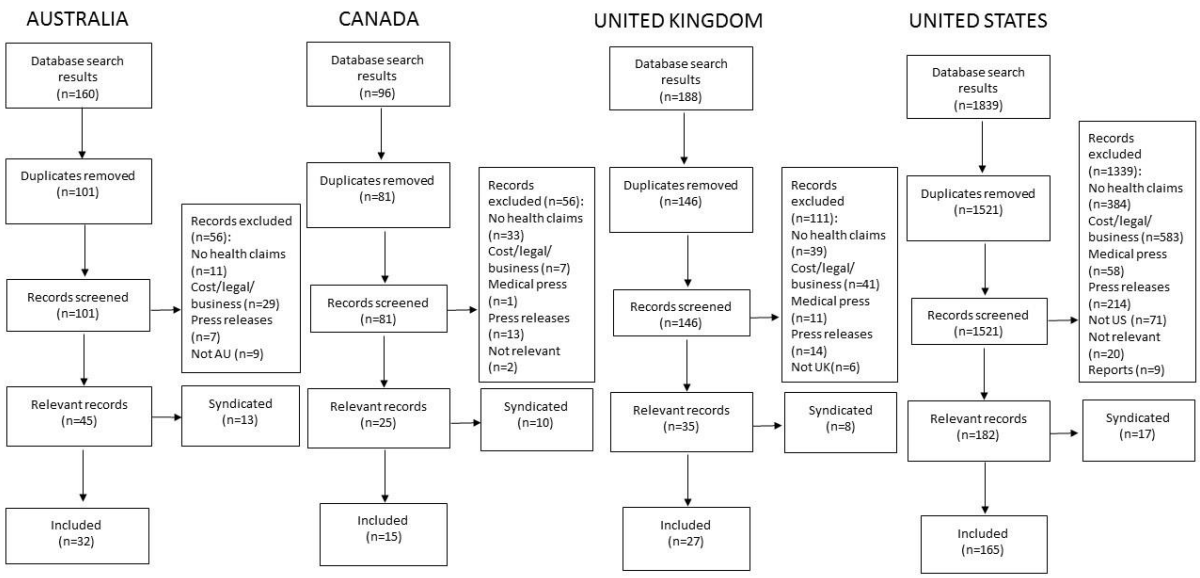

Figure 2. Study flow diagram - Denosumab

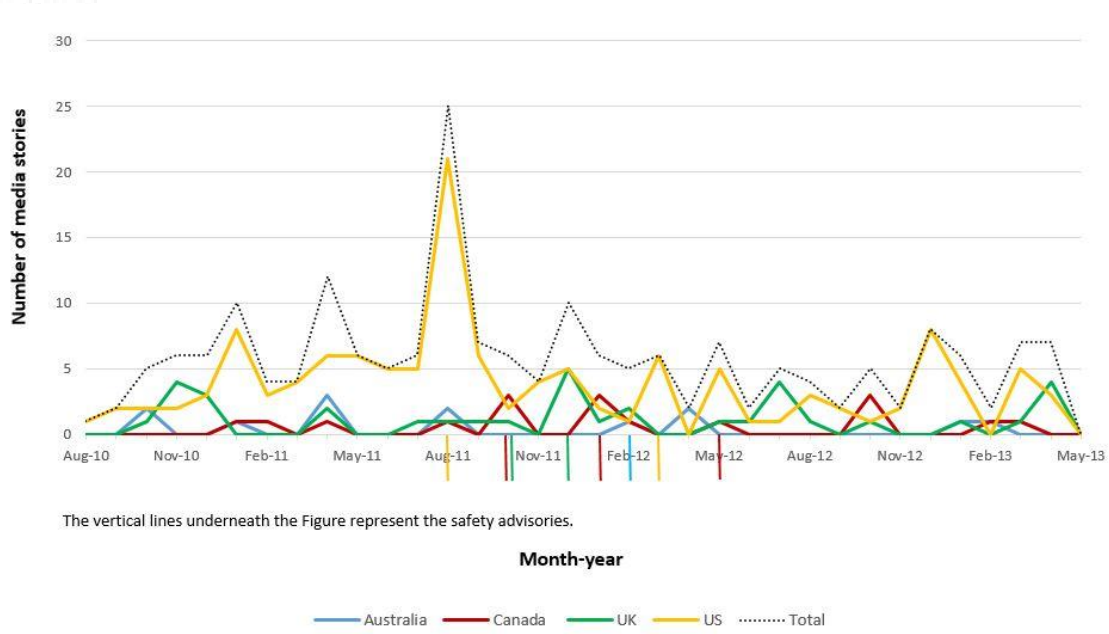

Figure 3. Number of media reports on Citalopram per month

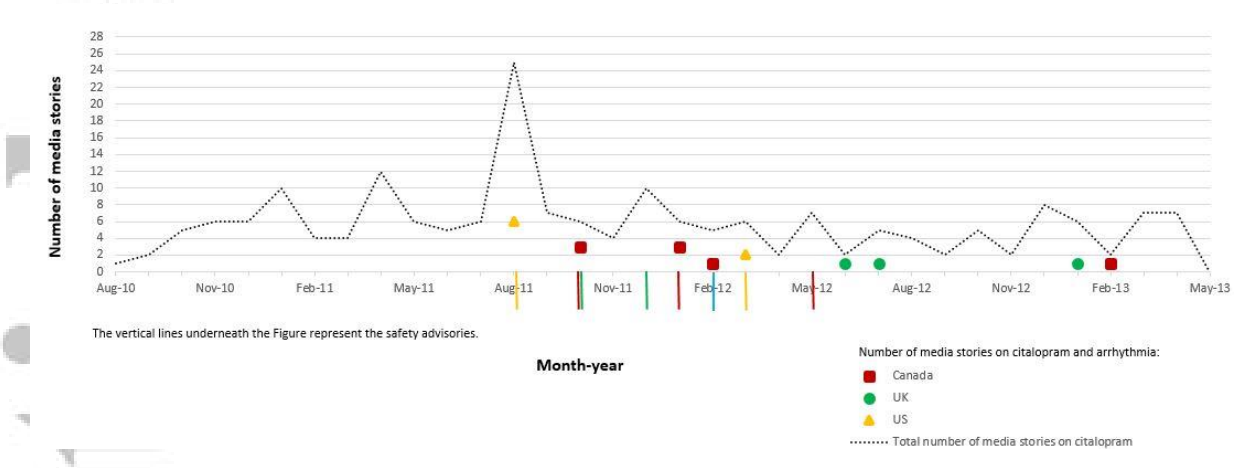

Figure 4. Number of media reports on citalopram and QT prolongation/cardiac arrhythmia per month

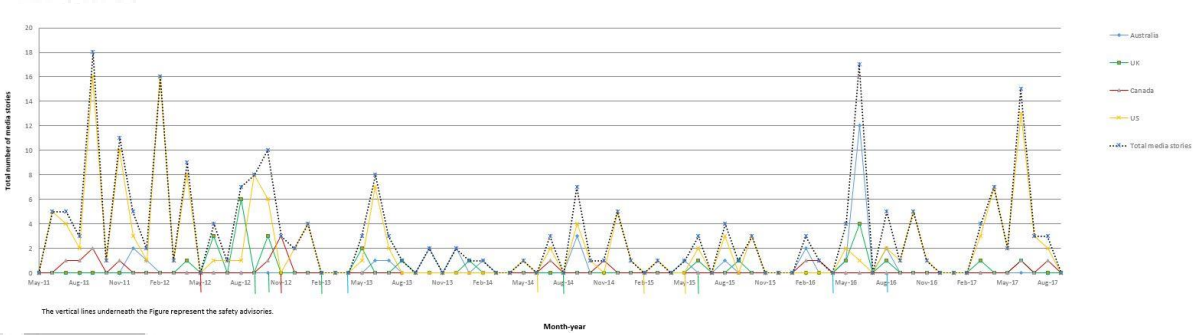

Figure 5. Number of media reports on Denosumab per month

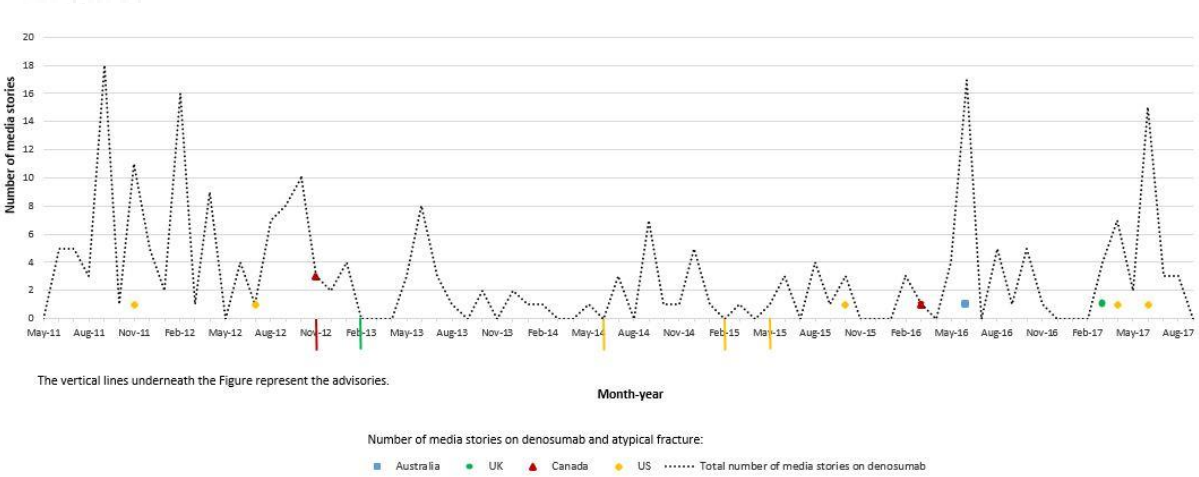

Figure 6. Number of media reports on denosumab and atypical fractures per month

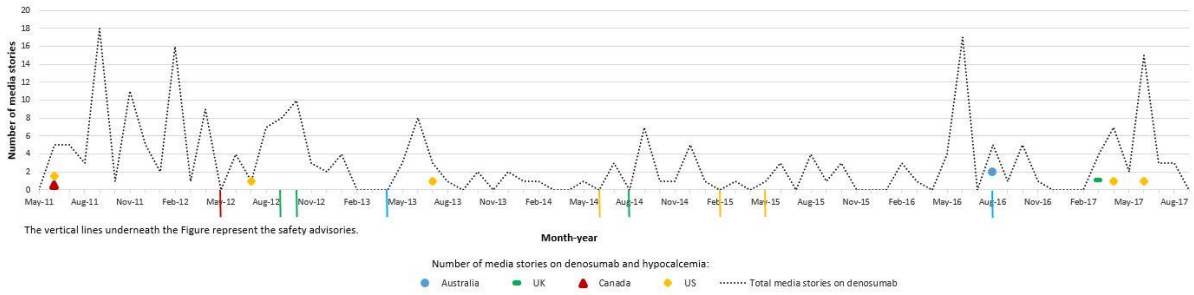

Figure 7. Number of media reports on denosumab and hypocalcemia per month

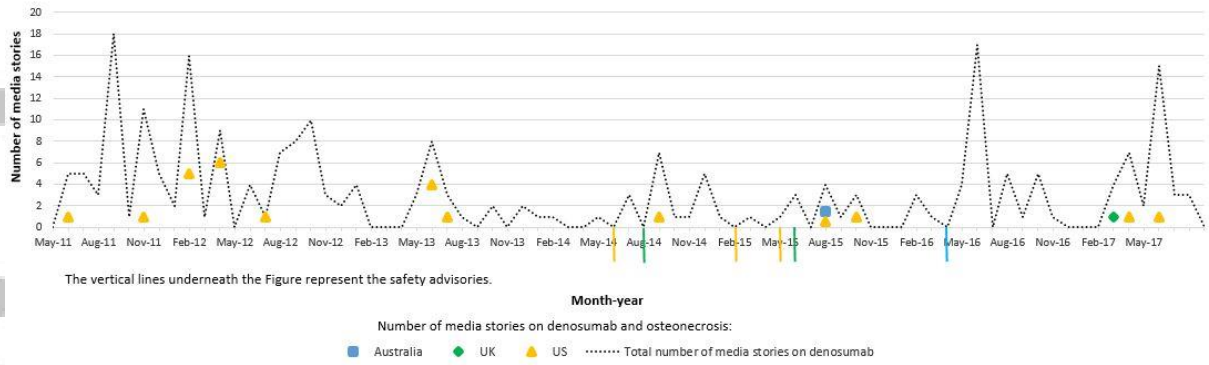

Figure 8. Number of media reports on denosumab and osteonecrosis per month

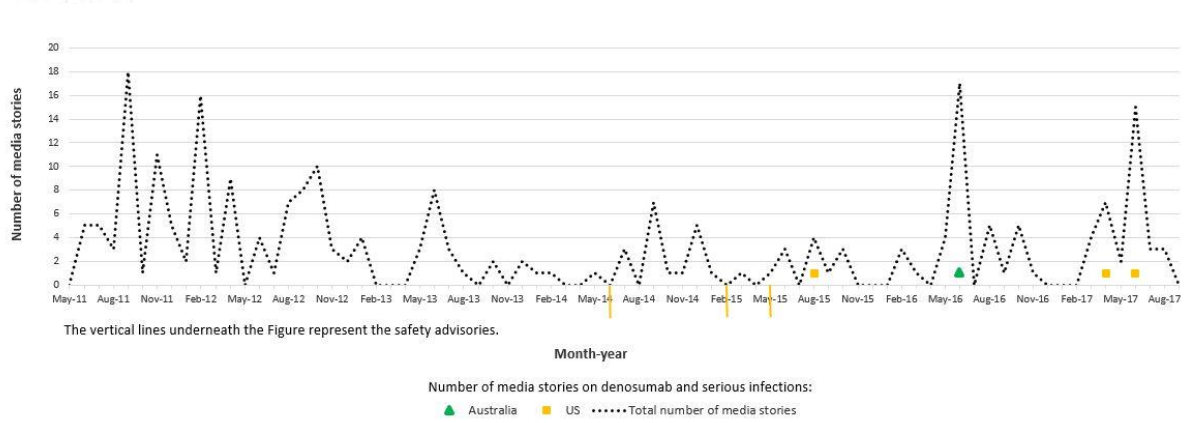

Figure 9. Number of media reports on denosumab and serious infections per month

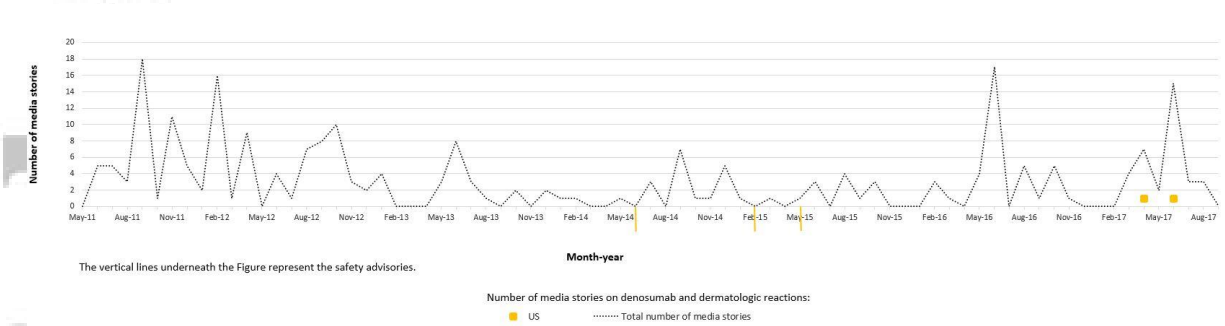

Figure 10. Number of media reports on denosumab and dermatologic reactions per month