

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## The views of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021582
Article Type:	Research
Date Submitted by the Author:	08-Jan-2018
Complete List of Authors:	Combiér, Aurélie; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale Bon, Lucile; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale VAN GANSE, Eric; Pharmacoépidémiologie CHU-Lyon, Faculté d'Odontologie, Université Claude Bernard Aubrun, Frédéric; Université de Lyon, HESPER EA 7425; Hospices civils de Lyon, Department of Anesthesiology and Critical Care Letrilliart, Laurent; Département de médecine générale, Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne; E.A. 4129 « Santé, Individu, Société », Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France
Keywords:	dextropropoxyphene, drug withdrawal, general practitioner, patient, qualitative study

SCHOLARONE™  
Manuscripts

# The views of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Aurélie Combiér,<sup>\*1</sup>

Lucile Bon L,<sup>\*1</sup>

Eric Van Ganse,<sup>2,3</sup>

Frédéric Aubrun,<sup>3,4</sup>

Laurent Letrilliart,<sup>1,3</sup>

<sup>1</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>2</sup>Université Claude-Bernard-Lyon 1, UMR CNRS 5558, faculté d'odontologie, Lyon, France; Hospices civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, service de pneumologie, Lyon, France;

<sup>3</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>4</sup>Department of Anesthesiology and Critical Care, Université Claude-Bernard-Lyon 1, hospices civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, Lyon, France.

\*Aurélie Combiér and Lucile Bon equally contributed to the study.

**Corresponding author:** Pr Laurent Letrilliart, Université Claude-Bernard-Lyon 1, Collège universitaire de médecine générale (CUMG), 8 avenue Rockefeller, 69373 Lyon cedex 08, France. Tel: 33 6 24 17 87 76; Fax: 33 4 78 93 22 97. E-mail:

[laurent.letrilliart@univ-lyon1.fr](mailto:laurent.letrilliart@univ-lyon1.fr)

1  
2  
3  
4  
5 **Word count: 3498**  
6  
7

8  
9 **Key words:** dextropropoxyphene; drug withdrawal; general practitioner; patient;  
10  
11 qualitative study.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Abstract

**Objectives** Dextropropoxyphene (DXP), a step 2 analgesic commonly prescribed in France, was withdrawn from the French market in 2011, following a European decision, due to its poor risk-benefit balance. The purpose of this study was to explore the views of French general practitioners (GPs) and patients regarding DXP withdrawal.

**Design** Qualitative study based on 26 individual semi-structured interviews.

**Setting** French Rhône-Alpes region.

**Participants** 13 patients and 13 general practitioners.

**Methods** Data were recorded concerning the status of DXP, its efficacy and safety, the conditions of DXP's withdrawal and its potential impact. The transcripts were analyzed using N'Vivo software.

**Results** DXP was a very popular drug among both patients and GPs. Its withdrawal was experienced badly by patients and part of GPs. They have misunderstood the reasons for its withdrawal, and several have denied them. They generally recognized more benefits than risks from DXP and considered the alternative drugs unsatisfactory. In the same period, a French court case regarding another drug led to distrust towards the pharmaceutical industry and health institutions, which contributed to the negative feelings reported. However, some GPs who had been alerted regarding the poor DXP risk-benefit balance well before its withdrawal experienced it positively.

**Conclusions** Apart from previously informed physicians, DXP withdrawal was not well-experienced by patients and GPs. Better anticipation by the health authorities, in terms of pharmaco-epidemiological surveillance and communication to health

1  
2  
3 professionals and the lay public, should provide better acceptance of such a decision  
4  
5 in the future.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### Strengths and limitations of this study

- To our knowledge, this study is the first to have explored and compared the views of both patients and GPs regarding DXP withdrawal.
- Although interviewed patients and GPs had diverse demographics and medical activities, our design could have fostered the recruitment of individuals particularly concerned by the DXP withdrawal and led to an under-representation of the most neutral opinions of this event.
- Due to the time lag between the withdrawal and the interviews (3 to 5 years), memory bias cannot be excluded.
- From this experience, we present a model based on careful monitoring of and communication for any drug safety warning..

## BACKGROUND

In 2006, a combination of acetaminophen and dextropropoxyphene (DXP, a step 2 analgesic), was the second-most prescribed analgesic in France, with approximately 48 million boxes, behind acetaminophen alone, with 192 million boxes.<sup>1</sup> However, DXP's risk-benefit balance had been controversial for many years. On the one hand, the efficacy of the DXP-acetaminophen combination had not been widely assessed for chronic pain, and there was no strong evidence that it provides better analgesia than other step 1 or step 2 analgesics for postoperative pain, arthritis, or musculoskeletal pain.<sup>2,3</sup> On the other hand, in cases of over-dosage, DXP exposed patients to risks of respiratory depression, cardiac conduction disorders, and death.<sup>4,5</sup> DXP toxicity is mainly due to its long half-life (15 to 37 hours),<sup>6</sup> and it can be increased by concomitant use of alcohol or sedative drugs.<sup>7</sup>

As a result of many deaths due to voluntary or involuntary intoxications in Sweden (200 per year per 9 million inhabitants) and the United Kingdom (UK, 300 to 400 per year per 60 million inhabitants), the health authorities in these countries took restrictive measures and finally withdrew DXP from their markets in 2005 and 2007, respectively. Consequently, the European Medicines Agency (EMA) reassessed the DXP risk-benefit balance and recommended its withdrawal from all European countries in 2009.<sup>8</sup> In France, mortality from DXP intoxications was estimated at an average of 65 deaths per year per 65 million inhabitants.<sup>9</sup> The French Medicines Agency was initially reluctant to withdraw DXP from the national market considering that the risk to public health was lower than in the UK or Sweden, and fearing a higher toxicity in cases of substitution with tramadol.<sup>9</sup> In 2010, a new study from the United States of America (USA) showed that DXP could cause fatal heart rhythm disorders even at the therapeutic doses allowed in this country.<sup>10</sup> Based on these



1  
2  
3 data, the French Medicines Agency finally decided to withdraw DXP in March,  
4  
5 2011.<sup>11</sup>  
6

7  
8 Many patients have not found a satisfactory alternative to DXP after its withdrawal in  
9  
10 England.<sup>12</sup> The popularity of DXP and its controversial withdrawal in France suggest  
11  
12 that this may have repercussions for pain management in primary care. A  
13  
14 quantitative study showed that there was no effect on pain intensity and daily  
15  
16 activities in French elderly patients,<sup>13</sup> but the experience of this withdrawal by GPs  
17  
18 and by other patients has not been studied in France, nor internationally. The  
19  
20 purpose of this study was therefore to explore the views of French GPs and patients  
21  
22 regarding DXP withdrawal.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## METHODS

We have conducted a qualitative study based on individual semi-structured interviews and according to the grounded-theory approach.<sup>14</sup> After a test phase, the interviews were held between April, 2014 and March, 2016.

### Sampling

We used a purposive sampling procedure for GPs and patients, in order to include participants of various genders, ages, locations and practice settings, and ultimately to collect a wide range of opinions. The GP sample consisted of private GPs from the Rhône-Alpes French region who had been practicing since at least January, 2009. They were recruited via an email sent to the list of GPs of the Regional Union of Health Professionals. The patient sample included adult patients who were regularly using DXP until its withdrawal. They were recruited in GP offices based on posters and flyers, and occasionally by using the snowball technique.

### Data collection

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. Patients and GPs chose the date and the place of the appointment, which could occur in a GP office, at the informant's home, or in a public place. The interviews were conducted by LB for patients and by AC for GPs. They lasted 36 minutes for patients and 22 minutes for GPs on average.

## Data analysis

Interviews were audio-recorded after obtaining participant consent and manually transcribed anonymously. They were then analyzed using N'Vivo Software.<sup>15</sup>

Thematic analysis was performed as the data were collected by three researchers (AC, LB and LL), in order to provide internal triangulation of the data. This consisted of an open coding of the transcripts to identify the different concepts emerging from the data. Then, the codes were grouped into subcategories and categories, according to axial and selective coding.

The study was approved by the Ethics Committee of the University of Lyon 1 (Lyon, France), and by the French national agency for national data protection (CNIL, n°19162013).

## RESULTS

Thirteen GPs and 13 patients were interviewed until data saturation was reached, which meant that no new significant concepts emerged (Table 1). The main themes identified from data analysis were: the DXP, its withdrawal (reasons, modalities, impact) and the analgesic risk management.

### The DXP

Among step 2 analgesics, DXP was commonly used, sometimes without having previously tried a step 1 analgesic. DXP was mainly prescribed for recurrent musculoskeletal pain such as low back pain and for various pains including traumatic pain, menstrual pain, headache or toothache.

*GP 05: "Propofan® (DXP-acetaminophen-caffeine), Diantalvic® (DXP-acetaminophen), we gave plenty of them, you know."*

*Patient (P) 12: "I was taking it ... I mean... like you could take a Doliprane® (acetaminophen)."*

The risk-benefit balance for DXP seemed very positive for GPs and patients. First, both groups considered DXP to be equally or more effective than the other step 2 analgesics, and sometimes miraculous. Second, according to them, DXP was tolerated better than other step 2 analgesics, which were frequently associated with nausea and vertigo (e.g., tramadol, codeine), or constipation and drowsiness (codeine). DXP was therefore popular among patients and GPs. Some patients were extraordinarily attached to it and sometimes used it off-label.

*P08: "It was even more like my... my Blessed Bread."*

1  
2  
3 *GP12: "The dextropropoxyphene from my past experience ... had a level that was*  
4  
5 *close to perfect."*  
6

7 Patients also used various strategies to relieve their pain in addition to DXP:  
8  
9 physiotherapy, joint injections, use of lumbar belt or orthopedic soles, weight loss,  
10  
11 psychotherapy, or alternative medicines such as osteopathy, homeopathy or  
12  
13 acupuncture.  
14

15  
16  
17 *P07: "When I was in crisis... well... the first two days I only took the drugs*  
18  
19 *because the physical therapist couldn't... touch. Then, sometimes, the physical*  
20  
21 *therapist, he could start... the care. Then, I reduced ... the Diantalvic® (DXP-*  
22  
23 *acetaminophen)."*  
24  
25

### 26 27 28 29 **The reasons for the DXP withdrawal** 30

31 Overall, both patients and GPs have misunderstood the reasons for the withdrawal.  
32  
33 They partly understood that it was due to potentially serious side effects observed in  
34  
35 other countries, especially in cases of misuse (i.e., addiction, suicide attempts) and  
36  
37 for different terms of use (packaging, dosage). Few were aware that DXP efficacy  
38  
39 was not well-assessed.  
40  
41

42  
43 *GP02: "I believe there were issues in some other countries with different doses,*  
44  
45 *issues that I haven't checked in depth, it might have been a mistake by the way."*  
46  
47

48 Apart from those who had been informed of the DXP risks a long time ago by reading  
49  
50 a professional journal, many GPs considered the arguments for the DXP withdrawal  
51  
52 excessive. For most patients, the withdrawal was not justified because they thought  
53  
54 they were getting many benefits from the DXP and were not concerned by the risks.  
55  
56

1  
2  
3 Several GPs and patients highlighted inconsistencies between the DXP withdrawal  
4  
5 and the maintenance of other drugs on the market.  
6

7  
8 *GP06: "But we already had the thought because we read (the journal) Prescrire,*  
9  
10 *which warned a lot against this kind of product back at that time."*

11  
12 *GP08: "I would have liked to know the rate, the number of people who, indeed,*  
13  
14 *have had issues with that drug. Because if someone tells me, ... that would make*  
15  
16 *me fall out of my seat... it's 15 to 20%, I'd say it was worth it. If it is 1 over*  
17  
18 *100 000, so then we have to remove all the drugs..."*

19  
20  
21 *P12: "But I don't have the feeling that it has disastrous consequences on me... in*  
22  
23 *fact it eased me... in my daily life."*  
24

## 25 26 27 28 **The modalities of the withdrawal** 29

30  
31 GPs and patients mainly heard about the DXP withdrawal through mainstream  
32  
33 media. GPs were also informed by the French Medicines Agency, and the patients by  
34  
35 their doctors. Many GPs and patients perceived the DXP withdrawal as a sudden  
36  
37 decision, and some of them regretted that no restrictive measures had been  
38  
39 previously taken. GPs made efforts to prepare and reassure their concerned patients  
40  
41 on this issue, but several of them faced difficulties in telling their patients that the  
42  
43 drug they had been taking for years was being removed.  
44

45  
46  
47 *P12: "Well it has been a source of stress because I told myself: crap, what am I*  
48  
49 *going to do?"*

50  
51 *GP08: "But there were no preventive measures like: [...] the emergency services*  
52  
53 *would be asked to give less of it (DXP-acetaminophen), doctors would be asked to*  
54  
55 *proceed with good judgment, to not give that like it was Doliprane®*  
56

1  
2  
3 *(acetaminophen), and eventually to use secured prescriptions... why not... I don't*  
4  
5 *know."*  
6

7  
8 GPs had different feelings about the delay between the announcement of the  
9  
10 decision and the withdrawal. Several were troubled that DXP prescription was still  
11  
12 possible during this time although the drug was presented as dangerous. Others  
13  
14 appreciated still being allowed to prescribe it as they had difficulties in finding an  
15  
16 alternative. Many patients regularly taking DXP had built up stockpiles of DXP and  
17  
18 used all tablets available, even after the withdrawal.  
19

20  
21 *GP07: "We get this kind of paradoxical message, a double bind where on one*  
22  
23 *hand, they suggest that we not prescribe it because it's toxic, and on the other*  
24  
25 *hand, they allow us to prescribe it because it is not forbidden yet. This makes us*  
26  
27 *think that if there was an issue it would be our responsibility."*  
28

29  
30 *GP10: "I thought it was good this... progressive removal as far as there were still*  
31  
32 *possibilities to prescribe it to people who could not live without it. And it gave us*  
33  
34 *more time to switch to a new drug."*  
35

36  
37 *P08: "Even the day when I heard that they were going to cancel it and stuff, I had*  
38  
39 *made my... stock. I stocked as much as I could... And then I kept taking it at least*  
40  
41 *... 2 years... yes over 2 years."*  
42

43  
44 The DXP withdrawal was an opportunity for GPs to reassess pain management and  
45  
46 to diversify their prescriptions. DXP was mainly replaced by either a step 2 analgesic  
47  
48 (i.e., codeine, tramadol, opium) or by acetaminophen, which was thereafter more  
49  
50 often used by patients as a first-line treatment. In some cases, a non-steroidal anti-  
51  
52 inflammatory drug or morphine was judged necessary. Some GPs easily replaced  
53  
54 DXP with one of the many other treatment options, but other GPs were concerned  
55  
56  
57  
58  
59  
60

1  
2  
3 about the possible side effects of the remaining opioid analgesics. Patients often felt  
4  
5 that their substitute drug was not as satisfying as DXP.  
6

7  
8 *GP07: "Then, it has helped to step down to the regular paracetamol. It helps to do*  
9  
10 *some cleaning."*

11  
12 *P05: "I used to tell them ... to the pharmacist... same as for the doctor, I said it's*  
13  
14 *not as effective as Diantalvic® (DXP-acetaminophen)!"*  
15

### 16 17 18 19 **The impact of the withdrawal** 20

21  
22 The withdrawal disrupted the balance found by part of patients with DXP and  
23  
24 sometimes affected their social life, their job or their mood. From then on, several  
25  
26 patients felt more painful, while recognizing that this may have been due merely to  
27  
28 the progression of their condition. According to GPs, patients were still well-relieved,  
29  
30 but their pain management was more complex, especially because of a poor  
31  
32 tolerance for most alternative drugs. Several GPs mentioned their interest in the  
33  
34 withdrawal in educating their patients on potential adverse drug events.  
35  
36  
37

38  
39 *P01: "It's like a brick, you take one off, then everything collapses."*

40  
41 *P11: "When I definitely stopped... there was the pain ... in the muscles as well as*  
42  
43 *in the joints... which was present, whereas it was not the case before."*

44  
45 *GP12: "Less easy, less comfortable in the pain treatment, that's it."*  
46

47  
48 Both GPs and patients perceived the DXP withdrawal as a very important and large-  
49  
50 scale event. Apart from a few patients who used DXP only occasionally, most of them  
51  
52 remembered the withdrawal as a bad experience and some expressed anger towards  
53  
54 it. Several of the GPs who had stopped prescribing DXP years earlier welcomed its  
55  
56  
57



1  
2  
3 withdrawal, as it justified their previous choice. Other GPs, as well as many patients,  
4  
5 regretted it and wished DXP would be marketed again.  
6

7  
8 *GP10: "We used to talk about it during parties: CME [continuing medical*  
9  
10 *education], peer groups; it was a pretty important event (laughs). So, we obviously*  
11  
12 *couldn't ignore it."*

13  
14 *P01: "I have literally been... I've got a bad trick."*

15  
16 *P08: "If it was still in countries, in other countries, I would go to get some."*  
17  
18  
19  
20  
21

## 22 **The analgesic risk management**

23  
24 GPs reported varying experiences with drug withdrawals: it did not matter to some of  
25  
26 them, while others felt that their therapeutic options had decreased over the years  
27  
28 without their approval.  
29

30  
31  
32 *GP05: "If Ixprim® (tramadol-acetaminophen) didn't exist, we would do [...] a hot*  
33  
34 *water bottle (laughs)."*

35  
36 *GP04: "We get the feeling of having fewer and fewer accessible things to treat the*  
37  
38 *patients. Between the market withdrawals, the stock shortages, it's scary. »*  
39  
40

41 GPs and patients interpreted the DXP withdrawal as resulting from occult strategies  
42  
43 of the pharmaceutical industry or even the health insurance system. Several court  
44  
45 cases contemporaneous with the DXP withdrawal, and inconsistencies in the drug  
46  
47 market regulations, reinforced their distrust.  
48

49  
50  
51 *GP04: "So I think they are drugs that might have been less used, or... might not*  
52  
53 *have been expensive enough, not profitable enough for the laboratory and which*  
54  
55 *led to... its suppression."*  
56  
57  
58  
59  
60

1  
2  
3 *P03: “ think that because of...Mediator® (benfluorex), we are more suspicious.”*

4  
5 *GP05: “I think that people, ... they get the feeling that the medical field has*  
6  
7 *betrayed them when a drug gets suppressed, for sure! Something is given to*  
8  
9 *them, and then they are told to not get any more because it’s toxic. It is like*  
10  
11 *someone tells you that you have been taking poison for 20 years!”*  
12  
13

## 14 15 16 17 **DISCUSSION**

18  
19  
20 DXP was a popular drug among patients and GPs in France. Its withdrawal in 2011  
21  
22 was experienced badly by patients and part of GPs. Both had misunderstood or did  
23  
24 not agree with the reasons for this decision, and patients sometimes built up stocks  
25  
26 of DXP. They saw more benefits than risks in using DXP, all the more when they  
27  
28 were not aware of the lack of evidence for its efficacy nor for its risks beyond misuse  
29  
30 situations. In addition, both groups found the alternative drugs to DXP unsatisfactory,  
31  
32 as patients and GPs reported a poor tolerance of the alternative step 2 analgesics  
33  
34 and patients felt more painful. Over the same period, a national court case, following  
35  
36 complaints by patients treated earlier by benfluorex, led to a general distrust of the  
37  
38 pharmaceutical industry and health institutions. This distrust has likely blurred the  
39  
40 understanding regarding the messages on DXP withdrawal and contributed to the  
41  
42 negative feelings experienced. However, some GPs, who had been alerted on the  
43  
44 poor DXP risk-benefit balance long before its withdrawal, experienced it positively.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Strengths and weaknesses

To our knowledge, this study is the first to have explored and compared the views of both patients and GPs regarding DXP withdrawal. We conformed to the standards for reporting qualitative research.<sup>16</sup>

Although interviewed patients and GPs had diverse demographics and medical activities, our design could have fostered the recruitment of individuals particularly concerned by the DXP withdrawal and led to an under-representation of the most neutral opinions of this event. However, various opinions and experiences were collected from both groups until reaching saturation. Due to the time lag between the withdrawal and the interviews (3 to 5 years), memory bias cannot be excluded. However, it would probably be limited as the event under study involved more of the emotional memory of patients and GPs than their factual memory.

### A rather denied decision

GPs and patients have not understood well the DXP withdrawal decision, as their perception of the risk-benefit balance differed from the health authorities' evaluation. Benefits of painkillers are especially difficult to grasp by patients, and even by GPs, because of their poor pharmacological assessment and the importance of the placebo effect. There was indeed no strong evidence to support the important benefits experienced by patients using DXP.<sup>2,3</sup> As with many other old drugs, the efficacy of DXP had been poorly assessed, as well as for acetaminophen.<sup>17</sup> Patients treated with DXP may have felt a benefit due to the placebo effect, which is particularly frequent and intense with painkillers. It can relieve pain in 15 to 52% of patients,<sup>18</sup> and even equal an injection of morphine in postoperative pain.<sup>19</sup> Serious

1  
2  
3 risks are also difficult to consider for GPs and even more so for patients, because  
4 they are rare and need time to be highlighted. Indeed, we can roughly estimate the  
5 number of deaths from DXP in France at 1.5 per 1000 private GPs in 2009.<sup>9,20</sup>  
6  
7

8  
9  
10 Many patients and GPs expressed distrust towards both health institutions and the  
11 pharmaceutical industry. A survey about the French population's relationship to  
12 medicines shows that only one in two people gives some credibility to information  
13 from the pharmaceutical industry, as well as from the health authorities.<sup>21</sup> Several  
14 patients and GPs have been struck by the French benfluorex case, which went public  
15 during the same period as the DXP withdrawal.<sup>22</sup> This case, considered in France to  
16 be a national scandal, may have altered confidence in the drug management system  
17 and made the acceptance of DXP withdrawal difficult for patients and GPs.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **A dissatisfaction with DXP substitutes**

31  
32  
33 Some GPs and most patients were unsatisfied with alternative drugs to DXP for three  
34 reasons. First, many patients felt their pain increased after DXP withdrawal. Such  
35 relapse was not observed in a French cohort, but this study was restricted to elderly  
36 people.<sup>12</sup> Second, many patients also did not tolerate other step 2 analgesics well.  
37 This observation is only partially consistent with French pharmacovigilance data,  
38 which show that the number of adverse drug reactions reported with tramadol, but  
39 not with codeine, is higher than with DXP.<sup>23</sup> Tolerance problems may help explain  
40 that patients largely turned to acetaminophen,<sup>24,25</sup> which could also contribute to  
41 relapsing pain. Finally, patients' dissatisfaction might also be due to DXP addiction.  
42 Indeed, behaviors close to addiction, such as stockpiling, fear of running out, off-label  
43 usage, or searching for backdoor procurement, have been reported by interviewed  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 patients. Such misuses could pertain to opioid addiction or eventually to pseudo-  
4  
5 addiction, which is a controversial syndrome resulting from inadequate pain  
6  
7 management.<sup>26,27</sup>  
8

9  
10 Another approach to improving pain management can be the use of specific  
11  
12 treatments, such as anti-neuropathic or migraine treatments, when they are  
13  
14 indicated.<sup>28</sup> Non-drug alternatives also have a place in pain management,<sup>29</sup> such as  
15  
16 exercise intervention in lower limb osteoarthritis.<sup>30</sup> From this perspective, the  
17  
18 classification of analgesics into three levels by the World Health Organization, initially  
19  
20 created for advanced cancer pain, should be revised to include more diverse drug  
21  
22 and non-drug strategies, especially for better management of neuropathic pain.<sup>31</sup>  
23  
24  
25  
26  
27

### 28 **Implications for future withdrawals**

29  
30  
31 Warnings given by several European countries led the EMA to reassess the DXP  
32  
33 risk-benefit balance and finally to recommend its withdrawal in all European Union  
34  
35 member states. The before/after evaluation performed in the UK has shown that the  
36  
37 overall number of deaths from poisoning did not decrease and that the number of  
38  
39 deaths involving codeine and tramadol increased.<sup>32</sup> In France, the investigation of  
40  
41 deaths due to analgesics was initiated in 2013, but it did not allow for the comparison  
42  
43 of changes in the number of deaths attributable to the various analgesics due to a  
44  
45 lack of consistent data prior to the withdrawal.<sup>33</sup> Indeed, DXP and alternative  
46  
47 analgesics were not specifically monitored before the European warning because no  
48  
49 risk had been identified in France during DXP post-marketing surveillance. Apart from  
50  
51 the surveillance process, there was probably insufficient communication of the  
52  
53 reasons for the withdrawal, all the more important given that DXP was a popular drug  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 among patients and GPs. In particular, it was very much focused on DXP risks and  
4 on recommendations for DXP substitution,<sup>34</sup> but it did not make clear enough the lack  
5 of evidence for DXP efficacy.  
6  
7

8  
9  
10 In cases of future warnings on drug safety (within the framework of the risk  
11 management plan for new or recently marketed drugs), national and European health  
12 authorities should start collecting prospective data well before the withdrawal  
13 decision and continue the monitoring thereafter, including qualitative studies. Such  
14 prospective monitoring is needed to assess the pharmaco-epidemiological impact of  
15 drug withdrawal, including the use of alternative drugs and strategies, and ultimately  
16 to validate the withdrawal decision. Additionally, appropriately informing health  
17 professionals and the lay public at each stage of the withdrawal process (i.e.,  
18 warning, withdrawal decision and assessment) would ease acceptance of the  
19 decision and reinforce trust in the drug management system (Figure 1). In addition,  
20 and before any safety warnings, an efficiency assessment of every blockbuster drug  
21 through randomized mega-trials should be considered if not available.<sup>35</sup>  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Acknowledgments

The authors would like to thank all patients and GPs who have been interviewed in the study, the Regional Union of Health Professionals for its logistical support, and Pr Behrouz Kassai Koupai for the discussions regarding the results. They are also grateful to the College Lyonnais des Généralistes Enseignants (CLGE) for funding the language editing.

## Contributors

LL, AC and LB conceived and designed the study, and they elaborated the topic schedules. AC and LB conducted the interviews and the analysis, under the supervision of LL. EVG and FA provided clinical and pharmaco-epidemiological context and contributed to the interpretation of the findings. LL, AC and LB drafted the manuscript. All authors reviewed and approved the final version of the article.

## Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## Competing interests

None declared.

## Ethics approval

1  
2  
3 The Ethics Committee of the University of Lyon 1 (Lyon, France) and the French  
4 national agency for national data protection (CNIL, n°19162013).  
5  
6  
7  
8  
9

### 10 **Data sharing statement**

11  
12  
13 The analysis framework is available on request from the corresponding author.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



## References

1. Prescrire rédaction. Dextropropoxyphène + paracétamol : toujours là... malgré les risques. *Rev Prescrire* 2007;27:735.
2. Li Wan Po A, Zhang W. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997;315:1565–71.
3. Moore RA, Collins SL, Edwards J, et al. Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev* 2000:CD001440.
4. Imbs JL, Welsch M. Un antalgique pas si banal le dextropropoxyphene. *Rev Prescrire* 1982;2:24–5.
5. Afshari R, Maxwell S, Dawson A, et al. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *Clin Toxicol* 2005;43:255–9.
6. Flanagan R, Johnston A, White AS, et al. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989;28:463–9.
7. Young RJ. Dextropropoxyphene overdose. Pharmacological considerations and clinical management. *Drugs* 1983;26:70–9.
8. European Medicines Agency. Press release: European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines. London; 2009.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2009/11/WC500010365.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010365.pdf) (Accessed 23 October 2017).

1  
2  
3 9. Agence Française de Sécurité Sanitaire des Produits de Santé. Médicaments  
4 contenant l'association dextropropoxyphène/paracétamol : Recommandation de  
5 l'EMA de retrait de ces médicaments à la suite de l'évaluation européenne et avis  
6 divergent de l'Afssaps. 2009.

7  
8  
9  
10  
11 <http://www.ansm.sante.fr/content/download/20487/248676/> (Accessed 23 October  
12 2017).

13  
14  
15  
16 10. Food and Drugs Administration. Recommendation on a Regulatory Decision for  
17 Propoxyphene-containing Products. 2010.

18  
19  
20  
21 [http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationfo](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf)  
22 [rPatientsandProviders/UCM234349.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf) (Accessed 23 October 2017).

23  
24  
25  
26 11. Agence Française de Sécurité Sanitaire des Produits de Santé. Questions /  
27 Réponses. Retrait des médicaments contenant l'association  
28 dextropropoxyphène/paracétamol (Di-Antalvic® et ses génériques) ou  
29 dextropropoxyphène/paracétamol/caféine (Propofan® et ses génériques). 2009.

30  
31  
32  
33 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/19ca2c73609691747d](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf)  
34 [72c18b65dfc21a.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf) (Accessed 23 October 2017).

35  
36  
37  
38  
39 12. Ottewell L, Walker DJ. Co-proxamol: where have all the patients gone?  
40 *Rheumatology* 2008;47:375.

41  
42  
43  
44 13. Becquemont L, Delespierre T, Bauduceau B, et al. Consequences of  
45 dextropropoxyphene market withdrawal in elderly patients with chronic pain. *Eur J*  
46 *Clin Pharmacol* 2014;70:1237–42.

47  
48  
49  
50  
51 14. Glaser BG, Strauss AL. The discovery of grounded theory: Strategies for  
52 Qualitative Research. Chicago, ILL: AldineTransaction 1967.

- 1  
2  
3 15. NVivo qualitative data analysis software; Doncaster: QSR International Pty Ltd.  
4  
5 Version 11, 2014.  
6  
7  
8 16. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative  
9  
10 research: a synthesis of recommendations. *Acad Med* 2014; 89:1245–51.  
11  
12  
13 17. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol  
14  
15 for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised  
16  
17 placebo controlled trials. *BMJ* 2015;350:h1225.  
18  
19  
20 18. Beecher HK. The powerful placebo. *JAMA* 1955;159:1602–6.  
21  
22  
23 19. Levine JD, Gordon NC, Smith R, et al. Analgesic responses to morphine and  
24  
25 placebo in individuals with postoperative pain. *Pain* 1981;10:379–89.  
26  
27  
28 20. Conseil National de l'Ordre des Médecins. Atlas de la démographie médicale en  
29  
30 France. Situation au 1er janvier 2009. [https://www.conseil-  
33  
34 national.medecin.fr/sites/default/files/atlas2009\\_0.pdf](https://www.conseil-<br/>31<br/>32 national.medecin.fr/sites/default/files/atlas2009_0.pdf) (Accessed 23 October 2017).  
35  
36 21. Ipsos. Observatoire sociétal du médicament 2015 : 5ème vague d'étude menée  
37  
38 par Ipsos pour le Leem sur le rapport des Français aux médicaments.  
39  
40 <http://www.leem.org/sites/default/files/Observatoire-societal-du-Medicament2015.pdf>  
41  
42 (Accessed 23 October 2017).  
43  
44 22. Mullard A. Mediator scandal rocks French medical community. *Lancet*  
45  
46 2011;377:890–2.  
47  
48  
49 23. Tavassoli N, Lapeyre-Mestre M, Sommet A, et al. Reporting rate of adverse drug  
50  
51 reactions to the French pharmacovigilance system with three step 2 analgesic drugs:  
52  
53 dextropropoxyphene, tramadol and codeine (in combination with paracetamol). *Br J*  
54  
55 *Clin Pharmacol* 2009;68:422–6.  
56  
57  
58  
59  
60

- 1  
2  
3 24. Gaubert S, Vié M, Damase-Michel C, et al. Dextropropoxyphene withdrawal from  
4 a French university hospital: impact on analgesic drug consumption. *Fundam Clin*  
5 *Pharmacol* 2009;23:247–52.  
6  
7  
8  
9  
10 25. Tamberou C, Cornu C, Muller E, et al. Identification des alternatives  
11 thérapeutiques mises en place en France suite au retrait du dextropropoxyphène.  
12 *Rev Epidemiol Santé Publique* 2014;62:S25.  
13  
14  
15  
16  
17 26. Greene MS, Chambers RA. Pseudoaddiction: Fact or Fiction? An Investigation of  
18 the Medical Literature. *Curr Addict Rep* 2015;2:310–7.  
19  
20  
21  
22 27. Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome.  
23 *Pain* 1989;36:363–6.  
24  
25  
26  
27 28. Cameron C, Kelly S, Hsieh S-C, et al. Triptans in the Acute Treatment of  
28 Migraine: A Systematic Review and Network Meta-Analysis. *Headache* 2015;55  
29 Suppl 4:221–35.  
30  
31  
32  
33  
34 29. Leung L. From ladder to platform: a new concept for pain management. *J Prim*  
35 *Health Care* 2012;4:254–8.  
36  
37  
38  
39 30. Uthman OA, van der Windt DA, Jordan JL, et al. Exercise for lower limb  
40 osteoarthritis: systematic review incorporating trial sequential analysis and network  
41 meta-analysis. *Br J Sports Med* 2014;48:1579.  
42  
43  
44  
45  
46 31. Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept  
47 gone astray. *BMJ* 2016;352:i20.  
48  
49  
50  
51 32. Handley S, Flanagan B. Drugs and other chemicals involved in fatal poisoning in  
52 England and Wales during 2000-2011. *Clin Toxicol* 2014;52:1–12.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 33. Agence nationale de sécurité du médicament et des produits de santé. Compte  
4 rendu de séance. Comité technique des Centres d'Evaluation et d'Information sur la  
5 Pharmacodépendance CT022015023. Séance du 19 mars 2015. 2015.  
6  
7

8  
9 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e9328677e7a48b7222](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf)  
10 [74b90159035d1b.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf) (Accessed 23 October 2017).  
11  
12

13  
14 34. AFSSAPS. Mise au point. Prise en charge des douleurs de l'adulte modérées à  
15 intenses. Recommandations après le retrait des associations  
16 dextropropoxyphène/paracétamol et dextropropoxyphène/paracétamol/caféine.  
17  
18

19 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/a6497f74fc2f18e8db00](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db0022973f9327e1.pdf)  
20 [22973f9327e1.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db0022973f9327e1.pdf) (Accessed 23 October 2017).  
21  
22  
23

24  
25 35. Loannidis JPA. Mega-trials for blockbusters. *JAMA* 2013;309:239–40.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1** Characteristics of interviewed GPs (N = 13) and patients (N = 13)

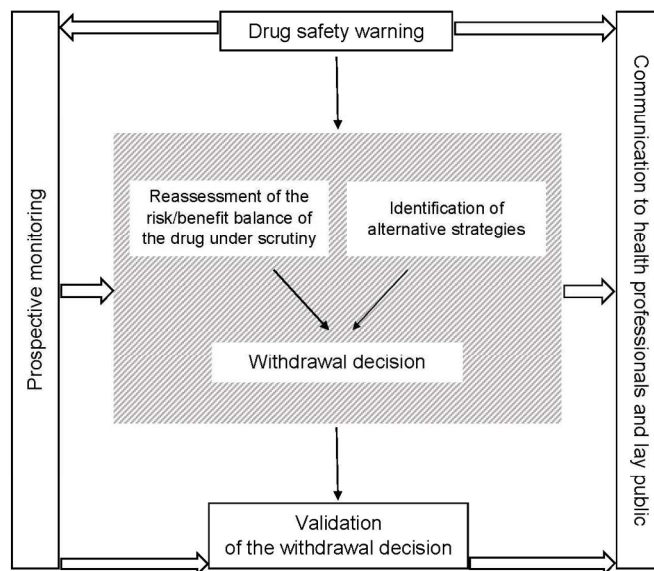
Characteristics		GPs	Patients
Gender	Female	5	8
	Male	8	5
Age (years)	25-34	2	2
	35-44	1	0
	45-54	3	3
	55-64	7	5
	65-74	0	3
Working/living area	Urban	5	5
	Semi-rural	4	6
	Rural	4	2
GP trainer	Yes	9	
	No	4	
Practice type	Solo	1	
	Group	12	
Specialization	Sports medicine/osteopathy	3	
	Homeopathy/Mesotherapy	1	
	Medical expertise	1	
	Addictology	1	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figure 1** Proposed model for drug withdrawal decisions

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1

Figure 1 Proposed model for drug withdrawal decisions

139x198mm (300 x 300 DPI)



# BMJ Open

## The perceptions of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021582.R1
Article Type:	Research
Date Submitted by the Author:	21-May-2018
Complete List of Authors:	Combiér, Aurélie; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale Bon, Lucile; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale VAN GANSE, Eric; Pharmacoépidémiologie CHU-Lyon, Faculté d'Odontologie, Université Claude Bernard Aubrun, Frédéric; Université de Lyon, HESPER EA 7425; Hospices civils de Lyon, Department of Anesthesiology and Critical Care Letrilliart, Laurent; Département de médecine générale, Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne; E.A. 4129 « Santé, Individu, Société », Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France
<b>Primary Subject Heading</b>:	Health services research
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice
Keywords:	dextropropoxyphene, drug withdrawal, general practitioner, patient, qualitative study

SCHOLARONE™  
Manuscripts

# The perceptions of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Aurélie Combier,<sup>\*1</sup>

Lucile Bon L,<sup>\*1</sup>

Eric Van Ganse,<sup>2,3</sup>

Frédéric Aubrun,<sup>3,4</sup>

Laurent Letrilliart,<sup>1,3</sup>

<sup>1</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>2</sup>Université Claude-Bernard-Lyon 1, UMR CNRS 5558, faculté d'odontologie, Lyon, France; Hospices Civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, service de pneumologie, Lyon, France;

<sup>3</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>4</sup>Department of Anesthesiology and Critical Care, Université Claude-Bernard-Lyon 1, Hospices Civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, Lyon, France.

\*Aurélie Combier and Lucile Bon equally contributed to the study.

**Corresponding author:** Pr Laurent Letrilliart, Université Claude-Bernard-Lyon 1, Collège universitaire de médecine générale (CUMG), 8 avenue Rockefeller, 69373 Lyon cedex 08, France. Tel: +33 6 24 17 87 76; Fax: +33 4 78 93 22 97. E-mail:

[laurent.letrilliart@univ-lyon1.fr](mailto:laurent.letrilliart@univ-lyon1.fr)

1  
2  
3  
4  
5 **Word count:** 4185  
6  
7

8  
9 **Key words:** dextropropoxyphene; drug withdrawal; general practitioner; patient;  
10  
11 qualitative study.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Abstract

**Objectives** Dextropropoxyphene (DXP), a step 2 analgesic commonly prescribed in France, was withdrawn from the French market in 2011 following a European decision due to its poor risk-benefit ratio. The purpose of this study was to explore the perceptions of French general practitioners (GPs) and patients regarding DXP withdrawal.

**Design** Qualitative study based on 26 individual semi-structured interviews.

**Setting** Rhône-Alpes region of France.

**Participants** Thirteen patients and 13 general practitioners.

**Methods** Interviews were conducted to collect data concerning the status of DXP, its efficacy and safety, the conditions of DXP's withdrawal, and its potential impact. The transcripts were analysed using NVivo software.

**Results** DXP was a very popular drug among both patients and GPs. Its withdrawal was a bad experience for patients and part of GPs; these misunderstood the reasons for its withdrawal and several contested them. They generally recognized more benefits than risks of DXP and considered alternative drugs unsatisfactory. In the same period, a French court case regarding another drug led to distrust towards the pharmaceutical industry and healthcare institutions, which contributed to the negative feelings reported. However, the experience was positive for the GPs who had been alerted to the poor DXP risk-benefit ratio well before its withdrawal.

**Conclusions** Apart physicians who were previously informed of its poor risk-benefit ratio, DXP withdrawal was not a good experience for patients and GPs. Better anticipation by the health authorities, in terms of pharmacoepidemiological surveillance and communication to healthcare professionals as well as the general public, should provide better acceptance of such a decision in the future.

### Strengths and limitations of this study

- To our knowledge, this study is the first to have explored and compared the views of both patients and GPs regarding DXP withdrawal.
- The collected data were independently coded by two authors, the codes being secondarily discussed with another author, in order to provide internal triangulation.
- Although interviewed patients and GPs had diverse demographics and medical activities, the study design could have led to the recruitment of individuals particularly concerned by the DXP withdrawal and to an under-representation of the most neutral opinions of this event.
- Due to the time lag between the withdrawal and the interviews (3 to 5 years), memory bias cannot be excluded.

## BACKGROUND

In 2006, the combination of paracetamol and dextropropoxyphene (DXP, a step 2 analgesic) was the second-most prescribed analgesic in France (approximately 48 million boxes).<sup>1</sup> However, the risk-benefit ratio of DXP had been controversial for many years. On the one hand, the efficacy of the DXP-paracetamol combination had not been widely assessed for chronic pain, and there was no strong evidence that it provided better analgesia than other step 1 or step 2 analgesics for postoperative pain, arthritis, and musculoskeletal pain.<sup>2,3</sup> On the other hand, in cases of overdose, DXP exposed patients to the risk of respiratory depression, cardiac conduction disorders, and death.<sup>4,5</sup> DXP toxicity is mainly due to its long half-life (15 to 37 hours),<sup>6</sup> and it can be increased by concomitant use of alcohol or sedative drugs.<sup>7</sup> As a result of many deaths due to voluntary or involuntary intoxications in Sweden (200 per year per 9 million inhabitants) and the United Kingdom (UK, 300 to 400 per year per 60 million inhabitants), the health authorities in these countries took restrictive measures and finally withdrew DXP from their markets in 2005 and 2007, respectively. Consequently, the European Medicines Agency (EMA) reassessed the DXP risk-benefit ratio and in 2009 recommended its withdrawal from all European member states.<sup>8</sup> In France, mortality from DXP intoxications was estimated to be around 65 deaths per year per 65 million inhabitants.<sup>9</sup> The French Medicines Agency was initially reluctant to withdraw DXP from the national market considering that the risk to public health was lower than in the UK or Sweden, and fearing a higher toxicity in cases of substitution with tramadol.<sup>9</sup> In 2010, a new study conducted in the United States of America (USA) found that DXP could cause fatal heart rhythm disorders even at the therapeutic doses allowed in this country.<sup>10</sup> Based on these data, the French Medicines Agency finally decided to withdraw DXP in March 2011.<sup>11</sup>

1  
2  
3 The before/after evaluation performed in the UK found that the overall number of  
4 deaths from poisoning did not decrease and that the number of deaths involving  
5 codeine and tramadol increased.<sup>12</sup> In France, the investigation of deaths due to  
6 analgesics was initiated in 2013, but it did not allow for the comparison of changes in  
7 the number of deaths attributable to the various analgesics due to a lack of  
8 consistent data prior to the withdrawal.<sup>13</sup> Indeed, DXP and alternative analgesics  
9 were not specifically monitored before the European warning because no risk had  
10 been identified in France during DXP post-marketing surveillance. Apart from the  
11 surveillance process, there was probably insufficient communication of the reasons  
12 for the withdrawal, all the more important given that DXP was a popular drug among  
13 patients and GPs. In particular, it was very much focused on DXP risks and on  
14 recommendations for DXP substitution,<sup>14</sup> without emphasizing the lack of evidence  
15 for DXP efficacy.

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31 Many patients in England and Wales have not found a satisfactory alternative to DXP  
32 after its withdrawal.<sup>15</sup> The popularity of DXP and its controversial withdrawal in  
33 France suggest that this may have repercussions for pain management in primary  
34 care. A quantitative study did, however, find that there was no effect on pain intensity  
35 and daily activities in elderly patients in France,<sup>16</sup> but the experience of this  
36 withdrawal by GPs and by other patients has not been studied in France, nor  
37 internationally. The purpose of this study was therefore to comparatively explore the  
38 perceptions of French GPs and patients regarding DXP withdrawal.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## METHODS

We conducted a qualitative study based on individual semi-structured interviews and according to the grounded-theory approach.<sup>17</sup> We were not aware of an established theory supporting the perceptions of the event under study. After a test phase, the interviews were held between April 2014 and March 2016.

### Sampling

We used a purposive sampling procedure for GPs and patients, in order to include participants of various genders, ages, locations and practice settings, and ultimately to collect a wide range of opinions. The GP sample consisted of private GPs from the Rhône-Alpes region of France who had been practicing since at least January 2009. They were recruited via an email sent to the list of GPs of the Regional Union of Healthcare Professionals. The patient sample included adults who were regularly using DXP until its withdrawal. They were recruited in GP surgeries based on posters and flyers, and occasionally by using snowball sampling.

### Data collection

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 effectiveness, and safety, the conditions of DXP withdrawal, and its potential impact. They were adjusted after the first interviews in each group. Patients and GPs chose the date and the place of the appointment, which could occur in a GP surgery, at the



1  
2  
3 informant's home, or in a public place. The interviews were conducted by LB for  
4 patients and by AC for GPs, who had been trained beforehand. They lasted a mean  
5  
6  
7 36 minutes for patients and a mean 22 minutes for GPs.  
8  
9

## 10 11 12 **Data analysis**

13  
14  
15 Interviews were audio-recorded after obtaining oral consent from participants, and  
16 manually transcribed anonymously. They were then analysed using NVivo  
17 software.<sup>18</sup> Our interpretive approach of GPs' and patients' perceptions (including  
18 experiences and views) was essentially inductive and the interview guides were  
19 modified according to the analysis of the first interviews. Data transcription, data  
20 entry, and data coding were performed on a continuous basis during the data  
21 collection process, which allowed emerging themes to be further explored in later  
22 interviews. Thematic analysis was performed as the data were collected. Data were  
23 independently coded by two authors (AC, LB); the codes were later discussed with  
24 another author (LL) in order to provide internal triangulation. Regular meetings were  
25 held to reflect on the analytical process and to compare and discuss findings in order  
26 to reach consensus on recurrent themes. According to the grounded theory  
27 approach, data analysis was based on the constant comparison process and  
28 followed three distinct stages: open, axial, and selective coding. The open coding of  
29 the transcripts identified the different concepts emerging from the data. Then, the  
30 codes were grouped into subcategories according to axial coding. Finally, selective  
31 codes emerged from the prioritization of the axial codes into overarching categories,  
32 which included the status of the DXP, the characteristics of its withdrawal, and the  
33 influence of past events.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Patient and Public Involvement

The development of the research question was informed by the clinical experience of two of the authors (LL and FA) in managing patients taking DXP. Some patients recruited other patients among their relations.

## RESULTS

Thirteen GPs and 13 patients were interviewed until data saturation was reached (i.e. when no new significant concepts emerged) (Table 1). The main themes identified from data analysis were: the DXP, its withdrawal (reasons, conditions, impact), and analgesic risk management.

### DXP: a popular drug

Among step 2 analgesics, DXP was commonly used, sometimes without having previously tried a step 1 analgesic. DXP was mainly prescribed for recurrent musculoskeletal pain, such as low back pain, and for various pains including traumatic pain, menstrual pain, headache, and toothache.

*GP05: "Propofan<sup>®</sup> [DXP-paracetamol-caffeine], Diantalvic<sup>®</sup> [DXP-paracetamol], we gave plenty of them, you know."*

*Patient (P) 12: "I was taking it, I mean, like you could take a Doliprane<sup>®</sup> [paracetamol]."*

1  
2  
3 The risk-benefit ratio for DXP seemed very positive for GPs and patients. First, both  
4 groups considered DXP to be equally or more effective than the other step 2  
5 analgesics, and sometimes miraculous. Second, DXP was reported to be better  
6 tolerated than other step 2 analgesics, which were frequently associated with nausea  
7 and vertigo (e.g. tramadol, codeine), or constipation and drowsiness (codeine). DXP  
8 was therefore popular among patients and GPs. Some patients were extraordinarily  
9 attached to it and sometimes used it off-label.  
10  
11  
12  
13  
14  
15  
16

17  
18 *P08: "It was even more like my, my blessed bread."*

19  
20 *GP12: "The dextropropoxyphene, from my past experience, had a tolerance that*  
21 *was close to perfect."*  
22  
23

24  
25 *M04: "For active patients having problems, it was something miraculous, which*  
26 *allowed us to often avoid sick leave."*  
27  
28

29  
30 *P01: "I was dependant, not to say, how to say, I could not go without it."*  
31  
32

33 Patients also used various strategies to relieve their pain in addition to DXP:  
34 physiotherapy, joint injections, use of lumbar belt or orthopaedic soles, weight loss,  
35 psychotherapy, or alternative medicines such as osteopathy, homeopathy, and  
36 acupuncture.  
37  
38  
39  
40

41  
42 *P07: "When I was in crisis, well, the first two days I only took the drugs because*  
43 *the physiotherapist couldn't touch me. Then, sometimes, the physiotherapist, he*  
44 *could start the therapy. Then, I reduced the Diantalvic® [DXP-paracetamol]."*  
45  
46  
47  
48  
49  
50  
51

## 52 **Misunderstanding and disagreement regarding DXP withdrawal**

53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Overall, both patients and GPs misunderstood the reasons for the withdrawal. They  
4 partly understood that it was due to potentially serious effects observed in other  
5 countries, especially in cases of misuse (i.e. addiction, suicide attempts) and for  
6 different terms of use (packaging, dosage). Few were aware that DXP efficacy was  
7 not well-assessed.  
8  
9  
10  
11  
12

13  
14 *GP02: "I believe there were issues in some other countries with different doses,*  
15 *issues that I haven't checked in depth, it might have been a mistake by the way."*  
16  
17

18  
19 *P08: "I had heard on the television that they said it had been removed in England,*  
20 *because of too many suicides."*  
21  
22  
23

24 Other than those who had been informed of the risks associated with DXP a long  
25 time ago through reading a professional journal, many GPs considered the  
26 arguments for the DXP withdrawal excessive. For most patients, the withdrawal was  
27 not justified because they thought they were getting many benefits from the DXP and  
28 were not concerned by the risks. Several GPs and patients highlighted  
29 inconsistencies between the DXP withdrawal and the maintenance of other drugs on  
30 the market.  
31  
32  
33  
34  
35  
36  
37  
38  
39

40 *GP06: "But we already had the thought because we read (the journal) Prescrire,*  
41 *which warned a lot against this kind of product at that time."*  
42  
43

44 *GP08: "I would have liked to know the rate, the number of people who have*  
45 *indeed had issues with that drug. Because if someone tells me, but that would*  
46 *make me fall off my chair, it's 15 to 20%, I'd say it was worth it. If it is 1 in 100 000,*  
47 *then we have to remove all drugs."*  
48  
49  
50  
51

52  
53 *P12: "But I don't have the feeling that it had disastrous consequences on me, in*  
54 *fact it eased me, in my daily life."*  
55  
56  
57  
58  
59  
60

1  
2  
3 *P01: "I did not understand why this drug was removed. And I have many echoes*  
4 *around me from people who have had the same reaction, who did not*  
5 *understand."*  
6  
7  
8  
9

## 10 11 12 **An unanticipated withdrawal**

13  
14  
15 GPs and patients mainly heard about the DXP withdrawal through mainstream  
16 media. GPs were also informed by the French Medicines Agency, and the patients by  
17 their physicians. Many GPs and patients perceived the DXP withdrawal as a sudden  
18 decision, and some of them regretted that no restrictive measures had been  
19 previously taken. GPs made efforts to prepare and reassure their patients, but  
20 several of them faced difficulties in telling their patients that the drug they had been  
21 taking for years was being removed.  
22  
23  
24  
25  
26  
27  
28  
29

30  
31 *M02: "Well, it is often like that anyway. We are sometimes informed through the*  
32 *press rather than by the authorities."*  
33  
34

35 *P12: "Well it has been a source of stress because I told myself: crap, what am I*  
36 *going to do?"*  
37  
38

39 *GP08: "But there were no preventive measures like: [...] the emergency services*  
40 *would be asked to give less of it [DXP-paracetamol], doctors would be asked to*  
41 *proceed with good judgment, to not give it out like it was Doliprane® [paracetamol],*  
42 *and eventually to use secured prescriptions, why not? I don't know."*  
43  
44  
45  
46  
47  
48

49 GPs had different feelings about the delay between the announcement of the  
50 decision and the withdrawal. Several were troubled that DXP prescription was still  
51 possible during this time although the drug was presented as dangerous. Others  
52 appreciated still being allowed to prescribe it as they had difficulties in finding an  
53  
54  
55  
56  
57

1  
2  
3 alternative. Many patients regularly taking DXP had built up stockpiles of DXP and  
4  
5 used all the tablets available, even after the withdrawal.  
6

7  
8 *GP07: "We get this kind of paradoxical message, a double constraint where on*  
9  
10 *one hand, they suggest that we not prescribe it because it's toxic, and on the other*  
11 *hand, they allow us to prescribe it because it is not yet forbidden. This makes us*  
12 *think that if there was a problem it would be our responsibility."*  
13  
14

15  
16 *GP10: "I thought it was good, this progressive removal, as far as there were still*  
17 *possibilities to prescribe it to people who could not live without it. And it gave us*  
18 *more time to switch to a new drug."*  
19  
20

21  
22 *P08: "Even the day when I heard that they were going to cancel it and stuff, I had*  
23 *stocked up. I stocked as much as I could. And then I kept taking it at least 2 years,*  
24 *yes over 2 years."*  
25  
26  
27  
28

29  
30 The DXP withdrawal was an opportunity for GPs to reassess pain management and  
31  
32 to diversify their prescriptions. DXP was mainly replaced by either a step 2 analgesic  
33  
34 (i.e. codeine, tramadol, opium) or by paracetamol, which was thereafter more often  
35  
36 used by patients as a first-line treatment. In some cases, a non-steroidal anti-  
37  
38 inflammatory drug or morphine was judged necessary. Some GPs easily replaced  
39  
40 DXP with one of the many other treatment options, but other GPs were concerned  
41  
42 about the possible side effects of the remaining opioid analgesics. Patients often felt  
43  
44 that their substitute drug was not as satisfying as DXP.  
45  
46

47  
48 *GP07: "So it helped to step down to regular paracetamol. It helps to do some*  
49 *sorting."*  
50

51  
52 *P05: "I used to tell them, both the pharmacist and the doctor, I said it's not as good*  
53 *as Diantalvic® [DXP-paracetamol]!"*  
54  
55  
56  
57

1  
2  
3 *P11: "I have tried other things, various dosages, etcetera, it has never been*  
4 *equivalent."*  
5  
6  
7  
8  
9

### 10 **DXP withdrawal: a rather bad experience**

11  
12  
13 The withdrawal disrupted the balance found by some patients with DXP, and  
14 sometimes affected their social life, their job, or their mood. From then on, several  
15 patients felt more painful, while recognizing that this may have been due merely to  
16 the progression of their condition. According to GPs, patients were still well-relieved,  
17 but their pain management was more complex, especially because of a poor  
18 tolerance for most alternative drugs. Several GPs mentioned their interest in the  
19 withdrawal in educating their patients on potential adverse drug events.  
20  
21  
22  
23  
24  
25  
26  
27  
28

29 *P01: "It's like a brick, you remove one, then everything collapses."*

30  
31 *P11: "When I completely stopped, there was pain, in the muscles as well as in the*  
32 *joints, which was present but which was not the case before."*  
33  
34

35 *GP12: "Less easy, less comfortable for pain treatment, that's it."*  
36  
37

38 *M03: "It was difficult because, well, we have been forced to switch to the other*  
39 *products available to us, but sometimes with big problems of tolerance."*  
40  
41  
42

43 Both GPs and patients perceived the DXP withdrawal as a very important and large-  
44 scale event. Apart from a few patients who used DXP only occasionally, most of them  
45 remembered the withdrawal as a bad experience and some expressed anger towards  
46 it. No patient reported improvement in his/her health status following DXP  
47 discontinuation. Several of the GPs who had stopped prescribing DXP years earlier  
48 welcomed its withdrawal, as it justified their previous choice. Other GPs, as well as  
49 many patients, regretted it and wished DXP would be marketed again.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 *GP10: "We used to talk about it during parties: CME [continuing medical*  
4 *education], peer groups; it was a pretty important event (laughs). So, we obviously*  
5 *couldn't ignore it."*

6  
7  
8  
9 *P01: "I have literally been.., it hurt me."*

10  
11 *P08: "If it still existed in countries, in other countries, I would go and get some."*

12  
13  
14 *M04: "I have much regretted it and I still regret it."*

15  
16  
17 *P10: "In my mind, there's an important regret, then one can say that it is equivalent*  
18 *to an absence."*

## 24 **The negative influence of past events**

25  
26  
27 GPs reported varying experiences with drug withdrawals: it did not matter to some of  
28 them, while others felt that their therapeutic options had decreased over the years  
29 without their approval.

30  
31  
32  
33  
34 *GP05: "If Ixprim<sup>®</sup> [tramadol-paracetamol] didn't exist, we would do [...] a hot water*  
35 *bottle (laughs)."*

36  
37  
38  
39 *GP04: "We get the feeling of having fewer and fewer things accessible to us to*  
40 *treat patients. Between the market withdrawals, the stock shortages, it's scary."*

41  
42  
43  
44 GPs and patients interpreted the DXP withdrawal as resulting from occult strategies  
45 of the pharmaceutical industry or even the health insurance system. Several court  
46 cases contemporaneous with the DXP withdrawal, and inconsistencies in the drug  
47 market regulations, reinforced their distrust.



1  
2  
3 *GP04: "So I think they are drugs that might have been less used, or might not*  
4 *have been expensive enough, not profitable enough for the pharmaceutical*  
5 *company and which led to its removal."*  
6  
7

8  
9 *P13: "You know, I see that when a drug is prescribed too much, it is removed."*  
10

11 *P03: "I think that because of Mediator<sup>®</sup> [benfluorex], we are more suspicious."*  
12

13 *GP05: "I think that people, they get the feeling that the medical field has betrayed*  
14 *them when a drug gets removed, for sure! Something is given to them, and then*  
15 *they are told that they should no longer take it because it's toxic. It's as if someone*  
16 *tells you that you have been taking poison for 20 years!"*  
17  
18  
19

20  
21  
22 *GP07: "We have seen it with the Mediator<sup>®</sup> [benfluorex] which has been sadly*  
23 *notorious. We knew since 99 that it's shit, it is withdrawn in 2011 or around. I*  
24 *mean that it's a real problem, a real problem. And we have had that several times*  
25 *in a 25-year career."*  
26  
27  
28  
29  
30  
31

32 To summarize, DXP was a popular drug among patients and GPs in France. Its  
33 withdrawal in 2011 was a bad experience for most patients and GPs. Both had  
34 misunderstood or did not agree with the reasons for this decision, and patients  
35 sometimes built up stocks of DXP. They saw more benefits than risks in using DXP,  
36 all the more when they were not aware of the lack of evidence for its efficacy nor for  
37 its risks beyond situations of misuse. In addition, both groups found the alternative  
38 drugs to DXP unsatisfactory, as patients and GPs reported poor tolerance of the  
39 alternative step 2 analgesics and patients felt more painful. Over the same period, a  
40 national court case, following complaints by patients treated earlier by benfluorex, led  
41 to a general distrust of the pharmaceutical industry and healthcare institutions. This  
42 distrust is likely to have blurred the understanding regarding the messages on DXP  
43 withdrawal and contributed to the negative feelings experienced. However, it was a  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 positive experience for some GPs who had been alerted to the poor DXP risk-benefit  
4 ratio well before its withdrawal (Table 2).  
5  
6  
7  
8  
9

## 10 **DISCUSSION**

11  
12 Healthcare professionals' and patients' perception of DXP withdrawal was primarily  
13 based on their experience of the benefits and risks of this drug as compared to other  
14 analgesics. Their perception was also influenced by their poor level of information  
15 and their distrust of the pharmaceutical industry and healthcare institutions. The  
16 importance of the clinical experience of the physician in the decision to prescribe  
17 DXP instead of paracetamol or aspirin has already been reported well before its  
18 withdrawal.<sup>19</sup> Although as many as 462 identified medicinal products have been  
19 withdrawn from the market worldwide between 1953 and 2013,<sup>20</sup> including 47  
20 analgesic medications between 1965 and 2011,<sup>21</sup> we were not able to identify any  
21 previous qualitative or quantitative study on the perception of healthcare  
22 professionals or patients to these withdrawals in any country. A few studies have,  
23 however, examined the impact of drug safety warning on parental or provider  
24 perceptions.<sup>22</sup> Limited quantitative data suggest that physicians disagreed with  
25 warnings from the Food and Drug Administration (FDA) on the use of droperidol<sup>23</sup> or  
26 antiepileptic drugs<sup>24</sup> as they felt that, according to their personal experience, there  
27 was no other drug with greater efficacy or improved safety profile. One study showed  
28 that parents disapproved of the FDA warning for over-the-counter cough and cold  
29 medications since they disagreed that they were dangerous and still believed they  
30 relieved symptoms.<sup>25</sup> These studies did not explore the influence of the  
31 communication modalities nor the (dis)trust of the pharmaceutical industry and  
32 healthcare institutions on the perceptions of the healthcare professionals and the  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 patients. Our findings therefore remain to be confirmed in future withdrawals of  
4  
5 popular drugs.  
6

7  
8 GPs and patients did not understand the DXP withdrawal decision, as their  
9  
10 perception of the risk-benefit ratio differed from the health authorities' evaluation.  
11  
12 Benefits of painkillers are especially difficult to grasp by patients, and even by GPs,  
13  
14 because of their poor pharmacological assessment and the importance of the  
15  
16 placebo effect. There was indeed no strong evidence to support the important  
17  
18 benefits experienced by patients using DXP.<sup>2,3</sup> As with many other old drugs, the  
19  
20 efficacy of DXP had been poorly assessed, as well as for paracetamol.<sup>26</sup> Patients  
21  
22 treated with DXP may have felt a benefit due to the placebo effect, which is  
23  
24 particularly frequent and intense with painkillers. It can relieve pain in 15 to 52% of  
25  
26 patients,<sup>27</sup> and may even equal an injection of morphine in postoperative pain.<sup>28</sup>  
27  
28 Serious risks are also difficult to consider for GPs and even more so for patients,  
29  
30 because they are rare, as illustrated by the number of deaths attributed to DXP in  
31  
32 France, which has been estimated to be around 1.5 case per 1000 private GPs in  
33  
34 2009.<sup>9</sup>  
35  
36

37  
38 Many patients and GPs expressed distrust towards both healthcare institutions and  
39  
40 the pharmaceutical industry. A survey about the French population's relationship with  
41  
42 medicines found that only one in two people gives some credibility to information  
43  
44 from the pharmaceutical industry and from the health authorities.<sup>29</sup> Several patients  
45  
46 and GPs have been struck by the French benfluorex case, which went public during  
47  
48 the same period as the DXP withdrawal.<sup>30</sup> Benfluorex was popular in France and  
49  
50 largely prescribed off-label as an appetite suppressant for more than thirty years until  
51  
52 it was discovered that it could cause valvular heart disease and pulmonary arterial  
53  
54 hypertension. As a consequence, many patients treated with this drug have sued the  
55  
56  
57  
58  
59  
60

1  
2  
3 pharmaceutical company marketing the drug and the French health authorities.<sup>31</sup>

4  
5 This case, considered in France to be a national scandal, may have altered  
6  
7 confidence in the drug management system and made the acceptance of DXP  
8  
9 withdrawal difficult for patients and GPs.

10  
11  
12 Some GPs and most patients were unsatisfied with alternative drugs to DXP for three  
13  
14 reasons. First, many patients felt their pain increased after DXP withdrawal. Such  
15  
16 relapse was not observed in a French cohort study, but it was restricted to elderly  
17  
18 people.<sup>15</sup> Second, many patients also did not tolerate other step 2 analgesics. This  
19  
20 observation is only partially consistent with French pharmacovigilance data, which  
21  
22 found that the rate of adverse drug reactions reported for tramadol, but not for  
23  
24 codeine, was higher than for DXP.<sup>32</sup> Tolerance issues may help explain why patients  
25  
26 largely turned to paracetamol,<sup>33</sup> which could also contribute to relapsing pain. Finally,  
27  
28 patients' dissatisfaction might also be due to DXP addiction. Indeed, behaviour close  
29  
30 to addiction, such as stockpiling, fear of running out, off-label use, or searching for  
31  
32 backdoor procurement, were reported by interviewed patients. Such misuse could  
33  
34 pertain to opioid addiction or even to pseudo-addiction, which is a controversial  
35  
36 syndrome resulting from inadequate pain management.<sup>34,35</sup> This is of note as  
37  
38 withdrawal from the market represented an imposed deprescription, which could  
39  
40 sometimes result in withdrawal syndrome, as observed with opioids or  
41  
42 benzodiazepines.<sup>36</sup>

### 43 44 45 46 47 48 49 **Strengths and weaknesses**

50  
51 The principal strength of the study is that it explored and compared the views of both  
52  
53 patients and GPs. Furthermore, the paper conforms to the standards for reporting  
54  
55 qualitative research.<sup>37</sup> A potential limitation is that preconceptions from the  
56  
57  
58  
59  
60

1  
2  
3 investigators may have influenced the findings. However, the two authors who  
4 performed interviews and primary analyses were medical interns (AC and LB), who  
5 had not been exposed to the DXP withdrawal. Conversely, the clinical experience of  
6 two authors (LL and FA) was useful to develop the interview guides. Another  
7 limitation is that, although interviewed patients and GPs had diverse demographics  
8 and medical activities, the study design could have fostered the recruitment of  
9 individuals particularly concerned by the DXP withdrawal and led to an under-  
10 representation of the most neutral opinions of this event. However, various opinions  
11 and experiences were collected from both groups until reaching saturation. Due to  
12 the 3 to 5-year interval between the withdrawal and the interviews, memory bias  
13 cannot be excluded but this is likely to be limited as the studied event involved more  
14 the emotional than the factual memory of patients and GPs.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 **Implications for future withdrawals**

32  
33  
34 In cases of future warnings on drug safety (within the framework of the risk  
35 management plan for new or recently marketed drugs), national and European health  
36 authorities should start collecting prospective data well before the withdrawal  
37 decision and continue the monitoring thereafter, including through qualitative studies.  
38 Such prospective monitoring is needed to assess the pharmacoepidemiological  
39 impact of drug withdrawal, including the use of alternative drugs and strategies, and  
40 ultimately to validate the withdrawal decision. Additionally, appropriately informing  
41 healthcare professionals and the general public at each stage of the withdrawal  
42 process (i.e. warning, withdrawal decision and assessment) would ease acceptance  
43 of the decision and reinforce trust in the drug management system (Figure 1). In  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 addition, and before any safety warnings, an assessment of every blockbuster drug  
4 through randomized mega-trials should be considered if not available.<sup>38</sup>  
5  
6  
7  
8  
9  
10  
11  
12

### 13 **Acknowledgments**

14  
15  
16 The authors would like to thank all patients and GPs who have been interviewed in  
17 the study, the Regional Union of Healthcare Professionals for its logistical support,  
18 and Pr Behrouz Kassai Koupai for the discussions regarding the results. They are  
19 also grateful to the College Lyonnais des Généralistes Enseignants (CLGE) and the  
20 Hospices Civils de Lyon for funding language editing.  
21  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **Contributors**

31  
32  
33 LL, AC, and LB conceived and designed the study, and they elaborated the interview  
34 guides. AC and LB conducted the interviews and the analysis, under the supervision  
35 of LL. EVG and FA provided clinical and pharmacoepidemiological context and  
36 contributed to the interpretation of the findings. LL, AC, and LB drafted the  
37 manuscript. All authors reviewed and approved the final version of the article.  
38  
39  
40  
41  
42  
43  
44  
45  
46

### 47 **Funding**

48  
49  
50 This research received no specific grant from any funding agency in the public,  
51 commercial or not-for-profit sectors.  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Competing interests

None declared.

### Ethics approval

The study was approved by the Ethics Committee of the University of Lyon 1 (Lyon, France) and the French national agency for national data protection (CNIL, n°19162013).

### Data sharing statement

The data analysis tree is available on request from the corresponding author.

## References

1. Prescrire rédaction. Dextropropoxyphène + paracétamol : toujours là... malgré les risques. *Rev Prescrire* 2007;27:735.
2. Li Wan Po A, Zhang W. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997;315:1565–71.
3. Moore RA, Collins SL, Edwards J, et al. Single dose oral dextropropoxyphene, alone and with paracetamol (paracetamol), for postoperative pain. *Cochrane Database Syst Rev* 2000:CD001440.
4. Young RJ. Dextropropoxyphene overdose. Pharmacological considerations and clinical management. *Drugs* 1983;26:70-9.
5. Afshari R, Maxwell S, Dawson A, et al. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *Clin Toxicol* 2005;43:255–9.
6. Flanagan R, Johnston A, White AS, et al. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989;28:463–9.
7. Young RJ. Dextropropoxyphene overdose. Pharmacological considerations and clinical management. *Drugs* 1983;26:70–9.
8. European Medicines Agency. Press release: European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines. London; 2009.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2009/11/WC500010365.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010365.pdf) (Accessed 23 October 2017).



1  
2  
3 9. Agence Française de Sécurité Sanitaire des Produits de Santé. Médicaments  
4 contenant l'association dextropropoxyphène/paracétamol : Recommandation de  
5 l'EMA de retrait de ces médicaments à la suite de l'évaluation européenne et avis  
6 divergent de l'Afssaps. 2009.

7  
8  
9  
10  
11 <http://www.ansm.sante.fr/content/download/20487/248676/> (Accessed 23 October  
12 2017).

13  
14  
15  
16 10. Food and Drugs Administration. Recommendation on a Regulatory Decision for  
17 Propoxyphene-containing Products. 2010.

18  
19  
20  
21 [http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationfo](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf)  
22 [rPatientsandProviders/UCM234349.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf) (Accessed 23 October 2017).

23  
24  
25  
26 11. Agence Française de Sécurité Sanitaire des Produits de Santé. Questions /  
27 Réponses. Retrait des médicaments contenant l'association  
28 dextropropoxyphène/paracétamol (Di-Antalvic<sup>®</sup> et ses génériques) ou  
29 dextropropoxyphène/paracétamol/caféine (Propofan<sup>®</sup> et ses génériques). 2009.

30  
31  
32  
33 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/19ca2c73609691747d](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf)  
34 [72c18b65dfc21a.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf) (Accessed 23 October 2017).

35  
36  
37  
38  
39 12. Handley S, Flanagan B. Drugs and other chemicals involved in fatal poisoning in  
40 England and Wales during 2000-2011. *Clin Toxicol* 2014;52:1-12.

41  
42  
43  
44 13. Agence nationale de sécurité du médicament et des produits de santé. Compte  
45 rendu de séance. Comité technique des Centres d'Evaluation et d'Information sur la  
46 Pharmacodépendance CT022015023. Séance du 19 mars 2015. 2015.

47  
48  
49  
50  
51 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e9328677e7a48b7222](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf)  
52 [74b90159035d1b.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf) (Accessed 23 October 2017).

1  
2  
3 14. AFSSAPS. Mise au point. Prise en charge des douleurs de l'adulte modérées à  
4 intenses. Recommandations après le retrait des associations

5 dextropropoxyphène/paracétamol et dextropropoxyphène/paracétamol/caféine.

6  
7  
8  
9 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/a6497f74fc2f18e8db00](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db00)  
10  
11 [22973f9327e1.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db00) (Accessed 23 October 2017).

12  
13  
14 15. Ottewell L, Walker DJ. Co-proxamol: where have all the patients gone?

15  
16 *Rheumatology* 2008;47:375.

17  
18  
19 16. Becquemont L, Delespierre T, Bauduceau B, et al. Consequences of

20 dextropropoxyphene market withdrawal in elderly patients with chronic pain. *Eur J*

21  
22 *Clin Pharmacol* 2014;70:1237-42.

23  
24  
25 17. Strauss A, Corbin J. Basics of qualitative research: Techniques and procedures

26 for developing grounded theory. Newbury Park: Sage publications, 2015.

27  
28  
29 18. NVivo qualitative data analysis software, version 11. Doncaster: QSR

30 International Pty Ltd., 2014.

31  
32  
33 19. Schwartz RK, Soumerai SB, Avorn J. Physician motivations for nonscientific drug

34 prescribing. *Soc Sci Med* 1989;28:577-82.

35  
36  
37 20. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462

38 medicinal products because of adverse drug reactions: a systematic review of the

39  
40 world literature. *BMC Med* 2016;14:10.

41  
42  
43 21. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of analgesic

44 medications because of adverse drug reactions: a systematic review. *Expert Opin*

45  
46  
47 *Drug Saf* 2018;17:63-72.

- 1  
2  
3 22. Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, Garfield  
4 CF, Alexander GC. Impact of FDA drug risk communications on health care utilization  
5 and health behaviors: a systematic review. *Med Care* 2012;50:466-78.  
6  
7  
8  
9  
10 23. Richards JR, Weiss SJ, Bretz SW, Schneir AB, Rinetti D, Derlet RW. The effects  
11 of the FDA warning on the use of droperidol by u.s. emergency physicians. *Cal J*  
12 *Emerg Med.* 2003;4:3-9.  
13  
14  
15  
16  
17 24. Shneker BF, Cios JS, Elliott JO. Suicidality, depression screening, and  
18 antiepileptic drugs: reaction to the FDA alert. *Neurology* 2009;72:987-91.  
19  
20  
21  
22 25. Garbutt JM, Sterkel R, Banister C, Walbert C, Strunk RC. Physician and parent  
23 response to the FDA advisory about use of over-the-counter cough and cold  
24 medications. *Acad Pediatr* 2010;10:64-9.  
25  
26  
27  
28  
29 26. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol  
30 for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised  
31 placebo controlled trials. *BMJ* 2015;350:h1225.  
32  
33  
34  
35  
36 27. Beecher HK. The powerful placebo. *JAMA* 1955;159:1602-6.  
37  
38  
39 28. Levine JD, Gordon NC, Smith R, et al. Analgesic responses to morphine and  
40 placebo in individuals with postoperative pain. *Pain* 1981;10:379-89.  
41  
42  
43  
44 29. Ipsos. Observatoire sociétal du médicament 2015 : 5ème vague d'étude menée  
45 par Ipsos pour le Leem sur le rapport des Français aux médicaments.  
46 <http://www.leem.org/sites/default/files/Observatoire-sociétal-du-Médicament2015.pdf>  
47  
48  
49  
50 (Accessed 23 October 2017).  
51  
52  
53 30. Mullard A. Mediator scandal rocks French medical community. *Lancet*  
54 2011;377:890-2.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 31. Menard J. Benfluorex: analysis of a drug-related public health crisis. *Diabetes*  
4  
5 *Metab* 2011 Jun;37:169-75.  
6  
7  
8 32. Tavassoli N, Lapeyre-Mestre M, Sommet A, et al. Reporting rate of adverse drug  
9  
10 reactions to the French pharmacovigilance system with three step 2 analgesic drugs:  
11  
12 dextropropoxyphene, tramadol and codeine (in combination with paracetamol). *Br J*  
13  
14 *Clin Pharmacol* 2009;68:422–6.  
15  
16  
17 33. Gaubert S, Vié M, Damase-Michel C, et al. Dextropropoxyphene withdrawal from  
18  
19 a French university hospital: impact on analgesic drug consumption. *Fundam Clin*  
20  
21 *Pharmacol* 2009;23:247–52.  
22  
23  
24 34. Greene MS, Chambers RA. Pseudoaddiction: Fact or Fiction? An Investigation of  
25  
26 the Medical Literature. *Curr Addict Rep* 2015;2:310–7.  
27  
28  
29 35. Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome.  
30  
31 *Pain* 1989;36:363–6.  
32  
33  
34 36. Le Couteur D, Gnjidic D, McLachlan A. Deprescribing. *Aust Prescr* 2011;34:182-  
35  
36 5.  
37  
38  
39 37. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative  
40  
41 research: a synthesis of recommendations. *Acad Med* 2014; 89:1245–51.  
42  
43  
44 38. Ioannidis JPA. Mega-trials for blockbusters. *JAMA* 2013;309:239–40.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1** Characteristics of interviewed general practitioners (GPs) and patients

Characteristics		GPs (n=13)	Patients (n=13)
Gender	Female	5	8
	Male	8	5
Age (years)	25-34	2	2
	35-44	1	0
	45-54	3	3
	55-64	7	5
	65-74	0	3
Working/living area	Urban	5	5
	Semi-rural	4	6
	Rural	4	2
GP trainer	Yes	9	
	No	4	
Practice type	Solo	1	
	Group	12	
Specialisation	Sports medicine/osteopathy	3	
	Homeopathy/mesotherapy	1	
	Medical expertise	1	
	Addictology	1	

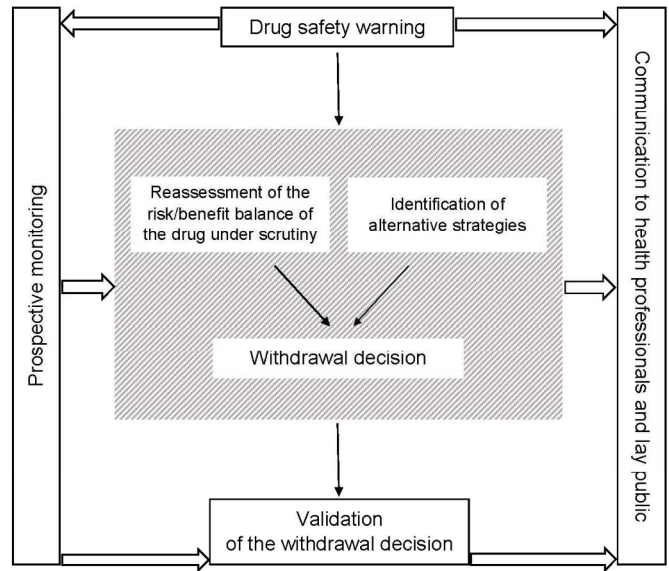
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

<b>Table 2</b> Summary of the main perceptions of general practitioners and patients regarding DXP withdrawal		
	General practitioners	Patients
DXP medication	Common prescription and use, high risk-benefit ratio, risk of dependence	Valued but non-exclusive strategy
Reasons for withdrawal	Misunderstanding, trend towards overestimation of benefits and underestimation of risks Some GPs earlier informed through a professional journal	
Conditions of withdrawal	Information through mainstream media, lack of anticipation Difficulties to inform patients Opportunity to reassess pain management, but concern about other analgesics	DXP stockpiling
Withdrawal impact	Rather bad experience due to poor tolerance of other analgesics Complex pain management, but opportunity to educate patients	Poor acceptance
Influence of past events	Distrust of the pharmaceutical industry and healthcare institutions Reduction of drugs available	

1  
2  
3  
4  
5 **Figure 1** Proposed model for drug withdrawal decisions  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1

Figure 1 Proposed model for drug withdrawal decisions  
139x198mm (300 x 300 DPI)



## Standards for Reporting Qualitative Research (SRQR)\*

<http://www.equator-network.org/reporting-guidelines/srqr/>

### Title and abstract

<b>Title</b> - 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
<b>Abstract</b> - 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

<b>Problem formulation</b> - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	YES
<b>Purpose or research question</b> - Purpose of the study and specific objectives or questions	YES

### Methods

<b>Qualitative approach and research paradigm</b> - 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
<b>Researcher characteristics and reflexivity</b> - 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
<b>Context</b> - Setting/site and salient contextual factors; rationale**	YES
<b>Sampling strategy</b> - 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
<b>Ethical issues pertaining to human subjects</b> - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	YES
<b>Data collection methods</b> - 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
<b>Data collection instruments and technologies</b> - 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
<b>Units of study</b> - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	YES
<b>Data processing</b> - 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
<b>Data analysis</b> - 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
<b>Techniques to enhance trustworthiness</b> - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	YES

### Results/findings

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

### Discussion

<b>Integration with prior work, implications, transferability, and contribution(s) to the field</b> - 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
<b>Limitations</b> - Trustworthiness and limitations of findings	YES

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Other**

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

For peer review only

# BMJ Open

## The perceptions of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021582.R2
Article Type:	Research
Date Submitted by the Author:	04-Jul-2018
Complete List of Authors:	Combiér, Aurélie; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale Bon, Lucile; Université Claude Bernard Lyon 1, Collège universitaire de médecine générale VAN GANSE, Eric; Pharmacoépidémiologie CHU-Lyon, Faculté d'Odontologie, Université Claude Bernard Aubrun, Frédéric; Université de Lyon, HESPER EA 7425; Hospices civils de Lyon, Department of Anesthesiology and Critical Care Letrilliart, Laurent; Département de médecine générale, Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne; E.A. 4129 « Santé, Individu, Société », Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France
<b>Primary Subject Heading</b>:	Health services research
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice
Keywords:	dextropropoxyphene, drug withdrawal, general practitioner, patient, qualitative study

SCHOLARONE™  
Manuscripts

# The perceptions of French general practitioners and patients regarding dextropropoxyphene withdrawal: A qualitative study

Aurélie Combiér,<sup>\*1</sup>

Lucile Bon L,<sup>\*1</sup>

Eric Van Ganse,<sup>2,3</sup>

Frédéric Aubrun,<sup>3,4</sup>

Laurent Letrilliart,<sup>1,3</sup>

<sup>1</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, Collège universitaire de médecine générale, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>2</sup>Université Claude-Bernard-Lyon 1, UMR CNRS 5558, faculté d'odontologie, Lyon, France; Hospices Civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, service de pneumologie, Lyon, France;

<sup>3</sup>Univ. Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Étienne, France;

<sup>4</sup>Department of Anesthesiology and Critical Care, Université Claude-Bernard-Lyon 1, Hospices Civils de Lyon, CHU de Lyon, groupe hospitalier Nord-hôpital de la Croix-Rousse, Lyon, France.

\*Aurélie Combiér and Lucile Bon equally contributed to the study.

**Corresponding author:** Pr Laurent Letrilliart, Université Claude-Bernard-Lyon 1, Collège universitaire de médecine générale (CUMG), 8 avenue Rockefeller, 69373 Lyon cedex 08, France. Tel: +33 6 24 17 87 76; Fax: +33 4 78 93 22 97. E-mail:

[laurent.letrilliart@univ-lyon1.fr](mailto:laurent.letrilliart@univ-lyon1.fr)

1  
2  
3  
4  
5 **Word count: 4173**  
6  
7

8  
9 **Key words:** dextropropoxyphene; drug withdrawal; general practitioner; patient;  
10  
11 qualitative study.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Abstract

**Objectives** Dextropropoxyphene (DXP), a step 2 analgesic commonly prescribed in France, was withdrawn from the French market in 2011 following a European decision due to its poor risk-benefit ratio. The purpose of this study was to explore the perceptions of French general practitioners (GPs) and patients regarding DXP withdrawal.

**Design** Qualitative study based on 26 individual semi-structured interviews.

**Setting** Rhône-Alpes region of France.

**Participants** Thirteen patients and 13 general practitioners.

**Methods** Interviews were conducted to collect data concerning the status of DXP, its efficacy and safety, the conditions of DXP's withdrawal, and its potential impact. The transcripts were analysed using NVivo software.

**Results** DXP was a very popular drug among both patients and GPs. Its withdrawal was a bad experience for patients and part of GPs; these misunderstood the reasons for its withdrawal and several contested them. They generally recognized more benefits than risks of DXP and considered alternative drugs unsatisfactory. In the same period, a French court case regarding another drug led to distrust towards the pharmaceutical industry and healthcare institutions, which contributed to the negative feelings reported. However, the experience was positive for the GPs who had been alerted to the poor DXP risk-benefit ratio well before its withdrawal.

**Conclusions** Apart from physicians who were previously informed of its poor risk-benefit ratio, DXP withdrawal was not a good experience for patients and GPs. Better anticipation by the health authorities, in terms of pharmacoepidemiological surveillance and communication to healthcare professionals as well as the general public, should provide better acceptance of such a decision in the future.

### Strengths and limitations of this study

- To our knowledge, this study is the first to have explored and compared the views of both patients and GPs regarding DXP withdrawal.
- The collected data were independently coded by two authors, the codes being secondarily discussed with another author, in order to provide internal triangulation.
- Although interviewed patients and GPs had diverse demographics and medical activities, the study design could have led to the recruitment of individuals particularly concerned by the DXP withdrawal and to an under-representation of the most neutral opinions of this event.
- Due to the time lag between the withdrawal and the interviews (3 to 5 years), memory bias cannot be excluded.

## BACKGROUND

In 2006, the combination of paracetamol and dextropropoxyphene (DXP, a step 2 analgesic) was the second-most prescribed analgesic in France (approximately 48 million boxes).<sup>1</sup> However, the risk-benefit ratio of DXP had been controversial for many years. On the one hand, the efficacy of the DXP-paracetamol combination had not been widely assessed for chronic pain, and there was no strong evidence that it provided better analgesia than other step 1 or step 2 analgesics for postoperative pain, arthritis, and musculoskeletal pain.<sup>2,3</sup> On the other hand, in cases of overdose, DXP exposed patients to the risk of respiratory depression, cardiac conduction disorders, and death.<sup>4,5</sup> DXP toxicity is mainly due to its long half-life (15 to 37 hours),<sup>6</sup> and it can be increased by concomitant use of alcohol or sedative drugs.<sup>7</sup> As a result of many deaths due to voluntary or involuntary intoxications in Sweden (200 per year per 9 million inhabitants) and the United Kingdom (UK, 300 to 400 per year per 60 million inhabitants), the health authorities in these countries took restrictive measures and finally withdrew DXP from their markets in 2005 and 2007, respectively. Consequently, the European Medicines Agency (EMA) reassessed the DXP risk-benefit ratio and in 2009 recommended its withdrawal from all European member states.<sup>8</sup> In France, mortality from DXP intoxications was estimated to be around 65 deaths per year per 65 million inhabitants.<sup>9</sup> The French Medicines Agency was initially reluctant to withdraw DXP from the national market considering that the risk to public health was lower than in the UK or Sweden, and fearing a higher toxicity in cases of substitution with tramadol.<sup>9</sup> In 2010, a new study conducted in the United States of America (USA) found that DXP could cause fatal heart rhythm disorders even at the therapeutic doses allowed in this country.<sup>10</sup> Based on these data, the French Medicines Agency finally decided to withdraw DXP in March 2011.<sup>11</sup>



1  
2  
3 The before/after evaluation performed in the UK found that the overall number of  
4 deaths from poisoning did not decrease and that the number of deaths involving  
5 codeine and tramadol increased.<sup>12</sup> In France, the investigation of deaths due to  
6 analgesics was initiated in 2013, but it did not allow for the comparison of changes in  
7 the number of deaths attributable to the various analgesics due to a lack of  
8 consistent data prior to the withdrawal.<sup>13</sup> Indeed, DXP and alternative analgesics  
9 were not specifically monitored before the European warning because no risk had  
10 been identified in France during DXP post-marketing surveillance. Apart from the  
11 surveillance process, there was probably insufficient communication of the reasons  
12 for the withdrawal, all the more important given that DXP was a popular drug among  
13 patients and GPs. In particular, it was very much focused on DXP risks and on  
14 recommendations for DXP substitution,<sup>14</sup> without emphasizing the lack of evidence  
15 for DXP efficacy.

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31 Many patients in England and Wales have not found a satisfactory alternative to DXP  
32 after its withdrawal.<sup>15</sup> The popularity of DXP and its controversial withdrawal in  
33 France suggest that this may have repercussions for pain management in primary  
34 care. A quantitative study did, however, find that there was no effect on pain intensity  
35 and daily activities in elderly patients in France,<sup>16</sup> but the experience of this  
36 withdrawal by GPs and by other patients has not been studied in France, nor  
37 internationally. The purpose of this study was therefore to comparatively explore the  
38 perceptions of French GPs and patients regarding DXP withdrawal.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## **METHODS**

We conducted a qualitative study based on individual semi-structured interviews and according to the grounded-theory approach.<sup>17</sup> We were not aware of an established theory supporting the perceptions of the event under study. After a test phase, the interviews were held between April 2014 and March 2016.

### **Sampling**

We used a purposive sampling procedure for GPs and patients, in order to include participants of various genders, ages and practice settings, and ultimately to collect a wide range of opinions. The GP sample consisted of private GPs from the Rhône-Alpes region of France who had been practicing since at least January 2009. They were recruited via an email sent to the list of GPs of the Regional Union of Healthcare Professionals. The patient sample included adults who were regularly using DXP until its withdrawal. They were recruited in GP surgeries based on posters and flyers, and occasionally by using snowball sampling.

### **Data collection**

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 effectiveness and safety, the conditions of DXP withdrawal, and its potential impact. Patients and GPs chose the date and the place of the appointment, which could occur in a GP surgery, at the informant's home, or in a public place. The interviews were conducted

1  
2  
3 by LB for patients and by AC for GPs, who had been trained beforehand. They lasted  
4  
5 a mean 36 minutes for patients and a mean 22 minutes for GPs.  
6  
7  
8  
9

## 10 **Data analysis**

11  
12  
13 Interviews were audio-recorded after obtaining oral consent from participants, and  
14  
15 manually transcribed anonymously. They were then analysed using NVivo  
16  
17 software.<sup>18</sup> Our interpretive approach of GPs' and patients' perceptions (including  
18  
19 experiences and views) was essentially inductive and the interview guides were  
20  
21 modified according to the analysis of the first interviews. Data transcription, data  
22  
23 entry, and data coding were performed on a continuous basis during the data  
24  
25 collection process, which allowed emerging themes to be further explored in later  
26  
27 interviews. Thematic analysis was performed as the data were collected. Data were  
28  
29 independently coded by two authors (AC, LB); the codes were later discussed with  
30  
31 another author (LL) in order to provide internal triangulation. Regular meetings were  
32  
33 held to reflect on the analytical process and to compare and discuss findings in order  
34  
35 to reach consensus on recurrent themes. According to the grounded theory  
36  
37 approach, data analysis was based on the constant comparison process and  
38  
39 followed three distinct stages: open, axial, and selective coding. The open coding of  
40  
41 the transcripts identified the different concepts emerging from the data. Then, the  
42  
43 codes were grouped into subcategories according to axial coding. Finally, selective  
44  
45 codes emerged from the prioritization of the axial codes into overarching categories,  
46  
47 which included the status of the DXP, the characteristics of its withdrawal, and the  
48  
49 influence of past events.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Patient and Public Involvement

The development of the research question was informed by the clinical experience of two of the authors (LL and FA) in managing patients taking DXP. Some patients recruited other patients among their relations.

## RESULTS

Thirteen GPs and 13 patients were interviewed until data saturation was reached (i.e. when no new significant concepts emerged) (Table 1). The main themes identified from data analysis were: the DXP, its withdrawal (reasons, conditions, impact), and analgesic risk management.

### DXP: a popular drug

Among step 2 analgesics, DXP was commonly used, sometimes without having previously tried a step 1 analgesic. DXP was mainly prescribed for recurrent musculoskeletal pain, such as low back pain, and for various pains including traumatic pain, menstrual pain, headache, and toothache.

*GP05: "Propofan<sup>®</sup> [DXP-paracetamol-caffeine], Diantalvic<sup>®</sup> [DXP-paracetamol], we gave plenty of them, you know."*

*Patient (P) 12: "I was taking it, I mean, like you could take a Doliprane<sup>®</sup> [paracetamol]."*

The risk-benefit ratio for DXP seemed very positive for GPs and patients. First, both groups considered DXP to be equally or more effective than the other step 2 analgesics, and sometimes miraculous. Second, DXP was reported to be better

1  
2  
3 tolerated than other step 2 analgesics, which were frequently associated with nausea  
4 and vertigo (e.g. tramadol, codeine), or constipation and drowsiness (codeine). DXP  
5 was therefore popular among patients and GPs. Some patients were extraordinarily  
6 attached to it and sometimes used it off-label.  
7  
8  
9

10  
11  
12 *P08: "It was even more like my, my blessed bread."*

13  
14 *GP12: "The dextropropoxyphene, from my past experience, had a tolerance that*  
15 *was close to perfect."*

16  
17  
18  
19 *M04: "For active patients having problems, it was something miraculous, which*  
20 *allowed us to often avoid sick leave."*

21  
22  
23  
24 *P01: "I was dependant, not to say, how to say, I could not go without it."*

25  
26  
27 Patients also used various strategies to relieve their pain in addition to DXP:  
28 physiotherapy, joint injections, use of lumbar belt or orthopaedic soles, weight loss,  
29 psychotherapy, or alternative medicines such as osteopathy, homeopathy, and  
30 acupuncture.  
31  
32  
33  
34  
35

36  
37 *P07: "When I was in crisis, well, the first two days I only took the drugs because*  
38 *the physiotherapist couldn't touch me. Then, sometimes, the physiotherapist, he*  
39 *could start the therapy. Then, I reduced the Diantalvic® [DXP-paracetamol]."*  
40  
41  
42  
43  
44  
45

### 46 **Misunderstanding and disagreement regarding DXP withdrawal**

47  
48  
49 Overall, both patients and GPs misunderstood the reasons for the withdrawal. They  
50 partly understood that it was due to potentially serious effects observed in other  
51 countries, especially in cases of misuse (i.e. addiction, suicide attempts) and for  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 different terms of use (packaging, dosage). Few were aware that DXP efficacy was  
4  
5 not well-assessed.

6  
7 *GP02: "I believe there were issues in some other countries with different doses,*  
8 *issues that I haven't checked in depth, it might have been a mistake by the way."*

9  
10  
11  
12 *P08: "I had heard on the television that they said it had been removed in England,*  
13 *because of too many suicides."*

14  
15  
16  
17 Other than those who had been informed of the risks associated with DXP a long  
18  
19 time ago through reading a professional journal, many GPs considered the  
20  
21 arguments for the DXP withdrawal excessive. For most patients, the withdrawal was  
22  
23 not justified because they thought they were getting many benefits from the DXP and  
24  
25 were not concerned by the risks. Several GPs and patients highlighted  
26  
27 inconsistencies between the DXP withdrawal and the maintenance of other drugs on  
28  
29 the market.  
30  
31

32  
33 *GP06: "But we already had the thought because we read [the journal] Prescrire,*  
34 *which warned a lot against this kind of product at that time."*

35  
36  
37 *GP08: "I would have liked to know the rate, the number of people who have*  
38 *indeed had issues with that drug. Because if someone tells me, but that would*  
39 *make me fall off my chair, it's 15 to 20%, I'd say it was worth it. If it is 1 in 100 000,*  
40 *then we have to remove all drugs."*

41  
42  
43  
44 *P12: "But I don't have the feeling that it had disastrous consequences on me, in*  
45 *fact it eased me, in my daily life."*

46  
47  
48  
49  
50  
51 *P01: "I did not understand why this drug was removed. And I have many echoes*  
52 *around me from people who have had the same reaction, who did not*  
53 *understand."*

## An unanticipated withdrawal

GPs and patients mainly heard about the DXP withdrawal through mainstream media. GPs were also informed by the French Medicines Agency, and the patients by their physicians. Many GPs and patients perceived the DXP withdrawal as a sudden decision, and some of them regretted that no restrictive measures had been previously taken. GPs made efforts to prepare and reassure their patients, but several of them faced difficulties in telling their patients that the drug they had been taking for years was being removed.

*M02: "Well, it is often like that anyway. We are sometimes informed through the press rather than by the authorities."*

*P12: "Well it has been a source of stress because I told myself: crap, what am I going to do?"*

*GP08: "But there were no preventive measures like: [...] the emergency services would be asked to give less of it [DXP-paracetamol], doctors would be asked to proceed with good judgment, to not give it out like it was Doliprane® [paracetamol], and eventually to use secured prescriptions, why not? I don't know."*

GPs had different feelings about the delay between the announcement of the decision and the withdrawal. Several were troubled that DXP prescription was still possible during this time although the drug was presented as dangerous. Others appreciated still being allowed to prescribe it as they had difficulties in finding an alternative. Many patients regularly taking DXP had built up stockpiles of DXP and used all the tablets available, even after the withdrawal.

1  
2  
3 *GP07: "We get this kind of paradoxical message, a double constraint where on*  
4 *one hand, they suggest that we not prescribe it because it's toxic, and on the other*  
5 *hand, they allow us to prescribe it because it is not yet forbidden. This makes us*  
6 *think that if there was a problem it would be our responsibility."*

7  
8  
9  
10  
11 *GP10: "I thought it was good, this progressive removal, as far as there were still*  
12 *possibilities to prescribe it to people who could not live without it. And it gave us*  
13 *more time to switch to a new drug."*

14  
15  
16  
17  
18 *P08: "Even the day when I heard that they were going to cancel it and stuff, I had*  
19 *stocked up. I stocked as much as I could. And then I kept taking it at least 2 years,*  
20 *yes over 2 years."*

21  
22  
23  
24  
25 The DXP withdrawal was an opportunity for GPs to reassess pain management and  
26 to diversify their prescriptions. DXP was mainly replaced by either a step 2 analgesic  
27 (i.e. codeine, tramadol, opium) or by paracetamol, which was thereafter more often  
28 used by patients as a first-line treatment. In some cases, a non-steroidal anti-  
29 inflammatory drug or morphine was judged necessary. Some GPs easily replaced  
30 DXP with one of the many other treatment options, but other GPs were concerned  
31 about the possible side effects of the remaining opioid analgesics. Patients often felt  
32 that their substitute drug was not as satisfying as DXP.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 *GP07: "So it helped to step down to regular paracetamol. It helps to do some*  
44 *sorting."*

45  
46  
47 *P05: "I used to tell them, both the pharmacist and the doctor, I said it's not as good*  
48 *as Diantalvic® [DXP-paracetamol]."*

49  
50  
51  
52 *P11: "I have tried other things, various dosages, etcetera, it has never been*  
53 *equivalent."*  
54  
55  
56  
57  
58  
59  
60



## DXP withdrawal: a rather bad experience

The withdrawal disrupted the balance found by some patients with DXP, and sometimes affected their social life, their job, or their mood. From then on, several patients felt more painful, while recognizing that this may have been due merely to the progression of their condition. According to GPs, patients were still well-relieved, but their pain management was more complex, especially because of a poor tolerance for most alternative drugs. Several GPs mentioned their interest in the withdrawal in educating their patients on potential adverse drug events.

*P01: "It's like a brick, you remove one, then everything collapses."*

*P11: "When I completely stopped, there was pain, in the muscles as well as in the joints, which was present but which was not the case before."*

*GP12: "Less easy, less comfortable for pain treatment, that's it."*

*M03: "It was difficult because, well, we have been forced to switch to the other products available to us, but sometimes with big problems of tolerance."*

Both GPs and patients perceived the DXP withdrawal as a very important and large-scale event. Apart from a few patients who used DXP only occasionally, most of them remembered the withdrawal as a bad experience and some expressed anger towards it. No patient reported improvement in his/her health status following DXP discontinuation. Several of the GPs who had stopped prescribing DXP years earlier welcomed its withdrawal, as it justified their previous choice. Other GPs, as well as many patients, regretted it and wished DXP would be marketed again.

1  
2  
3 *GP10: "We used to talk about it during parties: CME [continuing medical*  
4 *education], peer groups; it was a pretty important event (laughs). So, we obviously*  
5 *couldn't ignore it."*

6  
7  
8  
9 *P01: "I have literally been..., it hurt me."*

10  
11 *P08: "If it still existed in countries, in other countries, I would go and get some."*

12  
13  
14 *M04: "I have much regretted it and I still regret it."*

15  
16  
17 *P10: "In my mind, there's an important regret, then one can say that it is equivalent*  
18 *to an absence."*

## 24 **The negative influence of past events**

25  
26  
27 GPs reported varying experiences with drug withdrawals: it did not matter to some of  
28 them, while others felt that their therapeutic options had decreased over the years  
29 without their approval.

30  
31  
32  
33  
34 *GP05: "If Ixprim<sup>®</sup> [tramadol-paracetamol] didn't exist, we would do [...] a hot water*  
35 *bottle (laughs)."*

36  
37  
38  
39 *GP04: "We get the feeling of having fewer and fewer things accessible to us to*  
40 *treat patients. Between the market withdrawals, the stock shortages, it's scary."*

41  
42  
43  
44 GPs and patients interpreted the DXP withdrawal as resulting from occult strategies  
45 of the pharmaceutical industry or even the health insurance system. Several court  
46 cases contemporaneous with the DXP withdrawal, and inconsistencies in the drug  
47 market regulations, reinforced their distrust.

1  
2  
3 *GP04: "So I think they are drugs that might have been less used, or might not*  
4 *have been expensive enough, not profitable enough for the pharmaceutical*  
5 *company and which led to its removal."*

6  
7  
8  
9 *P13: "You know, I see that when a drug is prescribed too much, it is removed."*

10  
11 *P03: "I think that because of Mediator<sup>®</sup> [benfluorex], we are more suspicious."*

12  
13 *GP05: "I think that people, they get the feeling that the medical field has betrayed*  
14 *them when a drug gets removed, for sure! Something is given to them, and then*  
15 *they are told that they should no longer take it because it's toxic. It's as if someone*  
16 *tells you that you have been taking poison for 20 years!"*

17  
18  
19  
20  
21  
22 *GP07: "We have seen it with the Mediator<sup>®</sup> [benfluorex] which has been sadly*  
23 *notorious. We knew since 99 that it's shit, it is withdrawn in 2011 or around. I*  
24 *mean that it's a real problem, a real problem. And we have had that several times*  
25 *in a 25-year career."*

26  
27  
28  
29  
30  
31  
32 To summarize, DXP was a popular drug among patients and GPs in France. Its  
33 withdrawal in 2011 was a bad experience for most patients and GPs. Both had  
34 misunderstood or did not agree with the reasons for this decision, and patients  
35 sometimes built up stocks of DXP. They saw more benefits than risks in using DXP,  
36 all the more when they were not aware of the lack of evidence for its efficacy nor for  
37 its risks beyond situations of misuse. In addition, both groups found the alternative  
38 drugs to DXP unsatisfactory, as patients and GPs reported poor tolerance of the  
39 alternative step 2 analgesics and patients felt more painful. Over the same period, a  
40 national court case, following complaints by patients treated earlier by benfluorex, led  
41 to a general distrust of the pharmaceutical industry and healthcare institutions. This  
42 distrust is likely to have blurred the understanding regarding the messages on DXP  
43 withdrawal and contributed to the negative feelings experienced. However, it was a  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 positive experience for some GPs who had been alerted to the poor DXP risk-benefit  
4  
5 ratio well before its withdrawal (Table 2).  
6  
7  
8  
9

## 10 **DISCUSSION**

11  
12  
13 Healthcare professionals' and patients' perception of DXP withdrawal was primarily  
14 based on their experience of the benefits and risks of this drug as compared to other  
15 analgesics. Their perception was also influenced by their poor level of information  
16 and their distrust of the pharmaceutical industry and healthcare institutions. The  
17 importance of the clinical experience of the physician in the decision to prescribe  
18 DXP instead of paracetamol or aspirin has already been reported well before its  
19 withdrawal.<sup>19</sup> Although as many as 462 identified medicinal products have been  
20 withdrawn from the market worldwide between 1953 and 2013,<sup>20</sup> including 47  
21 analgesic medications between 1965 and 2011,<sup>21</sup> we were not able to identify any  
22 previous qualitative or quantitative study on the perception of healthcare  
23 professionals or patients to these withdrawals in any country. A few studies have,  
24 however, examined the impact of drug safety warning on parental or provider  
25 perceptions.<sup>22</sup> Limited quantitative data suggest that physicians disagreed with  
26 warnings from the Food and Drug Administration (FDA) on the use of droperidol<sup>23</sup> or  
27 antiepileptic drugs<sup>24</sup> as they felt that, according to their personal experience, there  
28 was no other drug with greater efficacy or improved safety profile. One study showed  
29 that parents disapproved of the FDA warning for over-the-counter cough and cold  
30 medications since they disagreed that they were dangerous and still believed they  
31 relieved symptoms.<sup>25</sup> These studies did not explore the influence of the  
32 communication modalities nor the (dis)trust of the pharmaceutical industry and  
33 healthcare institutions on the perceptions of the healthcare professionals and the  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 patients. Our findings therefore remain to be confirmed in future withdrawals of  
4  
5 popular drugs.

6  
7 GPs and patients did not understand the DXP withdrawal decision, as their  
8  
9 perception of the risk-benefit ratio differed from the health authorities' evaluation.  
10  
11 Benefits of painkillers are especially difficult to grasp by patients, and even by GPs,  
12  
13 because of their poor pharmacological assessment and the importance of the  
14  
15 placebo effect. There was indeed no strong evidence to support the important  
16  
17 benefits experienced by patients using DXP.<sup>2,3</sup> As with many other old drugs, the  
18  
19 efficacy of DXP had been poorly assessed, as well as for paracetamol.<sup>26</sup> Patients  
20  
21 treated with DXP may have felt a benefit due to the placebo effect, which is  
22  
23 particularly frequent and intense with painkillers. It can relieve pain in 15 to 52% of  
24  
25 patients,<sup>27</sup> and may even equal an injection of morphine in postoperative pain.<sup>28</sup>  
26  
27 Serious risks are also difficult to consider for GPs and even more so for patients,  
28  
29 because they are rare, as illustrated by the number of deaths attributed to DXP in  
30  
31 France, which has been estimated to be around 1.5 case per 1000 private GPs in  
32  
33 2009.<sup>9</sup>

34  
35  
36  
37  
38 Many patients and GPs expressed distrust towards both healthcare institutions and  
39  
40 the pharmaceutical industry. A survey about the French population's relationship with  
41  
42 medicines found that only one in two people gives some credibility to information  
43  
44 from the pharmaceutical industry and from the health authorities.<sup>29</sup> Several patients  
45  
46 and GPs have been struck by the French benfluorex case, which went public during  
47  
48 the same period as the DXP withdrawal.<sup>30</sup> Benfluorex was popular in France and  
49  
50 largely prescribed off-label as an appetite suppressant for more than thirty years until  
51  
52 it was discovered that it could cause valvular heart disease and pulmonary arterial  
53  
54 hypertension. As a consequence, many patients treated with this drug have sued the  
55  
56  
57  
58  
59  
60

1  
2  
3 pharmaceutical company marketing the drug and the French health authorities.<sup>31</sup>

4  
5 This case, considered in France to be a national scandal, may have altered  
6  
7 confidence in the drug management system and made the acceptance of DXP  
8  
9 withdrawal difficult for patients and GPs.  
10

11  
12 Some GPs and most patients were unsatisfied with alternative drugs to DXP for three  
13  
14 reasons. First, many patients felt their pain increased after DXP withdrawal. Such  
15  
16 relapse was not observed in a French cohort study, but it was restricted to elderly  
17  
18 people.<sup>15</sup> Second, many patients also did not tolerate other step 2 analgesics. This  
19  
20 observation is only partially consistent with French pharmacovigilance data, which  
21  
22 found that the rate of adverse drug reactions reported for tramadol, but not for  
23  
24 codeine, was higher than for DXP.<sup>32</sup> Tolerance issues may help explain why patients  
25  
26 largely turned to paracetamol,<sup>33</sup> which could also contribute to relapsing pain. Finally,  
27  
28 patients' dissatisfaction might also be due to DXP addiction. Indeed, behaviour close  
29  
30 to addiction, such as stockpiling, fear of running out, off-label use, or searching for  
31  
32 backdoor procurement, were reported by interviewed patients. Such misuse could  
33  
34 pertain to opioid addiction or even to pseudo-addiction, which is a controversial  
35  
36 syndrome resulting from inadequate pain management.<sup>34,35</sup> This is of note as  
37  
38 withdrawal from the market represented an imposed deprescription, which could  
39  
40 sometimes result in withdrawal syndrome, as observed with opioids or  
41  
42 benzodiazepines.<sup>36</sup>  
43  
44  
45  
46  
47  
48

### 49 **Strengths and weaknesses**

50  
51 The principal strength of the study is that it explored and compared the views of both  
52  
53 patients and GPs. Furthermore, the paper conforms to the standards for reporting  
54  
55 qualitative research.<sup>37</sup> A potential limitation is that preconceptions from the  
56  
57  
58  
59  
60

1  
2  
3 investigators may have influenced the findings. However, the two authors who  
4 performed interviews and primary analyses were medical interns (AC and LB), who  
5 had not been exposed to the DXP withdrawal. Conversely, the clinical experience of  
6 two authors (LL and FA) was useful to develop the interview guides. Another  
7 limitation is that, although interviewed patients and GPs had diverse demographics  
8 and medical activities, the study design could have fostered the recruitment of  
9 individuals particularly concerned by the DXP withdrawal and led to an under-  
10 representation of the most neutral opinions of this event. However, various opinions  
11 and experiences were collected from both groups until reaching saturation. Due to  
12 the 3 to 5-year interval between the withdrawal and the interviews, memory bias  
13 cannot be excluded but this is likely to be limited as the studied event involved more  
14 the emotional than the factual memory of patients and GPs.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 **Implications for future withdrawals**

32  
33  
34 In cases of future warnings on drug safety (within the framework of the risk  
35 management plan for new or recently marketed drugs), national and European health  
36 authorities should start collecting prospective data well before the withdrawal  
37 decision and continue the monitoring thereafter, including through qualitative studies.  
38 Such prospective monitoring is needed to assess the pharmacoepidemiological  
39 impact of drug withdrawal, including the use of alternative drugs and strategies, and  
40 ultimately to validate the withdrawal decision. Additionally, appropriately informing  
41 healthcare professionals and the general public at each stage of the withdrawal  
42 process (i.e. warning, withdrawal decision and assessment) would ease acceptance  
43 of the decision and reinforce trust in the drug management system (Figure 1). In  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 addition, and before any safety warnings, an assessment of every blockbuster drug  
4  
5 through randomized mega-trials should be considered if not available.<sup>38</sup>  
6  
7  
8  
9  
10  
11  
12

### 13 **Acknowledgments**

14  
15  
16 The authors would like to thank all patients and GPs who have been interviewed in  
17  
18 the study, the Regional Union of Healthcare Professionals for its logistical support,  
19  
20 and Pr Behrouz Kassai Koupai for the discussions regarding the results. They are  
21  
22 also grateful to the College Lyonnais des Généralistes Enseignants (CLGE) and the  
23  
24 Hospices Civils de Lyon for funding language editing.  
25  
26  
27  
28  
29

### 30 **Contributors**

31  
32  
33 LL, AC, and LB conceived and designed the study, and they elaborated the interview  
34  
35 guides. AC and LB conducted the interviews and the analysis, under the supervision  
36  
37 of LL. EVG and FA provided clinical and pharmacoepidemiological context and  
38  
39 contributed to the interpretation of the findings. LL, AC, and LB drafted the  
40  
41 manuscript. All authors reviewed and approved the final version of the article.  
42  
43  
44  
45  
46

### 47 **Funding**

48  
49  
50 This research received no specific grant from any funding agency in the public,  
51  
52 commercial or not-for-profit sectors.  
53  
54  
55  
56  
57  
58  
59  
60



### Competing interests

None declared.

### Ethics approval

The study was approved by the Ethics Committee of the University of Lyon 1 (Lyon, France) and the French national agency for national data protection (CNIL, n°19162013). Before each interview, the interviewer informed the participant on the subject of the interview and asked for his/her oral consent to recording and analysing the data to be collected. Written consent was not required at the time of study approval.

### Data sharing statement

The data analysis tree is available on request from the corresponding author.

## References

1. Prescrire rédaction. Dextropropoxyphène + paracétamol : toujours là... malgré les risques. *Rev Prescrire* 2007;27:735.
2. Li Wan Po A, Zhang W. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997;315:1565-71.
3. Moore RA, Collins SL, Edwards J, et al. Single dose oral dextropropoxyphene, alone and with paracetamol (paracetamol), for postoperative pain. *Cochrane Database Syst Rev* 2000:CD001440.
4. Young RJ. Dextropropoxyphene overdose. Pharmacological considerations and clinical management. *Drugs* 1983;26:70-9.
5. Afshari R, Maxwell S, Dawson A, et al. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *Clin Toxicol* 2005;43:255-9.
6. Flanagan R, Johnston A, White AS, et al. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989;28:463-9.
7. Young RJ. Dextropropoxyphene overdose. Pharmacological considerations and clinical management. *Drugs* 1983;26:70-9.
8. European Medicines Agency. Press release: European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines. London; 2009.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2009/11/WC500010365.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010365.pdf) (Accessed 23 October 2017).

1  
2  
3 9. Agence Française de Sécurité Sanitaire des Produits de Santé. Médicaments  
4 contenant l'association dextropropoxyphène/paracétamol : Recommandation de  
5 l'EMA de retrait de ces médicaments à la suite de l'évaluation européenne et avis  
6 divergent de l'Afssaps. 2009.

7  
8  
9  
10  
11 <http://www.ansm.sante.fr/content/download/20487/248676/> (Accessed 23 October  
12 2017).

13  
14  
15  
16 10. Food and Drugs Administration. Recommendation on a Regulatory Decision for  
17 Propoxyphene-containing Products. 2010.

18  
19  
20  
21 [http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationfo](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf)  
22 [rPatientsandProviders/UCM234349.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234349.pdf) (Accessed 23 October 2017).

23  
24  
25  
26 11. Agence Française de Sécurité Sanitaire des Produits de Santé. Questions /  
27 Réponses. Retrait des médicaments contenant l'association  
28 dextropropoxyphène/paracétamol (Di-Antalvic<sup>®</sup> et ses génériques) ou  
29 dextropropoxyphène/paracétamol/caféine (Propofan<sup>®</sup> et ses génériques). 2009.

30  
31  
32  
33 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/19ca2c73609691747d](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf)  
34 [72c18b65dfc21a.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/19ca2c73609691747d72c18b65dfc21a.pdf) (Accessed 23 October 2017).

35  
36  
37  
38  
39 12. Handley S, Flanagan B. Drugs and other chemicals involved in fatal poisoning in  
40 England and Wales during 2000-2011. *Clin Toxicol* 2014;52:1-12.

41  
42  
43  
44 13. Agence nationale de sécurité du médicament et des produits de santé. Compte  
45 rendu de séance. Comité technique des Centres d'Evaluation et d'Information sur la  
46 Pharmacodépendance CT022015023. Séance du 19 mars 2015. 2015.

47  
48  
49  
50  
51 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e9328677e7a48b7222](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf)  
52 [74b90159035d1b.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e9328677e7a48b722274b90159035d1b.pdf) (Accessed 23 October 2017).

- 1  
2  
3 14. AFSSAPS. Mise au point. Prise en charge des douleurs de l'adulte modérées à  
4 intenses. Recommandations après le retrait des associations  
5 dextropropoxyphène/paracétamol et dextropropoxyphène/paracétamol/caféine.  
6  
7 [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/a6497f74fc2f18e8db00](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db0022973f9327e1.pdf)  
8 [22973f9327e1.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/a6497f74fc2f18e8db0022973f9327e1.pdf) (Accessed 23 October 2017).  
9  
10  
11  
12  
13  
14 15. Ottewell L, Walker DJ. Co-proxamol: where have all the patients gone?  
15 *Rheumatology* 2008;47:375.  
16  
17  
18  
19 16. Becquemont L, Delespierre T, Bauduceau B, et al. Consequences of  
20 dextropropoxyphene market withdrawal in elderly patients with chronic pain. *Eur J*  
21 *Clin Pharmacol* 2014;70:1237-42.  
22  
23  
24  
25  
26 17. Strauss A, Corbin J. Basics of qualitative research: Techniques and procedures  
27 for developing grounded theory. Newbury Park: Sage publications, 2015.  
28  
29  
30  
31 18. NVivo qualitative data analysis software, version 11. Doncaster: QSR  
32 International Pty Ltd., 2014.  
33  
34  
35  
36 19. Schwartz RK, Soumerai SB, Avorn J. Physician motivations for nonscientific drug  
37 prescribing. *Soc Sci Med* 1989;28:577-82.  
38  
39  
40  
41 20. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462  
42 medicinal products because of adverse drug reactions: a systematic review of the  
43 world literature. *BMC Med* 2016;14:10.  
44  
45  
46  
47  
48 21. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of analgesic  
49 medications because of adverse drug reactions: a systematic review. *Expert Opin*  
50 *Drug Saf* 2018;17:63-72.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 22. Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, Garfield  
4 CF, Alexander GC. Impact of FDA drug risk communications on health care utilization  
5 and health behaviors: a systematic review. *Med Care* 2012;50:466-78.  
6  
7  
8  
9  
10 23. Richards JR, Weiss SJ, Bretz SW, Schneir AB, Rinetti D, Derlet RW. The effects  
11 of the FDA warning on the use of droperidol by u.s. emergency physicians. *Cal J*  
12 *Emerg Med.* 2003;4:3-9.  
13  
14  
15  
16  
17 24. Shneker BF, Cios JS, Elliott JO. Suicidality, depression screening, and  
18 antiepileptic drugs: reaction to the FDA alert. *Neurology* 2009;72:987-91.  
19  
20  
21  
22 25. Garbutt JM, Sterkel R, Banister C, Walbert C, Strunk RC. Physician and parent  
23 response to the FDA advisory about use of over-the-counter cough and cold  
24 medications. *Acad Pediatr* 2010;10:64-9.  
25  
26  
27  
28  
29 26. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol  
30 for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised  
31 placebo controlled trials. *BMJ* 2015;350:h1225.  
32  
33  
34  
35  
36 27. Beecher HK. The powerful placebo. *JAMA* 1955;159:1602-6.  
37  
38  
39 28. Levine JD, Gordon NC, Smith R, et al. Analgesic responses to morphine and  
40 placebo in individuals with postoperative pain. *Pain* 1981;10:379-89.  
41  
42  
43  
44 29. Ipsos. Observatoire sociétal du médicament 2015 : 5ème vague d'étude menée  
45 par Ipsos pour le Leem sur le rapport des Français aux médicaments.  
46 <http://www.leem.org/sites/default/files/Observatoire-sociétal-du-Médicament2015.pdf>  
47  
48  
49  
50 (Accessed 23 October 2017).  
51  
52  
53 30. Mullard A. Mediator scandal rocks French medical community. *Lancet*  
54 2011;377:890-2.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 31. Menard J. Benfluorex: analysis of a drug-related public health crisis. *Diabetes*  
4  
5 *Metab* 2011;37:169-75.  
6  
7  
8 32. Tavassoli N, Lapeyre-Mestre M, Sommet A, et al. Reporting rate of adverse drug  
9  
10 reactions to the French pharmacovigilance system with three step 2 analgesic drugs:  
11  
12 dextropropoxyphene, tramadol and codeine (in combination with paracetamol). *Br J*  
13  
14 *Clin Pharmacol* 2009;68:422-6.  
15  
16  
17 33. Gaubert S, Vié M, Damase-Michel C, et al. Dextropropoxyphene withdrawal from  
18  
19 a French university hospital: impact on analgesic drug consumption. *Fundam Clin*  
20  
21 *Pharmacol* 2009;23:247-52.  
22  
23  
24 34. Greene MS, Chambers RA. Pseudoaddiction: Fact or Fiction? An Investigation of  
25  
26 the Medical Literature. *Curr Addict Rep* 2015;2:310-7.  
27  
28  
29 35. Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome.  
30  
31 *Pain* 1989;36:363-6.  
32  
33  
34 36. Le Couteur D, Gnjidic D, McLachlan A. Deprescribing. *Aust Prescr* 2011;34:182-  
35  
36 5.  
37  
38  
39 37. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative  
40  
41 research: a synthesis of recommendations. *Acad Med* 2014; 89:1245-51.  
42  
43  
44 38. Ioannidis JPA. Mega-trials for blockbusters. *JAMA* 2013;309:239-40.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1** Characteristics of interviewed general practitioners (GPs) and patients

Characteristics		GPs (n=13)	Patients (n=13)
Gender	Female	5	8
	Male	8	5
Age (years)	25-34	2	2
	35-44	1	0
	45-54	3	3
	55-64	7	5
	65-74	0	3
Working/living area	Urban	5	5
	Semi-rural	4	6
	Rural	4	2
GP trainer	Yes	9	
	No	4	
Practice type	Solo	1	
	Group	12	
Specialisation	Sports medicine/osteopathy	3	
	Homeopathy/mesotherapy	1	
	Medical expertise	1	
	Addictology	1	

**Table 2** Summary of the main perceptions of general practitioners and patients regarding DXP withdrawal

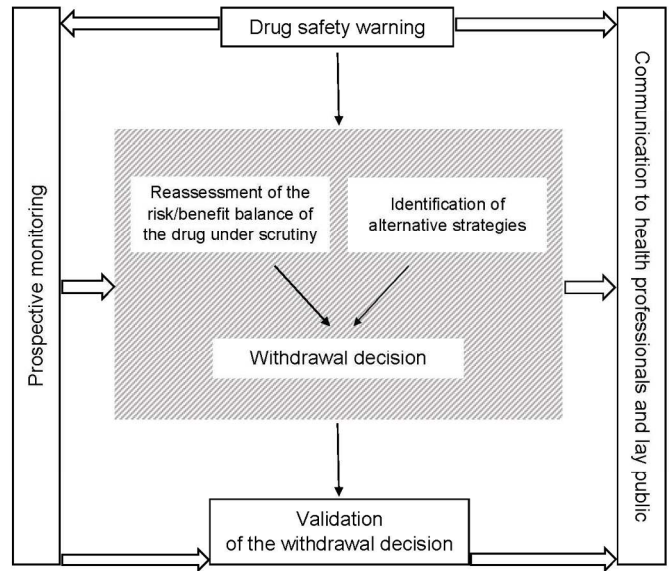
	General practitioners	Patients
DXP medication	Common prescription and use, high risk-benefit ratio, risk of dependence Valued but non-exclusive strategy	
Reasons for withdrawal	Misunderstanding, trend towards overestimation of benefits and underestimation of risks Some GPs earlier informed through a professional journal	
Conditions of withdrawal	Information through mainstream media, lack of anticipation Difficulties to inform patients Opportunity to reassess pain management, but concern about other analgesics	
Withdrawal impact	Rather bad experience due to poor tolerance of other analgesics Complex pain management, but opportunity to educate patients	DXP stockpiling Poor acceptance
Influence of past events	Distrust of the pharmaceutical industry and healthcare institutions Reduction of drugs available	



1  
2  
3  
4  
5 **Figure 1** Proposed model for drug withdrawal decisions  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1

Figure 1 Proposed model for drug withdrawal decisions  
139x198mm (300 x 300 DPI)

## Standards for Reporting Qualitative Research (SRQR)\*

<http://www.equator-network.org/reporting-guidelines/srqr/>

### Title and abstract

<b>Title</b> - 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	p1
<b>Abstract</b> - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	p3

### Introduction

<b>Problem formulation</b> - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	p5-6
<b>Purpose or research question</b> - Purpose of the study and specific objectives or questions	p6

### Methods

<b>Qualitative approach and research paradigm</b> - 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**	p7
<b>Researcher characteristics and reflexivity</b> - 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	p7-8 +p19-20
<b>Context</b> - Setting/site and salient contextual factors; rationale**	p7-8
<b>Sampling strategy</b> - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	p7-9
<b>Ethical issues pertaining to human subjects</b> - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	p22
<b>Data collection methods</b> - 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**	p7-8
<b>Data collection instruments and technologies</b> - 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	p7-8
<b>Units of study</b> - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	p8 and Table 1
<b>Data processing</b> - 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	p8
<b>Data analysis</b> - 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**	p8
<b>Techniques to enhance trustworthiness</b> - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	p8

### Results/findings

<b>Synthesis and interpretation</b> - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	p16-17 + Figure 1
<b>Links to empirical data</b> - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	p9-16

### Discussion

<b>Integration with prior work, implications, transferability, and contribution(s) to the field</b> - Short	p17-21
---	--------

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	
<b>Limitations</b> - Trustworthiness and limitations of findings	p19-20

**Other**

<b>Conflicts of interest</b> - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	p22
<b>Funding</b> - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	p21

For peer review only