PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The perceptions of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study
AUTHORS	Combier, Aurélie; Bon, Lucile; VAN GANSE, Eric; Aubrun, Frédéric; Letrilliart, Laurent

VERSION 1 – REVIEW

REVIEWER	Silje Maeland Uni Research and Western Norway University of Applied Sciences, Norway
REVIEW RETURNED	22-Feb-2018

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript The views of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study Although not familiar with the topic of research; experiences with drug withdrawal, I found the paper interesting for review based on my own research on GP experiences with sick leave and return to work and qualitative research methods. General comments: The authors say they have applied grounded theory. Based on this I expected that the authors to generate theory based on their empirical data, however my impression is that this study is a description of the phenomenon “experiences with withdrawal” and I question if this qualifies for calling It grounded theory. In grounded theory data collection and analysis should happen parallel and I find no description of this in the method section. The authors report following the SRQR (ref Academic Medicine, Bridget et al 2014. I applied the check list in table 1 and my interpretation is that the authors only follow 12 of the 21 topics in the SRQR standards. My judgement is that S3, 5, 6, 11, 12, 13, 14, 15, and 16 is completely or partly missing. I appreciate that it is interesting to explore GP and patients experiences with withdraw of such a popular drug, but I question how the results is relevant beyond this withdrawal based on the discussion in the paper. I believe this could be improved to highlight how the results from this qualitative study can be relevant in other similar settings. Applying grounded theory, generating new theory would have been interesting, however currently the manuscript does not succeed in this. Data processing and analysis: I urge the authors to give a description of this process to aid transparency. Currently, the use of N’vivo is declared bur this is merely an analytical method but at tool for organizing the data. In Data sharing statement the authors report having used an analytic framework – this should be included in the paper with a reference.

	The result section needs a thorough revision for publication to be accepted. The result headings should be revised to give the reader a better description of what follows. The quotations are often not relevant for the results and they are too “trimmed down” resulting in loss of meaning. Generally there is room for language improvements throughout, use of past and present tense, and a clearer description of the importance of this study in the area of medication withdrawal. The question: Are the references up-to-date and appropriate? Thi is a question difficult to answer as I am not familiar with the research area. However, more than half of the references is from before 2010 and many are in French.

REVIEWER	Thierry Christiaens Heymans Institute of Pharmacology, Ghent, Belgium
REVIEW RETURNED	17-Mar-2018

GENERAL COMMENTS	Qualitative methodology is well described and correct Relevant discussion and conclusion Some more patients' and GPs' quotes would be an option to feed more the discussion

REVIEWER	Katharine Wallis University of Auckland, New Zealand
REVIEW RETURNED	25-Mar-2018

GENERAL COMMENTS	This is an interesting study interviewing both GPs and patients about the compulsory withdrawal of a popular drug with abuse potential. It is not clearly stated why the authors felt it necessary or appropriate to interview both patients and GPs. The paper suffers from poor English. It would be greatly helped by having someone with English as their first language read through and correct the paper. The introduction and methods sections are fairly well set out. The results section might benefit from having a table briefly summarising findings. It would be nice to know whether any patients felt any better in any way having come off the drug. Authors mention the French benfluorex case a few times and that this case may have influenced participant responses. It is not clear that any participants reported being influenced by this case, or even being aware of the case. It would help an international audience if the authors briefly described the case for this journal’s international audience – what were the complaints and court case about? The Discussion section is rather long and introduces some new findings that would be better placed in the Results section. Authors should focus their Discussion on interpretation of study findings. It is not necessary to pontificate on alternative strategies for pain management. First part of “Implications …” section belongs in Introduction. Regarding references, I am not sure how useful it is to have French references in English language journal. It might also be good for the authors to consider the literature on deprescribing and opiate and benzodiapine withdrawal to put their research into context. Figure 1 heading is on a different page to the figure.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Silje Maeland
Institution and Country: Uni Research and Western Norway University of Applied Sciences, Norway
Competing Interests: None declared

Thank you for the opportunity to review this manuscript The views of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Although not familiar with the topic of research; experiences with drug withdrawal, I found the paper interesting for review based on my own research on GP experiences with sick leave and return to work and qualitative research methods.
General comments:
The authors say they have applied grounded theory. Based on this I expected that the authors to generate theory based on their empirical data, however my impression is that this study is a description of the phenomenon “experiences with withdrawal” and I question if this qualifies for calling It grounded theory. In grounded theory data collection and analysis should happen parallel and I find no description of this in the method section.
Actually, we applied the grounded theory as developed by Strauss and Corbin (Strauss A, Corbin J. Basics of qualitative research: Techniques and procedures for developing grounded theory. Newbury Park: Sage publications, 2015). Our interpretive approach of GPs’ and patients’ perceptions (including experiences and views) was essentially inductive and the interview guides were modified according to the analysis of the first interviews. We were not aware of an established theory supporting the perceptions of the event under study. According to the grounded-theory approach, data analysis was based on the constant comparison process and followed three distinct stages: open, axial and selective coding. All these points have been developed in detail in the revised Methods section.
At the beginning of the revised Discussion section, we have introduced the emerging theory built from our findings, upon which the proposed model for drug withdrawal decisions (Figure 1), presented in the Implications for future withdrawals section, is based.

The authors report following the SRQR (ref Academic Medicine, Bridget et al 2014. I applied the check list in table 1 and my interpretation is that the authors only follow 12 of the 21 topics in the SRQR standards. My judgement is that S3, 5, 6, 11, 12, 13, 14, 15, and 16 is completely or partly missing.

We have added to the manuscript the missing information needed to make more visible that we comply also with these 9 SRQR standards.
S3 We have mentioned the absence of an established theory supporting the perception of the event under study.
S5 We have better explained our use of the grounded theory.
S6 We have indicated that the two interviewers had been trained in the Methods section, and discussed the medical status of the researchers in the Strengths and weaknesses section.
S11 This was in the Data collection section of the original version of the manuscript: “the two semi-structured interview guides were developed based on a bibliographic review and discussion between the authors, one for GPs and the other for patients. Both included open-ended questions concerning the status of DXP, its efficacy and safety, the conditions of DXP withdrawal and its potential impact. They were adjusted after the first interviews in each group.”
S12 The characteristics of GPs and patients interviewed were presented in Table 1 and the mean duration of the interviews was reported in the original version of the manuscript.
S13 We have specified that the data transcription, data entry and data coding were performed on a continuous basis during the data collection process, which allowed emerging themes to be further explored in later interviews.

S14 We have specified that data analysis was based on the constant comparison process and followed three distinct stages: open, axial and selective coding, according to the grounded-theory approach.
S15 We have added that data were independently coded by two authors (AC, LB), the codes being secondarily discussed with another author (LL), in order to provide internal triangulation. . Regular meetings were held to reflect on the analytical process and to compare and discuss findings in order to reach consensus on recurrent themes.
S16 We now present our main findings at the end of the Results section, along with a summarizing table (Table 2). They support the emerging theory which is stated at the beginning of the Discussion section.
Below are all the SRQR criteria that we think the manuscript now fulfils.
Title and abstract
S1 Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended YES
S2 Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions YES

Introduction
S3 Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement YES after revision
S4 Purpose or research question - Purpose of the study and specific objectives or questions YES

Methods
S5 Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale** YES after revision
S6 Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability YES after revision

S7 Context - Setting/site and salient contextual factors; rationale** YES
S8 Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale** YES
S9 Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues YES
S10 Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale** YES
S11 Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study YES

S12 Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results) YES
S13 Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts YES after revision
S14 Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale** YES after revision
S15 Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale** YES after revision

Results/findings
S16 Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory YES after revision
S17 Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings YES

Discussion
S18 Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field YES
S19 Limitations - Trustworthiness and limitations of findings YES

Other
S20 Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed YES
S21 Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting YES

I appreciate that it is interesting to explore GP and patients experiences with withdraw of such a popular drug, but I question how the results is relevant beyond this withdrawal based on the discussion in the paper. I believe this could be improved to highlight how the results from this qualitative study can be relevant in other similar settings. Applying grounded theory, generating new theory would have been interesting, however currently the manuscript does not succeed in this.
As discussed above, we have introduced the emerging theory built from our findings. This emerging theory states that healthcare professionals' and patients' perception of DXP withdrawal was primarily based on their experience of the benefits and risks of this drug as compared to other analgesics. Their perception was also influenced by their poor level of information and their distrust of the pharmaceutical industry and healthcare institutions. The importance of the clinical experience of the physician in the decision to prescribe DXP instead of paracetamol or aspirin has already been reported well before its withdrawal (Schwartz, Soc Sci Med, 1989). Although as many as 462 identified medicinal products have been withdrawn from the market worldwide between 1953 and 2013 (Onakpoya et al, BMC Med, 2016), including 47 analgesic medications between 1965 and 2011 (Onakpoya et al, Expert Opin Drug Saf, 2018), we were not able to identify any previous qualitative or quantitative study on the perception of health professionals or patients to these withdrawals in any country. A few studies have, however, examined the impact of drug safety warning on parental or

provider perceptions (Dusetzina, Med Care, 2012). Limited quantitative data suggest that physicians disagreed with warnings from the Food and Drug Administration (FDA) on the use of droperidol (Richards, Cal J Emerg Med, 2003) or antiepileptic drugs (Shneker, Neurology, 2009) as they felt that, according to their personal experience, there was no other drug with greater efficacy or improved safety profile. One study showed that parents disapproved of the FDA warning for over-the-counter cough and cold medications since they disagreed that they were dangerous and still believed they relieved symptoms (Garbutt, Acad Pediatr, 2010). These studies did not explore the influence of the communication modalities nor the (dis)trust of the pharmaceutical industry and healthcare institutions on the perceptions of the healthcare professionals and the patients. Our findings therefore remain to be confirmed in future withdrawals of popular drugs. We have developed this point at the beginning of the revised Discussion section.
Data processing and analysis: I urge the authors to give a description of this process to aid transparency. Currently, the use of N'vivo is declared bur this is merely an analytical method but at tool for organizing the data. In Data sharing statement the authors report having used an analytic framework – this should be included in the paper with a reference.
The reviewer is correct, we only used the NVivo software to support data analysis. As reported above, we have added details regarding the analytic process in the Methods section. In the Data sharing statement, we meant the data analysis tree instead of an analytic framework, which we have corrected.

The result section needs a thorough revision for publication to be accepted. The result headings should be revised to give the reader a better description of what follows. The quotations are often not relevant for the results and they are too "trimmed down" resulting in loss of meaning.
We have revised the headings in the Results section to make them more meaningful. We usually did not reduce the quotations. However, we have removed the ellipses, which only denoted a pause in the sentence, to avoid misunderstanding. We have added additional quotations to better cover the main themes.

Generally there is room for language improvements throughout, use of past and present tense, and a clearer description of the importance of this study in the area of medication withdrawal.
The manuscript has been fully edited again by a native English speaking professional.
The importance and originality of our findings have been further discussed in this regard as developed above.

The question: Are the references up-to-date and appropriate? Thi is a question difficult to answer as I am not familiar with the research area. However, more than half of the references is from before 2010 and many are in French.
Among nine references in French, we have removed two non-essential references and substituted one for an international reference. The remaining references are mainly from the French drug agency, and are needed to document the regulatory context of DXP withdrawal in France. Since the DXP was withdrawn from the French market in 2011, following other European countries, many references are older.

Reviewer: 2
Reviewer Name: Thierry Christiaens
Institution and Country: Heymans Institute of Pharmacology, Ghent, Belgium
Competing Interests: None declared

Qualitative methodology is well described and correct
Relevant discussion and conclusion
Some more patients' and GPs' quotes would be an option to feed more the discussion

We have supplemented the patients' and GPs' quotes to better cover the main themes.

Reviewer: 3
Reviewer Name: Katharine Wallis
Institution and Country: University of Auckland, New Zealand
Competing Interests: None declared

This is an interesting study interviewing both GPs and patients about the compulsory withdrawal of a popular drug with abuse potential. It is not clearly stated why the authors felt it necessary or appropriate to interview both patients and GPs.
The study aimed at exploring and comparing the perceptions of French GPs and patients regarding DXP withdrawal. We have added this point to the corresponding sentence at the end of the Background section..

The paper suffers from poor English. It would be greatly helped by having someone with English as their first language read through and correct the paper.
The paper has been revised for language by a native English-speaker.

The introduction and methods sections are fairly well set out. The results section might benefit from having a table briefly summarising findings. It would be nice to know whether any patients felt any better in any way having come off the drug.
We have added a table (Table 2) summarizing the main perceptions of general practitioners and patients regarding DXP withdrawal. No patient reported improvement in his/her health status following DXP discontinuation, and we have added this point to the Results section.

Authors mention the French benfluorex case a few times and that this case may have influenced participant responses. It is not clear that any participants reported being influenced by this case, or even being aware of the case. It would help an international audience if the authors briefly described the case for this journal's international audience – what were the complaints and court case about?
We collected several verbatim from both patients and doctors. One patient directly reported being more suspicious due to the benfluorex case (his quotation is included in the Results section). One physician made a parallel between the DXP and the benfluorex, and we have added his verbatim. Benfluorex was popular in France and largely prescribed off-label as an appetite suppressant for more than thirty years until it was discovered that it could cause valvular heart disease and pulmonary arterial hypertension. As a consequence, many patients treated with this drug have sued the pharmaceutical company marketing the drug and the French health authorities (Menard. Benfluorex: analysis of a drug-related public health crisis. Diabets Metab, 2011). We have added this information to the Discussion section.

The Discussion section is rather long and introduces some new findings that would be better placed in the Results section. Authors should focus their Discussion on interpretation of study findings. It is not necessary to pontificate on alternative strategies for pain management. First part of "Implications …" section belongs in Introduction.
We have reorganized the Discussion section as suggested. We have moved the first paragraph at the end of the Results section, and added a new table (Table 2). We have removed the paragraph relating to alternative strategies for pain management. We have moved the first paragraph of the Implications for future withdrawals (after deleting the first sentence, which was redundant) to the

Background section. We have also moved forward the Strengths and weaknesses, just before the Implications for future withdrawals, and removed the other headings.

Regarding references, I am not sure how useful it is to have French references in English language journal. It might also be good for the authors to consider the literature on deprescribing and opiate and benzodiapine withdrawal to put their research into context.
We have removed references in French in order to limit them to the minimum required (see above). We agree that withdrawal from the market represented an imposed deprescription, which could sometimes result in withdrawal syndrome, as observed with opioids or benzodiazepines (Le Couteur, Australian Prescriber, 2011). We have mentioned this point in the revised Discussion section.

Figure 1 heading is on a different page to the figure.
The Figure is an image in jpeg format, and does not include the heading at this stage, according to author instructions.

VERSION 2 – REVIEW

REVIEWER	Silje Mæland Uni Research
REVIEW RETURNED	09-Jun-2018

GENERAL COMMENTS	Thank you for a thoroughly revised manuscript.