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Analgesic switching in chronic users of dextropropoxyphene in France

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Abstract

Background: The combination dextropropoxyphene/paracetamol (DXP/P) was the most prescribed opioid analgesic until its withdrawal in 2011.

Objectives: This study investigated dispensations of analgesics in chronic users of DXP/P during the 18 months following its withdrawal.

Methods: A cross-sectional study repeated yearly was conducted by using the French reimbursement database from 2006 to 2015. Chronic DXP/P users were defined as patients who received at least 40 boxes of DXP/P in the year prior to withdrawal. Data on analgesic dispensing were analyzed at DXP/P withdrawal (T0) and then every 6 months for 18 months.

Results: A total of 63 671 subjects had a DXP/P reimbursement in the year prior to its discontinuation, of whom 7.1% were identified as chronic users (mean age: 71.5 years, women: 68.7%). Among the patients taking DXP/P alone at T0 (74.6%), one fourth switched to a peripheral analgesic, one fourth to a combination of peripheral analgesic/opioid, one fourth to another opioid, and the others mainly discontinued their treatment (14.1%) or died. During the following 12 months, most of the subjects taking only peripheral analgesics continued this treatment, while half of the subjects with a combination of opioid/peripheral analgesic or taking only an analgesic remained on this type of treatment.

Conclusion: Eighteen months after DXP/P withdrawal, more than 10% of patients stopped taking an analgesic. Vigilance is required regarding any change in analgesics by regularly reassessing patients' pain and, in the case of opioid treatments, by monitoring the risk of use disorders.

KEYWORDS
addictovigilance, analgesics, dextropropoxyphene, drug utilization, safety-based drug withdrawals

Abbreviations: ATC, Anatomical Therapeutic Chemical; DXP, Dextropropoxyphene; DXP/P, Dextropropoxyphene/paracetamol; EGB, Echantillon Généraliste de Bénéficiaires; GP, General practitioner; NSAIDs, Nonsteroidal anti-inflammatory drugs; PMSI, National hospital discharge summaries database system; SD, Standard deviation; T, Time.

1 | INTRODUCTION

Dextropropoxyphene (DXP), a synthetic opioid structurally similar to methadone, was approved in France 1964 and became a popular opioid analgesic worldwide. In combination with paracetamol, it was indicated for the treatment of low-to-moderate intensity pain and was the most widely prescribed opiate in France in 2006 [1–4]. DXP alone was withdrawn by the manufacturer in 2001 [5].

Reports of DXP-related hepatotoxicity, frequent associations with suicidal poisonings in Northern Europe, United States, and Australia [6] and controversy about the benefit of associating DXP with paracetamol (DXP/P) progressively, led to its withdrawal worldwide. The UK and Sweden withdrew it as early as 2005 [7]. In 2010, the US Food and Drug Administration issued a warning against the prescription and use of DXP because of reports of serious cardiac toxicity, even when used at therapeutic doses, and requested that companies voluntarily withdraw it from the US market [8]. Re-evaluation of its risk–benefit ratio led the European Commission on June 14, 2010 to recommend its withdrawal from the European market within 15 months [7], a measure that became effective in France in March 2011.

Numerous studies on the consequences of that withdrawal have been undertaken. Following the withdrawal in the UK, there was a reduction in DXP-related deaths and suicidal poisoning [5]. However, little is known about switching to another medication. Pageot et al. [9] showed that reimbursements of tramadol and codeine increased after DXP/P was withdrawn, but it was not possible to specify which analgesics were prescribed (or not) to patients who were treated with DXP/P after its withdrawal [3, 4]. An analysis of aggregated dispensation data between January 2009 and December 2012 in a French region investigated the effects of DXP/P market withdrawal [6]: Data showed that DXP/P withdrawal was accompanied by an increased use of analgesics of the same pharmacological potency and by an increased use of paracetamol in monotherapy. This study was limited because it only assessed changes in DXP/P consumption for the entire population and suggested that analyses of individual longitudinal drug history were needed.

The current study further probed these drug choices with the use of individual longitudinal drug histories. Using the French health insurance reimbursement data, the study aimed first to describe dispensations of analgesics to chronic users of DXP/P after its withdrawal and during the following 18 months. The secondary objective was to describe their drug changes every 6 months after the discontinuation of DXP/P.

2 | MATERIALS AND METHODS

2.1 | Study design, data source, and variables

This project is derived from the DANTE study [3]. A cross-sectional study repeated yearly was conducted by using data from a sample of the French reimbursement database, the *Echantillon Généraliste de Bénéficiaires (EGB*), for the period from January 2006 to December 2015 (http://www.snds.gouv.fr/). The EGB database is a representative sample of the population covered by the national healthcare insurance system (approximately 98% of the whole population, irrespective of socioeconomic status) obtained by 1/97th random sampling with stratification on gender and age [10, 11]. Among other data, it contains the exhaustive records of drug reimbursements for all beneficiaries. Details on the EGB database have been described elsewhere [10–13]. It has been used extensively to characterize drug use and its main trends in France [11–15]. The EGB is linked to the national hospital discharge summaries database system (National hospital discharge summaries database system [PMSI]) and the national death registry. In accordance with French regulations, ethics committee approval was not required for this observational study conducted on anonymized medico-administrative data.

2.2 | Participants

All subjects aged 18 years and over, alive on January the first of each year and covered at least 1 day by the general health insurance scheme for the period of January 1, 2007 to December 31, 2012, were included. Chronic users of DXP/P were defined as patients who received at least 40 boxes of DXP/P in the year preceding the discontinuation of DXP/P. This choice was made because the median value of received boxes was 40 per year and because the actual use of DXP/P in daily practice could be intermittent, as it could depend on the analgesic requirements of the patient. At that time, DXP/P was sold in boxes of 20 capsules. Patients could be dispensed only 1 month's supply of DXP/P products. The product information stated that the adult dose was one capsule or two capsules every 4 h with a maximum dose of six capsules per day [16].

The index date (T0) was defined as the date of the last delivery of DXP/P, which was used to describe the characteristics of former DXP/P chronic users in terms of age, gender, presence of chronic disease, and year of death. Any other analgesic drugs (defined below) ±7 days of the index date were counted as concomitant medications.

2.3 | Exposure

The dispensing data of former DXP/P chronic users were analyzed to see whether analgesics were dispensed after the DXP/P discontinuation and if so, which ones. The analgesics considered belonged to analgesic drug classes (Anatomical Therapeutic Chemical [ATC] code N02) and anti-inflammatory and antirheumatic products (ATC code M01) [3, 17]. Among the nonsteroidal anti-inflammatory drugs (NSAIDs), drugs exclusively for analgesic purposes were identified by crossing the ATC code (M01A) and the EphMRA classification (N02). Thus, some products containing mefenamic acid, diclofenac, fenoprofen, ibuprofen, ketoprofen, naproxen, or nimesulide were selected [17]. Analgesics were classified in three groups according to their pharmacological potency [18]:

- peripheral analgesics for mild-to-moderate pain: aspirin at analgesic dose (ATC code N02BA01), fenoprofen, floctafenin, ibuprofen, ketoprofen, mefenamic acid, naproxen, nimesulide, paracetamol;
- analgesics for moderate-to-severe pain (called here "weak"): codeine combinations, dihydrocodeine, opium combinations, nefopam, tramadol (single ingredient or in combination);
- analgesics for very intense pain (called here "strong"): buprenorphine as analgesic (i.e., low-dose buprenorphine, ATC code: N02AE01), fentanyl, hydromorphone, morphine, oxycodone.

High-dose buprenorphine used as opiate maintenance treatment (ATC code: N07BC01) [19] as well as methadone and other "specific" analgesics such as anti-depressants, anticonvulsants, and antimigraine agents used for specific pain were not included nor were pediatric forms. Regarding aspirin (acetylsalicylic acid), low dosages used as platelet aggregation inhibitors or as antimigraine agents (dosages from 75 to 325 mg and their combinations (with metoclopramide and clopidogrel) were not considered in the study.

2.4 | Study population

All prevalent DXP/P users between 2009 and 2011 were included and then tracked for 18 months after the DXP/P termination date. Their current analgesic treatments at the time of discontinuation (concomitant analgesic treatments) and after discontinuation were described. Subjects with no subsequent analgesic therapy, as well as patients who died during the study, were also considered.

2.5 | Data analysis

To assess the evolution of analgesics type dispensed after the index date, the distribution of quantitative variables (mean, standard error, median …) and proportions were estimated among the total population of chronic users of DXP/P alive before time T0, T6, T12, or T18, according to the follow-up time considered (T0, T6, T12, and T18). The number of subjects was recalculated at each period by considering only subjects alive before the time considered.

An overview of the evolution of treatment of each patient was performed: Distribution of quantitative variables and proportions were estimated among the total population of chronic users of DXP/P at T0.

SAS software version 9.4 (SAS Institute, North Carolina, USA) was used for the analyses. R version 3.4.1 was used to create the Sankey diagram.

3 | RESULTS

3.1 | Patient characteristics

From the EGB database, 63 671 subjects were identified as being prescribed DXP/P in the 12 months before DXP/P withdrawal in France. From this subset, 4495 patients (7.1%) who met the criteria for former DXP/P chronic users were identified. Chronic users had a mean age of 71.5 years (SD ± 13.8), were more frequently women (68.7%), and had at least one chronic disease in 61.7% of cases, mainly severe arterial hypertension, diabetes, or cancer (Table 1).

TABLE 1 Main characteristics of chronic users of DXP/P at T0.

	Total $n = 4495$
Age, mean (± SD)	71.5 (13.8)
Median	74.0
[p25% – p75%]	[62.0;82.0]
Range	[20.0;105.0]
Gender, female	3090 (68.7)
Chronic disease at index date[a], *n* (%)	2772 (61.7)
Severe arterial hypertension	585 (13.0)
Diabetes	573 (12.7)
Cancer	540 (12.0)
Coronary heart disease	363 (8.1)
Long-term psychiatric conditions	347 (7.7)
Other severe heart disorders	282 (6.3)

[a]The listed chronic disorders had a prevalence of >5% at index date.
Abbreviation: DXP/P, dextropropoxyphene/paracetamol.

3.2 | Description of treatments of former DXP/P chronic users

Figure 1 presents the evolution of analgesic type dispensed after the index date. Within 6 months after DXP/P discontinuation, 8.6% of chronic users died. The death rate remained low for the rest of the study (3.4% up to 12 months and 2.7% up to 18 months after the index date).

Within 6 months, 11.7% of chronic users had stopped receiving an analgesic of interest. The rate remained stable during the study period (11.0% between T6 and T12; 11.6% between T12 and T18) (Table 2).

Within 6 months after DXP/P withdrawal, 79.7% of patients were treated with at least one analgesic. More than half of former DXP/P chronic users had switched to at least a peripheral analgesic (58.8% at T6), essentially paracetamol, while NSAID use was negligible (Table 2). The prevalence of use of peripheral analgesics slightly increased over time (64.7% between T6 and T12; 64.5% between T12 and T18).

Within 6 months, nearly half of former DXP/P chronic users had switched to at least a weak opioid (Table 2). The prevalence of use of weak analgesics was stable over time in former DXP/P users (Table 2). Tramadol alone or in combination with paracetamol (13.4% and 26.3% at T6, respectively), opium, and codeine was the most frequent weak analgesics (Table 2).

Within 6 months, a minority of former DXP/P chronic had switched to at least a strong analgesic (6.3% at T6), essentially fentanyl (3.6% at T6), and morphine (3.2% at T6). The prevalence of use of strong analgesics decreased over time (Table 2).

3.3 | Trajectory of treatments for each former DXP/P chronic user

The Sankey diagram shows an overview of the evolution of treatment of each patient (Figure 2; see Figure S1 and supporting information digital content S1, which is an interactive version of Figure 2) and the most common switching patterns. Among the 3352 patients taking DXP/P alone at T0 (74.6%), one quarter switched to a peripheral analgesic, one quarter to a combination of peripheral and weak analgesics, and one quarter to a weak analgesic. The other quarter mainly discontinued their analgesic treatment (14.1%) or died (7.9%; for details, see Figure 3 and Table S1 in the supporting information digital content S2, which describes the distribution of analgesics reports following discontinuation of DXP/P).

Among the 555 patients taking a combination of DXP/P and a peripheral analgesic at T0 (12.3%), the main switch was to a peripheral analgesic (38.0%) or a combination of a peripheral and a weak analgesic (39.8%) at 6 months (Figure 3 and Table S1 in the supporting information digital content S2).

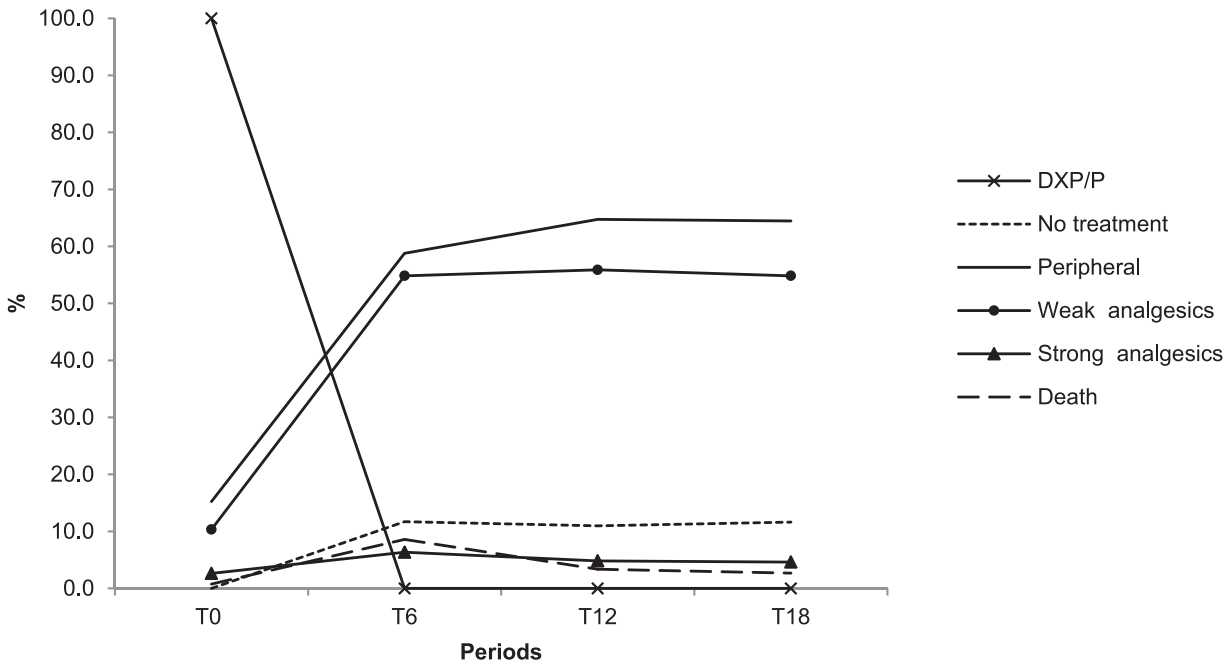

FIGURE 1 Evolution of analgesic types dispensed after index date to all chronic users. T0: time of treatment discontinuation ±7 days. T6: within 6 months of treatment discontinuation. T12: 6 to 12 months after treatment discontinuation. T18: 12 to 18 months after treatment discontinuation.

TABLE 2 Focus on analgesics at each time period.

	T0 *n* (%)	T6 *n* (%)	T12 *n* (%)	T18 *n* (%)
Number of subjects alive before time T	**4495 (100)**	**4461 (100)**	**4078 (100)**	**3941 (100)**
DXP/P	**100**	**0 (0)**	**0 (0)**	**0 (0)**
No treatment	**0 (0)**	**522 (11.7)**	**447 (11.0)**	**458 (11.6)**
Death	**34 (0.8)**	**383 (8.6)**	**137 (3.4)**	**106 (2.7)**
Peripheral analgesics	**685 (15.2)**	**2622 (58.8)**	**2640 (64.7)**	**2540 (64.5)**
Paracetamol	581 (12.9)	2518 (56.4)	2535 (62.2)	2434 (61.8)
Ibuprofen	67 (1.5)	218 (4.9)	211 (5.2)	209 (5.3)
Nimesulide	47 (1.0)	70 (1.6)	57 (1.4)	39 (1.0)
Aspirin	16 (0.4)	55 (1.2)	47 (1.2)	44 (1.1)
Diclofenac	3 (0.1)	6 (0.1)	5 (0.1)	5 (0.1)
Floctafenine	2 (0.0)	19 (0.4)	15 (0.4)	13 (0.3)
Naproxen	2 (0.0)	5 (0.1)	3 (0.1)	2 (0.1)
Ketoprofen	2 (0.0)	8 (0.2)	7 (0.2)	5 (0.1)
Mefenamic acid	1 (0.0)	7 (0.2)	5 (0.1)	4 (0.1)
Fenoprofen	0 (0.0)	1 (0.0)	2 (0.0)	3 (0.1)
Weak analgesics	**465 (10.3)**	**2446 (54.8)**	**2279 (55.9)**	**2161 (54.8)**
Tramadol and paracetamol	112 (2.5)	1172 (26.3)	1048 (25.7)	979 (24.8)
Opium	103 (2.3)	757 (17.0)	645 (15.8)	582 (14.8)
Codeine	89 (2.0)	660 (14.8)	600 (14.7)	524 (13.3)
Tramadol	172 (3.8)	599 (13.4)	546 (13.4)	533 (13.5)
Nefopam	20 (0.4)	45 (1.0)	45 (1.1)	44 (1.1)
Dihydrocodeine	2 (0.0)	5 (0.1)	5 (0.1)	7 (0.1)
Strong analgesics	**118 (2.6)**	**283 (6.3)**	**197 (4.8)**	**182 (4.6)**
Fentanyl	72 (1.6)	159 (3.6)	107 (2.6)	98 (2.5)
Morphine	53 (1.2)	141 (3.2)	95 (2.3)	88 (2.2)
Oxycodone	7 (0.2)	50 (1.1)	32 (0.8)	28 (0.7)
Buprenorphine	1 (0.0)	3 (0.1)	2 (0.0)	1 (0.0)
Hydromorphone	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)

Note: T0: time of treatment discontinuation ±7 days. T6: 6 months after treatment discontinuation ±7 days. T12: 12 months after treatment discontinuation ±7 days. T18: 18 months after treatment discontinuation ±7 days. The number of subjects was recalculated at each period by considering only people alive.
Abbreviation: DXP/P, dextropropoxyphene/paracetamol.

Among the 343 patients taking a combination of DXP/P and a weak analgesic at T0 (7.6%), the main switch was to a weak analgesic (39.1%) or a combination of a peripheral and a weak analgesic (35.9%) at 6 months (Figure 3 and Table S1 in the supporting information digital content S2).

Over the following 12 months, among subjects taking peripheral analgesics only, the majority continued to take them (65.8% from T6 to T12 and 67.8% from T12 to T18), while only half of the subjects who were taking a weak/peripheral analgesic combination and half of those taking only a weak analgesic continued to take them (Figure 3 and Table S1 in supporting information digital content S2).

At the 18-month follow-up, a total of 660 patients had died (i.e., 14.7% of the initial population included) and 458 (10.2%) had discontinued all analgesic treatment.

4 | DISCUSSION

This is the first nationwide study of former chronic DXP/P users and their consumption patterns conducted within 18 months of its market withdrawal. The average age of patients was 71.5 years, and the majority were women (68.7%). Former chronic DXP/P users mainly switched to peripheral analgesics (mainly paracetamol, with NSAID prescriptions remaining low, which is quite reassuring in this elderly population [20]) and weak opioids (mainly tramadol with paracetamol or not, then, opium and codeine). This confirms previous findings in France and in other countries [5, 6, 21–23] but highlights the tendency to switch to paracetamol rather than to a weak opioid analgesic. Bequemont et al. [21] found that the majority of elderly patients with chronic pain (53.4%) were treated with another weak opioid analgesic (primarily tramadol), while 40.8% were

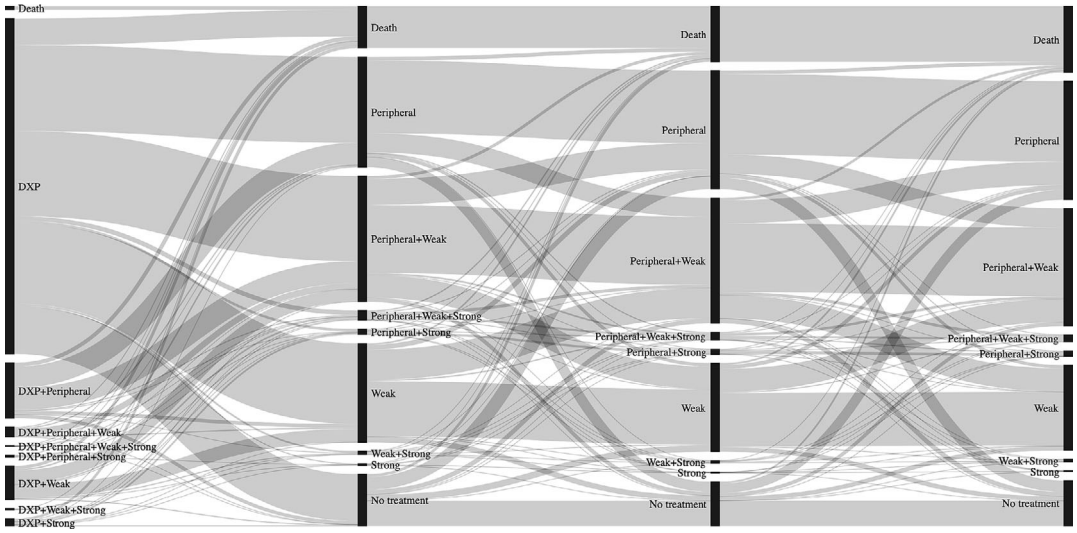

FIGURE 2 Sankey diagram showing evolution of treatments according to analgesic classes. Results are proportions of treatments according to their analgesic classes following the discontinuation of DXP/P-containing medications among all chronic users of DXP/P. Each column represents a point in time: the first column is situation at the index time, including analgesics taken within ±7 days. Then from left to right, each column is each 6-month period within the 18-month study period. Each node (black) is a treatment choice or health outcome, and each flow (gray) shows the direction of the treatment choices. It shows the percentage of subjects with treatment within each 6-month period as well as the change in the number of subjects with each treatment over the 18 months following treatment. The relative number of reimbursements underlying each treatment/outcome is depicted by the thickness of the lines linking the terms (interactive version in the supporting information digital content S1). For presentation reasons, the DXP/P combination has been abbreviated to DXP in figure. DXP/P, dextropropoxyphene/paracetamol.

no longer treated with paracetamol alone. In another study, general practitioners (GP) were found to be more likely to prescribe high doses of paracetamol or tramadol (alone or in combination with paracetamol) as an alternative for chronic pain [22].

One of the strengths of this study is that it was possible to distinguish different periods of treatment for each individual, thus demonstrating how difficult it was for some patients to stay on the same analgesic, even though their treatment seemed stable before DXP/P was discontinued. This is in line with a UK study showing that many patients previously treated with DXP were unable to find a satisfactory alternative to it [24]. Moreover, Reset et al. explained how some patients in Norway continued to be prescribed DXP after its market withdrawal thanks to 'compassionate prescribing' [5]. In France, some GPs and most patients were also dissatisfied with alternative drugs for three reasons: (a) many patients felt their pain increased after the withdrawal of DXP, (b) many patients did not tolerate other weak opioid analgesics, and (c) their dissatisfaction may also have been due to addiction to DXP [25]. Indeed, in that study, patients reported behaviors close to addiction, such as stocking up, fear of running out, off-label use, and seeking DXP/P on the black market [25].

Another important finding of our study is that a significant number of these patients (10.2%) stopped all analgesic drugs within 18 months of discontinuing DXP/P. This is higher than in the study by Bequemont et al. who found that only 3% of the subjects included in their study had stopped all drugs [21]. This raises questions about the strong attachment that patients had to DXP, the possible lack of pain reassessment in chronic patients, [26], and to a potential DXP-related use disorder. However, we cannot rule out the possibility that these patients were treated with another analgesic not investigated in the study (in particular, pregabalin or gabapentin, even if these drugs were rarely prescribed in 2015) or that they benefited from nondrug analgesic treatments.

Very few former chronic DXP/P users switched to a strong opioid analgesic, unlike in Norway [5]. However, some prescriptions both before and after the withdrawal of DXP/P combined a weak analgesic with a strong one, an association of two opioid agonists that was not pharmacologically relevant and did not comply with international guidelines. Prevalence and sales studies carried out in France [3, 4, 6] showed that in the years following the withdrawal of DXP/P, the total consumption of weak analgesics decreased, with an increase in the consumption of tramadol, codeine, and opium. The prevalence of oxycodone use also increased [27], but this does not appear to have been related to the withdrawal of DXP/P.

The discontinuation of DXP in Europe followed the re-evaluation of the risk/benefit ratio by the EMA, after Sweden and the UK took restrictive measures following the occurrence of numerous deaths after voluntary and involuntary intoxications (respectively 200 deaths per

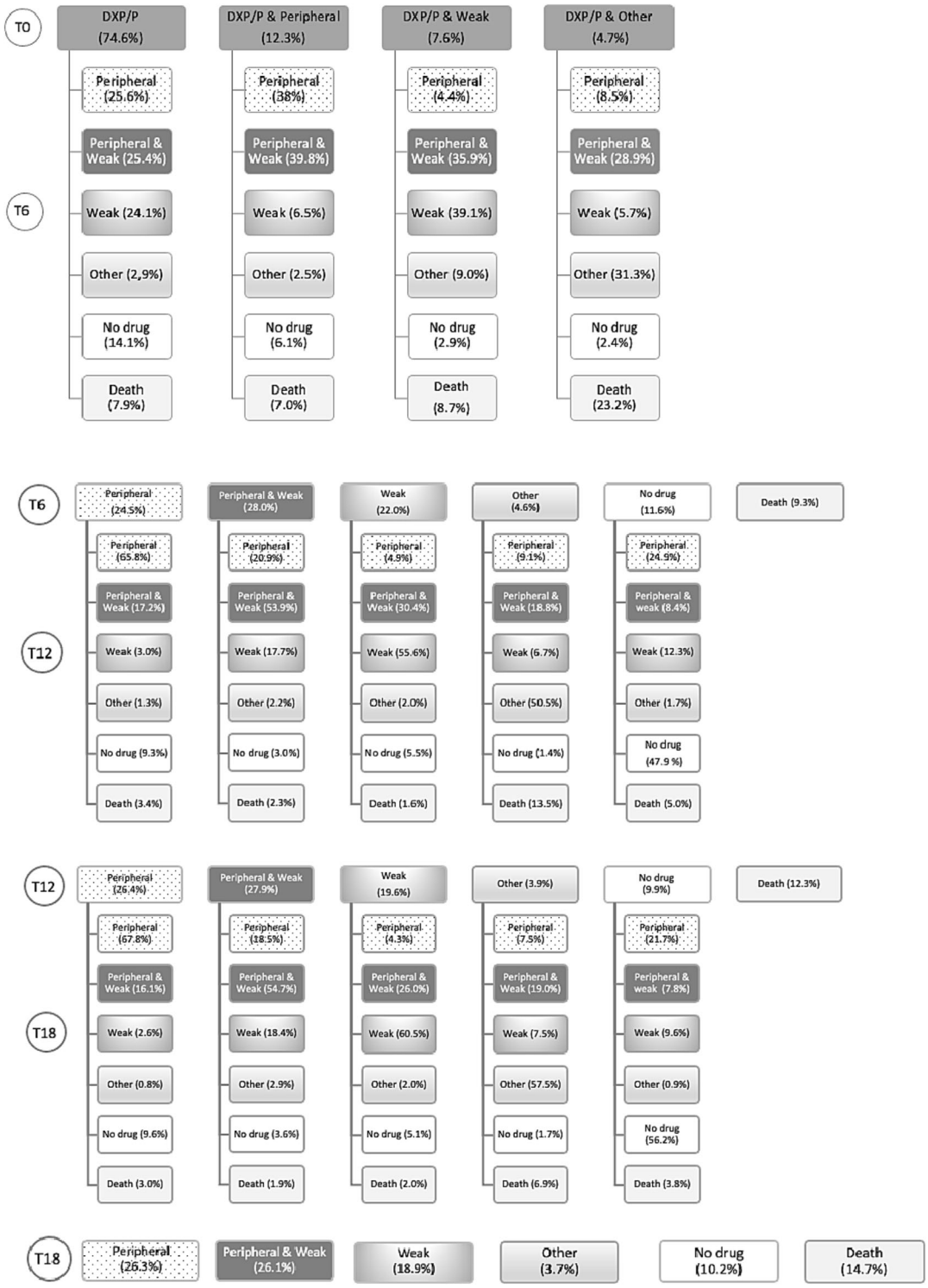

FIGURE 3 Trajectory of each patient according to analgesic classes. Percentage of subjects with treatment within each 6-month period as well as change in proportion of subjects with each treatment over the 18 months following treatment. DXP/P, dextropropoxyphene/paracetamol.

year, per 9 million inhabitants and 300 to 400 per year, per 60 million inhabitants). In France, deaths from DXP/P intoxication were much lower with an estimated 65 deaths per year per 65 million inhabitants. This explains why the French Medicines Agency was initially reluctant to withdraw DXP/P from the market, considering that the risk to public health was much lower than in Sweden or the UK and fearing that tramadol would be more risky than DXP, both in terms of death [1, 28] and use disorders [29].

This study has certain limitations, most of which are common to studies based on reimbursement

databases. As with any study based on the EGB, the assumption that what is reimbursed is consumed is not necessarily correct. In the case of analgesics, reserves are often built up for personal or family medicine cabinets. A person who has been reimbursed for paracetamol or ibuprofen may not have used it after a few months. While this is true for acute pain, it is probably less true for chronic pain. In addition, the EGB data only include reimbursed outpatient consumption data, so the data presented here do not include self-medication through over-the-counter purchases, use in healthcare institutions or hospitals, or medicines bought on the black market in the street. For NSAIDs indicated as analgesics and paracetamol, use for indications other than pain, including fever or rheumatological conditions, cannot be ruled out.

On the other hand, the use of such a database has significant advantages. It represents a large random sample of affiliates of the national health insurance system, which covers more than 98% of the French population. For the affiliates included in the sample, it includes all reimbursements for outpatient healthcare expenditure. These two aspects are important because the French drug market is one of the largest in the world, providing access to around 66 million people through a unique reimbursement system. Finally, the database also provides a monitoring tool that enables changes in drug prescribing and consumption to be studied over a long period [30].

5 | CONCLUSION

Following the discontinuation of DXP/P, switches were made mostly to paracetamol and tramadol. In addition, more than 10% of patients discontinued any analgesic of interest. This study highlights the need to be careful with any change in analgesics, in particular by regularly reassessing pain and, in the case of opioid treatments, by monitoring patients for substance use disorders [26].

AUTHOR CONTRIBUTIONS

All listed authors have contributed to the manuscript and have agreed the final submitted version.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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