02-Aug-2019

Dear Dr. Frouard

Manuscript ID BMJ-2019-050887 entitled "Association between benefits paid by pharmaceutical companies to French general practitioners and their drug prescriptions in 2016: a retrospective study using the French Transparency in Healthcare and National Health Data System databases"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Jose Merino
Dr Jose Merino
US Research Editor
jmerino@bmj.com
 Dear Jose Merino,
Thank you for your interest in our paper.

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (chair), Rafael Perera (chair), Elizabeth Loder, Tiago Villanueva, Timothy Feeney, José Merino

- We liked the research question.
Thank you very much for your interest in our research question. We hope that our answers to the reviewers' and the BMJ committee's comments below will improve our manuscript.

- Several editors commented that the choice of words for "benefits" and "acts" may not be ideal. By "benefits", you mean payments of gifts. Why not use those words?

1-Thank you for your suggestion. We agree that these words are not clear enough. Under the French 2011 legislation, the word "benefits" ("avantages" in French) describes what is allocated or paid by pharmaceutical companies without any counterpart. We agree that the word "gift" is an equivalent easier to understand, so used this word in the whole manuscript. We also changed the word "acts" to "visits", which is more accurate.

- Several editors also thought that the paper was hard to follow. Could you provide tables and boxes with some of the most relevant information, including the efficiency indicators?

2-Thank you for pointing out this difficulty. To improve the reading of the paper we added:
-in Box 1, details on the databases used and some important definitions;
-in Table 1 and Appendix 1, details on the indicators used.

- For proper assessment of the association that 'benefits' have biased behavior, we need a technical note (possibly as supplementary material) providing information on how the indicators used were created. In particular, we need to know:

a) What information was used in the creation of these indicators? Which methods were used (e.g. simple aggregation or based on some standardisation)?

3-We apologize to have been unclear on this point and we will try to specify this in the revised manuscript. Thank you for suggesting supplementary material. We added details on the construction of the 12 outcomes in Table 1 and Appendix 1.
Information used for the creation of the 12 outcomes came from: number of patients registered with each GP, number of items of each drug prescribed, dispensed and reimbursed by the National Health Insurance for each GP, or global amount of drug prescription reported to the number of visits for each GP.
In details:
-Data on each drug prescribed, dispensed and reimbursed (drug name, dispensation date and number of units) are automatically and systematically collected in the National Health Data System. Such data are automatically linked to the specific GP and the patient, using their professional identification numbers;[1]
-A national health insurance (NHI) data officer extracted these data from the NHI Data System;

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[1] Bezin J, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954–62

-A NHI data officer aggregated these data for each GP to calculate the indicator values. For this calculation no standardization method is used.[2]

In particular, we need reassurance that these indicators are not just a reflection of workload by the GP which could then act as a critical confounder in the association.

4-To address this question, GP's workload was defined as a confounder in our protocol through two pre-specified covariates: number of visits to the GP, and number of patients seen in 2016. GPs' workload was not used for calculating the indicators (see our response 3).

       In the first step analysis, we found differences between groups according to the GP's workload (see Appendix 3). Then, we included workload (number of visits and number of patients in 2016) with the other covariates in all multivariate analyses. We clarified this point in the revised manuscript by adding the following phrase in the chapter "Results", paragraph "Description of the study population":

"Multivariate analyses were adjusted for GPs' workload (i.e., number of visits and number of patients in 2016), as well as for all covariates."

b) if these indicators are indeed reflecting 'adequate' vs. 'inadequate' behavior as well as having a clear specification as the directionality of these indicators (e.g. higher levels = 'inadequate behavior' or the other way around).

4- Thank you for this comment. The NHI site describes the directionality of the indicators used[3]. Some of the indicators are the same as the World Health Organisation recommendations (i.e., percentage of drugs prescribed using the generic name, percentage of visits with antibiotic prescription)[4] and the Openprescribing initiative in the UK (i.e., volume of antibiotic prescription, average number of hypnotics or anxiolytics prescribed per 1 000 patients, prescription of high cost PPIs, prescription of high cost ACE inhibitors)[5].
To support our choices and interpretations, we added references for each indicator in Appendix 1. Considering the large audience of BMJ readers, for more clarity, we added in Table 1 an interpretation column ("High value indicates…") with the indicator directionality.

There are also some statistical issues that require addressing such as the use of a 0.001 as threshold. If there are a total of 12 X 5 comparisons made (indicators x groups compared) then a conservative p-value would be more like 0.0005. More information regarding stats methods used is also necessary.

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[2]See chapter 8, page 144 http://www.euro.who.int/__data/assets/pdf_file/0020/271073/Paying-for-Performance-in-Health-Care.pdf
[3]See page 21
https://www.ameli.fr/fileadmin/user_upload/documents/ROSP_2015_MT_NOTE_METHODO_PRATIQUE_CLINIQUE.pdf
[4] see http://apps.who.int/medicinedocs/en/d/Jh3011e/3.html
[5] see https://openprescribing.net/measure/; https://openprescribing.net/measure/ktt9_antibiotics/; https://openprescribing.net/measure/bdzper1000/; https://openprescribing.net/measure/ppi/ ; https://openprescribing.net/measure/ace/; https://openprescribing.net/measure/arb/

5-Thank you for highlighting this point. We respectfully disagree with this comment, but are open to change our analyses in case of disagreement.

We carried out the analyses in two steps. First, we used the omnibus test for each of the 12 indicators with a risk alpha=0.05. The Bonferroni correction was 0.05/12= 0.00416. Therefore, we chose *a priori* (see our pre-registered protocol) a 0.001 p-value that is even more conservative. For the second step, we compared to the group "none" only the indicators that were significant in the first step (this was pre-specified in our pre-registered protocol). This concerned 9 indicators as detailed in the manuscript and shown in Appendix 4. Therefore, for a total of 9X5 comparisons made, the p-value (0.05/45=0.00111) was still valid for this secondary analysis.

We have edited the text accordingly in the chapter "Methods":

"Primary analysis

We did the primary analyses using a linear regression model. Specifically, after univariate analysis, we performed a multivariate analysis with the different Transparency in Healthcare GP groups and the potential confounding factors (i.e., covariates: GPs and patients' characteristics) identified as associated with the outcome (threshold: $p=0.25$). We used a step-by-step strategy to retain the most parsimonious model and verified the application conditions of the final model. We chose a significance threshold of 0.001 for all statistical analyses with an omnibus test from the linear model. This is slightly more conservative that the Bonferroni's correction with a threshold of 0.05 that takes into account the 12 different outcomes analysed (0.05/12=0.00416).

Secondary analyses

On the basis of literature data, we hypothesized that the group "None" should display the most efficient prescribing patterns, and used this group as reference group to explore the differences detected with the omnibus test in the primary analyses (significance threshold of 0.001)."

In addition, we added a specific explanation on this point in the legends to Figure 2, Table 2, and Appendix 4.

- It is unclear if at least some of the observed associations are directly linked to volume (doctors' workload) and therefore this association could mainly be explained due to confounding. 'The GPs performed 5 359 ± 2 510 acts for 1 681 ± 774 patients', seems a very low number.

6- In response to your questions:

- Workload (number of visits and number of patients seen in 2016) was used as an adjustment variable for the analyses (see response #4)
- The number of visits to the GP and the number of patients registered with each GP correspond to the standard level of workload for French GPs (around 5 000 visits per GP per year).[6]

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[6] see https://www.legeneraliste.fr/actualites/article/2019/03/15/les-generalistes-realisent-en-moyenne-22-consultations-par-jour_317903

- One editor wondered "if use of these "prescription efficiency indicators" really is the best way to study this matter." Can you please justify your choice of outcome?

7-We agree that is a key point in our study. A prescribing quality indicator is a "*measurable element of prescribing performance for which there is evidence or consensus that it can be used to assess quality*".[7] We agree that there is no "gold standard" measure to assess the quality and the efficiency of prescription. Hundreds of drug prescription indicators can be found.[8] In our study, we chose to focus on some indicators that are highly relevant for the French context and have been validated in the literature.

- Regarding the 11 indicators used for performance-related financial incentives in our study: After a trial of a Pay-for-performance programme (named "Contrat d'Amélioration des Pratiques Individuelles") in 2009, in 2011 the NHI generalized the performance-related financial incentive programme to all French GPs (renamed "Rémunération sur Objectifs de Santé Publique", **ROSP**). In 2011, the choice of indicators was discussed by the NHI, the French GP colleges, and GP unions. The indicators were validated by the French National Authority for Health. The European Observatory on Health Systems and Policies Series described the choice of these indicators in France: "*Most of the performance measures had been selected based on objectives and criteria defined by the 2004 Public Health Law as well as different HAS* [French National Authority for Health] *guidelines. Not surprisingly, these indicators are consistent with those already validated and in use internationally in programmes such as the UK Quality and Outcomes Framework (QOF) and the US National Quality Forum.*"[9]
In the NHI own words, the ROSP goals should encourage "*more relevant and efficient prescriptions and help to control health expenditure*". Some of indicators used by the NHI were also used for the same purpose by other organizations (WHO, Openprescribing, see response #4).

- Regarding the 12th indicator (Amount of drug prescriptions reimbursed per visit):
In their report, the NHI highlighted an important heterogeneity on the amount of drugs prescribed per visit among GPs[10]. This drug cost indicator was also used in a recent study in the United States to address the link with payments from industry.[11] We think that this indicator has very high face validity.

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[7] Hoven JL and al., DURQUIM Scientific Committee. Indicators of prescribing quality in drug utilisation research: report of a European meeting Eur J Clin Pharmacol. 2005 Jan;60(11):831–4

[8] Denig P and al. Assessment of quality of prescribing using quality indicators. In: Drug Utilization Research. John Wiley & Sons, Ltd; 2016. p. 433–42. see http://onlinelibrary.wiley.com/doi/abs/10.1002/9781118949740.ch43

[9] See chapter 8, page143 http://www.euro.who.int/__data/assets/pdf_file/0020/271073/Paying-for-Performance-in-Health-Care.pdf

[10] CNAM, Les prescriptions de médicaments des médecins généralistes : un approfondissement de l'analyse des dispersions géographiques. 2004 Jul p. 61. (Point de conjoncture). Report No.: 25–27, see https://bdsp-ehesp.inist.fr/vibad/controllers/getNoticePDF.php?path=/Cnamts/PointDeConjoncture/26-27/1.pdf

[11] Perlis RH, Perlis CS. Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs. PLoS ONE. 2016 May 16;11(5):1.

Therefore, without being comprehensive, we retained these 12 indicators because they seemed to assess an important part of the quality, efficiency and health expenditure of drug prescription. We added in Table 1 and Appendix 1 the calculation and references for each indicator.

We added the European Observatory on Health Systems and Policies Series reference (ref. 8) in the relevant part of the Discussion.

"Our literature search did not find a unique and/or validated indicator to evaluate in a general way the GPs' drug prescription quality.[16] Therefore, we used multiple indicators validated by the French National Health Insurance to assess prescribing patterns.[8] Some of them are also used in drug utilization studies.[17] However, their validity is somehow questionable.[18]"

The outcomes are the 11 variables for financial incentives. They should tell us what the financial benefits exactly are, so we can interpret these accordingly. They speak of reimbursements, but how does that work?

8- Among the 12 indicators we used, 11 are drug indicators used for the performance-related financial incentive programme. For each of them, NHI sets two targets: an intermediate target defined as the value of the indicator obtained by the 30th percentile of GPs, and a target defined as the value obtained by the 80th percentile of GPs. This encourages theoretically the 30% "worst" GPs to reach the 70% "best" GPs (intermediate target), and all GPs to reach the 20% "best" GPs (target). For example, for the proportion of >65-year-old patients treated with long-life benzodiazepines, the intermediate target is ≤11% and the target is ≤5%.

Every year, GPs earn points for each indicator according to their achievement of the target: maximum points if the target is achieved, fewer points if only the intermediate target is achieved. For example, 35 points are allocated for the long-life benzodiazepine indicator if the target is reached.

At the end of the year, the NIH calculates the total of points obtained for all the indicators by each GP. This total is then weighted with the number of patients of that GP (with a reference number of 800 patients to obtain the full score). Then, the total score is converted into money by the NHI at the rate of 1 point= €7.[12].

In total, each GP earn a mean of €7 000 per year with this system[13]. In comparison, payment for each procedure/visit remains the main source of remuneration for French GP (every visit is paid €25). The mean remuneration of a GP in France is around €78 700 per year[14].

We added in Box 1 information on the French performance-related financial incentive system, but we did not add such details because we only used raw data in our study. Therefore, we were not

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[12]See chapter eight page 144, http://www.euro.who.int/__data/assets/pdf_file/0020/271073/Paying-for-Performance-in-Health-Care.pdf
[13] See https://www.ameli.fr/medecin/actualites/rosp-2016-7-000-euros-en-moyenne-pour-les-medecins-generalistes
[14]See page 63 https://www.epsilon.insee.fr/jspui/bitstream/1/62022/1/panoramasante_prof_2016.pdf

concerned by the weighting in function of the patient number for each GP or by the calculation of the final score. However, we may add more information if you think that is necessary.

This suggests that GPs can benefit from industry or the government, and they possible calculate the trade-offs.

9-Thank you for spotting this key omission. We did not include the amount of the performance-related financial incentive in the confounding factors because we did not have this information. Nevertheless, GPs do not need to calculate the trade-offs. This is an important comment that we added in the Discussion section:

" French GPs may benefit from industry (gifs, etc.) and from the NHI through the performance-related financial incentive programme. Gifts from industry and performance-related financial incentives programme cannot be directly linked to each other because no indicator assessed GPs' financial links with industry. Actually, a GP may receive the maximum remuneration from the performance-related financial incentive programme and concomitantly many gifts from the industry. Nevertheless, if we assume that the desire of profit is a confounder, our results are not suggesting optimization trade-offs by GPs. Indeed, in our study GPs with the best drug prescription indicator results and the highest NHI financial incentive seemed to receive fewer gifts from the industry."

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1
We thank Reviewer 1 for the interest in our study.

Summary:
This study evaluated the association between payments from pharmaceutical companies to general practitioner physicians in France and their prescribing practices by linking two French prescription databases. There was significant association between higher payments by pharmaceutical companies and lower quality prescribing practices by General Practitioners (GPs).
Broad Comments:
The study's novelty lies in the first time evaluation of this association in France. The authors have interpreted the results appropriately and the conclusions are supported by the results. The authors have specified their underlying assumptions and have done a good job in listing the major limitations of the study.

R1#1-Thank you for your comment, we appreciate that you underlie the originality of our work.

The primary outcomes studied were prescription efficiency indicators as continuous variables and authors employed ANOVA, Chi-square and multivariate linear regression (my interpretation – can authors please confirm this?) for studying the associations between independent and dependent

variables.

R1#2-Yes, we employed a linear model (e.g. ANOVA, ANCOVA) for quantitative variables. In Table 1 we also provided results of the Chi-square tests for the two qualitative variables (GP sex and size of the city where the GP works).

The primary independent variable evaluated is the amount of payment made by the pharmaceutical companies to the GPs. The authors categorized these for meaningful interpretations. The methods for study design and analysis are scientifically sound and are described in sufficient detail except specifically mentioning the statistical analyses employed (e.g., Authors do not specify if linear regression was used).

R1#3-In response to your question, we did use a linear model for the primary and secondary analyses. We made this clear in the revised text.

Overall, publishing this work will add to the literature on potential health and economic impacts of pharmaceutical promotions.

R1#4-Thank you very much for your comment. Actually, a complementary research on economic impacts would probably be of great interest.

One major comment I have is how are the prescription efficiency indicators evaluated to be better or worse?
Is there a reference that specifies this comparison?

R1#5-Thank you, this is a key point of our study. We tried to answer this point to the editors (see response #7). To clarify the expected variation of each indicator, we created Table 1 and added references for each indicator in Appendix 1.

Specific comments:
1.   Page 7, line 43: "Drug prescriptions per act": What does this mean? Does it mean prescriptions prescribed on a single patient visit?

R1#6-We agree with you and the editors' comment that the word "act" was unclear and changed that to "visit" throughout the manuscript.

2.   Page 8, line 49-50: "on Internet since 2013": the use of term 'on Internet' is not clear. Can authors clarify what this statement means?

R1#7-We agree that this term is not clear. We added in Box 1 definition to clarify this point:

"Data are searchable through a French government public website (transparence.sante.gouv.fr) and can be downloaded (data.gouv.fr)"

3.   Page 10, line 23: "We recruited GPs…." seems incorrect terminology, since it's a retrospective study, authors can say, "We included GPs…"

R1#8- We modified the paper accordingly with the correct terminology.

4.   Page 10, line 32-33: Its unclear why second matching could not be performed for 6.2% of all listed GPs?

R1#9- This matching was not made by us but by the NHI data officer. When he matched our list of GPs with the National Health Data System, the match failed for 6.2% of GPs. For confidential reason, we were not allowed to have the NHI information in clear (without anonymization), therefore we unfortunately could not assess directly the reasons for this failure. We can only suppose that there were failures in the information of one or both databases concerning the family names, first names, and/or the postal code of the area where the GP practice is located used for the matching.
For more clarity we added a specific comment to explain this issue in the Discussion section of the manuscript:

" The 6.2% of failed matches for GPs might have introduced some bias, especially because the matching failure rate was different among GP groups. As we had no access to the GPs' identification information for confidential reasons, we could not compare lists and could not identify the specific reasons of this failure. We could hypothesize gaps in one or both databases concerning the data used for the matching (e.g., GP family name, first name, and/or the postal code of the area where the GP practice is located)."

5.   Page 10, line 42-54: The reference for the 11 indicators is missing here.

R1#10- We added a reference for the 11 indicators and for this paragraph we added Table 1 and Appendix 1 with supplementary references (See response #7 to editors).

6.   Page 11, line 8-9: "number of acts performed per year": its not clear what this means? (Similar to comment#1)

R1#11-We have changed the word into "visit". See response R1#6.

7.   Page 12, line 50-51: "they performed 5359…" Is it an average (mean and SD) reported? Please specify.

R1#12- We reported the mean with standard deviation. We clarified this point in the revised paper, in the "Description of the Study population" paragraph:

''They performed 5 359 ± 2 510 visits (mean ± standard deviation) for 1 681 ± 774 patients"

8.   Figure 2: It's not clear what is being reported in the figure 2? Is the legend missing for the figure?

R1#-13 Figure 2 presents the results of the secondary analyses. We added the missing legend:

"Figure 2. Comparison of explanatory variables with the group "None" in multivariate analysis
Values are the adjusted mean differences and their corresponding 99.9% confidence interval
Threshold p=0.001 (Bonferroni correction for p-value: 0.05/(9X5)=0.0011)"

9.   In limitations, are any of the drugs evaluated available as over-the-counter (OTC) ie without prescription in France? Eg Aspirin and PPIs are available without prescription in US and many other countries. If these are available as OTC, how does this limit the interpretations for the prescription efficiency indicators using these two drug classes?

R1#14--Thank you for highlighting this element. The drug prescription efficiency indicators are calculated with data for the drugs prescribed, dispensed and reimbursed by the NHI and are not concerned by OTC medications. Actually, aspirin and PPIs are also available as OTC drugs in France. In France, OTC medication is marginal. In 2015, about 97% of PPI dispensed were prescribed.[15] In 2017, drugs used for blood circulation (including aspirin) represented 5% of all OTC medications, which is particularly low in France relative to other European countries.[16] We have added details in Box 1 to specify this point:

"Over-the-counter medications are not used in drug prescription indicators"

10.   Page 16, line 55-56: "…suggest a possible gradual association..." what does gradual mean here?

R1#15- By 'gradual' we meant a "dose-effect" association. Prescriptions seemed to become more expensive and less efficient in function of the number of gifts received by the GPs.
We rephrased this to be clearer:

"Our post-hoc analyses suggest a possible "dose-effect" association between gifts paid by pharmaceutical companies and the cost of drug prescriptions per visit and drug prescription efficiency indicators."

Reviewer: 2

Thank you for your interest in our study.

"Association between benefits paid by pharmaceutical companies to French general practitioners and their drug prescriptions in 2016: a retrospective study using the French Transparency in Healthcare and National Health Data System databases"

The researchers have used administrative data for research purposes to draw associations between GPs prescribing patterns and payment from pharmaceutical companies. This is an area of

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[15]Agence nationale de sécurité du médicament et des produit de santé. Utilisation des inhibiteurs de la pompe à protons (IPP) [Internet]. 2018 Dec p.54/77. Available from:
https://www.ansm.sante.fr/var/ansm_site/storage/original/application/cd53a115d61537a049f16954c021313c.pdf
[16] Association française de l'industrie pharmaceutique pour une automédication responsable. Baromètre AFIPA des produits du selfcare [Internet]. 2017. See page 7 and 23: https://www.afipa.org/wp-content/uploads/2018/02/16eme-barometre-afipa-du-selfcare-2017-et-4eme-observatoire-europeen-automedication-2016.pdf

research that needs more data and I applaud them for their use of these data to bring further attention to this area.

However, I cannot recommend this paper for publication. To draw these conclusions, the researchers either need to determine the drugs the company sells that contributed to each physician, or the frequency with which the physician prescribed the drugs of that company. The link is strong enough in this case. Rather, this paper demonstrates how prescribing patterns differ across physicians. One factor may be payments, but the link in this paper is not strong enough to enter the peer reviewed literature.

R2#1: Thank you for your thoughtful comment.

Unfortunately, the French Transparency in Healthcare database (transparence.sante.gouv.fr) does not include this level of details, and did not in 2016. The names of the drugs marketed by each company are not disclosed[17], only the company names are, and most of them produce many different drugs. For example, the firm Sanofi commercializes antihypertensive drugs, antibiotics, benzodiazepines and aspirin[18], all of them used in the drug indicators studied. Therefore, it is not possible to address your remark using our database.

We are aware that other studies explored a related research question by assessing the link between payments and marketed medication(s), such as gabapentinoids[19] or opioids[20]. We have now added more emphasis on these studies in our Discussion. We also want to stress that these studies explore a different question compared with ours, and are perhaps more convincing in highlighting a causal link, although also these studies, observational by nature, are concerned by the confounding issue. We agree that confounding is crucial, and have addressed it carefully in our manuscript. We have therefore clarified these issues based on the following reasons:

-Our study has a different aim, more global; indeed, the sum of payments without specific information on the marketed drugs has recently been used to assess the association with prescribing costs or with drug class prescriptions[21,22,23,24].

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[17] see https://united-kingdom.taylorwessing.com/synapse/ti_frenchhealthindustry.html

[18] See https://www.sanofi.fr/fr/nous-connaitre/Nos-medicaments-et-produits-de-sante

[19] Rhee TG, Ross JS. Association Between Industry Payments to Physicians and Gabapentinoid Prescribing. JAMA Intern Med [Internet]. 2019 Jul 8 [cited 2019 Sep 12]; Available from: http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2737748

[20] Hadland and al. Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians With Subsequent Opioid Prescribing. JAMA Intern Med. 2018 Jun 1;178(6):861–3

[21] Perlis RH, Perlis CS. Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs. PLoS ONE. 2016 May 16;11(5):1

[22] Yeh et al, Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. JAMA Intern Med. 2016 Jun 1;176(6):763–8

[23] Sharma M, Vadhariya A, Johnson ML, Marcum ZA, Holmes HM. Association between industry payments and prescribing costly medications: an observational study using open payments and medicare part D data. BMC Health Services Research. 2018 Apr 2;18(1):236.

[24] Mejia J, Mejia A, Pestilli F. Open data on industry payments to healthcare providers reveal potential hidden costs to the public. Nat Commun. 2019 Sep 20;10(1):1–8.

-Other authors have described the impact of pharmaceutical promotion on physicians prescribing behaviours in a "general way". Cognitive biases induced by drug promotion have been described. For example, some studies show that receiving gifts is correlated with a better trust in pharmaceuticals companies[25]. The World Health Organisation and Health Action International describe this issue: "*Pharmaceutical companies only have an incentive to promote medicines. Non-drug treatments and the option not to treat are unlikely to receive equal attention, even when are the best option for a specific patient*"[26]. Studies on the impact of promotion on the overall sales show increased overall sales after promotional activities.[27] We used this hypothesis to build our protocol study and our results seem to reinforce this hypothesis.

-Offering gifts is not the only strategy used by industry to promote medications. Sponsored medical press, advertising directed towards doctors, sponsoring Continuing Medical Education modules possibly with Key Opinion Leaders, one-to-one sale representative visit, sample delivery etc. are many other ways to influence the physician's prescriptions. Receiving a gift from a firm may reflect a higher acceptation, an appetite for novelty, a belief in the promotion, a favourable image of the firms, and a belief in medication as first solution to health problems. Somehow, receiving gifts from a company may not only be the direct cause of prescription of that company drugs, but also a symptom of a general behavior.[26] In our study, we tried to address this problem.

-It was one of the reasons why we discussed the causality with a lot of prudence and only talked about associations. In our manuscript, as a conclusion, we encourage new prospective studies to assess this causality link between drug promotion and prescribing patterns. Anyway, the paper missed this specific point and we thank you for highlighting this important point. We added the following paragraph in the Discussion chapter:

" Other studies have shown a link between payments from industry and specific prescriptions (e.g., opioids, gabapentinoids).[13][14] As the Transparency in Healthcare Database does not specify the marketed drug(s) associated with each listed gift, we could not link a gift to a specific prescription.[5] Our study explores prescription patterns in a more global way. Indeed, providing gifts is not the only way industry uses to promote medications. For instance, sponsored medical press, advertising directed towards doctors, sponsored continuing medical education courses (possibly with key opinion leader), one-to-one sale representative visits, and sample delivery are many other methods to influence the physician's prescriptions. Receiving a gift from a company may reflect a higher acceptation, an appetite for novelty, a belief in the promotion, a favourable image of the firms, and a belief in medication as first solution to health problems.[2] In other words, receiving gifts from a company may not only be the direct cause of a prescription pattern, but also a symptom of a general behaviour."

[25]Wazana A. Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift? JAMA. 2000 Jan 19;283(3):373–80.

[26]World Health Organization, Health Action International. Understanding and responding to pharmaceutical promotion: a practical guide [Internet]. 2009. See chap 1 and 2 http://haiweb.org/wp-content/uploads/2015/05/Pharma-Promotion-Guide-English.pdf

[27] Perlis RH, Perlis CS. Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs. PLoS ONE. 2016 May 16;11(5):1.

I also had other questions the researchers need to address if it was to be considered for publication:

Questions

1. What is the "the health scandal concerning benfluorex (Mediator®)" elaborate for international readers:

R2#2: For the international readership of BMJ, we added some information on the health scandal of benfluorex in the Introduction section:

"In France, the health scandal concerning benfluorex (Mediator®), marketed as an appetite suppressant, exploded in 2010 when the public and politicians discovered that the firm Servier had known and concealed the deaths caused by the use of this drug for years. Following this scandal, the French version of the "Sunshine Act" legislation was put in place in 2011, including the creation of the Transparency in Healthcare Database."

2. Are the data for drug dispensing or prescription? In the data description it is unclear as both types of datasets are mentioned. Are the researchers able to analyse drug prescription and drug reimbursed data? If so, it would be interesting to see if there are any discrepancies in the two datasets. Prescription data would be better data to answer this question as dispensed data have the inherent bias of relying on patients to fill the prescription.

R2#3: Thank you for this comment. Data collected in the National Health Data System –and used in our study- are data on the drugs dispensed and reimbursed by the NHI. Over-the-counter medication data are not collected. We agree that it would be interesting to assess these discrepancies, but we do not have a prescription dataset.
We have added precision on the National Health Data System in Box 1 and in our manuscript, as follows:

" We considered these 11 drug prescription efficiency indicators (11 variables), and the amount reimbursed by the National Health Insurance for the drugs prescribed and dispensed per visit (to the practice and home visit) in 2016 (1 variable) as outcomes of interest."

See Box 1 in separate file:

> **(…)**
> **National Health Data System**
> ● This database was created and is managed by the French National Health Insurance
> ● It collects information on all reimbursement claims from all French healthcare insurances
> ● It includes anonymous data on patients, data on prescribers, physician visits, dispensed and reimbursed medications, chronic medical conditions, etc.
> (...)

3. The meaning of this phrase is unclear. "i) GPs who worked with a particular mode of exercise." Does it mean physicians with a particular specialty? Please reword.

R2#4: In France, the qualification of GP authorizes to work not only as a GP but also in a variety of domains like angiology, emergency, allergology, gerontology[28] that are not standard family medicine domains, as define by the WONCA. However, a GP is not allowed to work as a specialist (i.e., cardiologist or lung specialist). We rephrased this to avoid confusion, see in the Methods chapter, under "Study population" paragraph:

", we excluded: i) GPs who didn't work as a family doctor (e.g. allergists, angiologists, geriatricians, emergency physicians, and other modes listed by the National Health Insurance)"

4. The meaning of this phrase is unclear. "postal code of the commune of exercise". Please reword.

R2#5: This is the postcode of the area where the GP's practice is located. We rephrased in the manuscript.

5. Was database linkage only performed on GPs meeting the inclusion criteria, or all GPs listed in the National Council of the College of Physicians? I.e. was the 6.2% of all GPs or of those we met the inclusion criteria? Please clarify.

R2#6: The first reviewer highlighted also this point that we clarified. See our response R1#9.

6. The meaning of this phrase is unclear. "Number of acts performed per year". Does it mean number of prescriptions written, number of prescriptions filled, number of patients seen? Replace acts with a clearer word for what this represents.

R2#7: We have reworded this point and the term "visit" seems more appropriate.

7. The term "best prescribing behaviours" is problematic. The researchers are examining 11 indicators of prescription efficiency. Relabelling the behaviour as 'most efficient prescribing patterns' is more accurate.

R2#8 Thank you for your suggestion. Indeed, the term "best prescribing behaviours" refers to an interpretation, whereas the term "most efficient prescribing pattern" seems more factual. We applied this change in our text.

8. In the flow chart, the monetary breakdown for each step of the inclusion and exclusion are not required. If they are deemed as required, then include in a table in the appendix, one column per cohort inclusion criteria. Also, use absolute numbers and proportions to clearly demonstrate if there was one GP reimbursement group that was affected by an of the inclusion criteria.

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[28] See http://www.ecosante.fr/DEPAFRA/2362.html

R2#9- Thank you for your suggestion. We have modified the flowchart accordingly and added Appendix 2 for details.

9.   In line with my overall comments above, is there any way to link the types of drugs physicians prescribe and the drug company that paid them? If a hypertension drug company contributed, but the physician prescribes benzodiazepines, then this is not evidence that the contribution affected their prescribing pattern, rather this demonstrate the variability in physician prescribing patterns.

R2#10: This is an important point. We already developed this point in our response R2#1.