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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Consequences of dextropropoxyphene market withdrawal in elderly patients with chronic pain

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Abstract
Objective Describe the consequences of dextropropoxyphene (DXP) market withdrawal on analgesic prescriptions and on the quality of therapeutic management of chronic pain.

Patients and methods From a cohort of non-institutionalised elderly patients with chronic pain recruited by general practitioners, we selected patients who were treated with DXP daily for at least 6 months just prior to DXP market withdrawal and

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who had an evaluation of pain and its impact on daily activities before and after DXP withdrawal.
Results One hundred three patients took DXP daily for chronic pain. Immediately after DXP market withdrawal, 42 (40.8 %), 55 (53.4 %) and 3 (2.9 %) patients were treated with step 1, 2 and 3 analgesics, respectively, and 3 patients (2.9 %) were no longer receiving any analgesic medication. Among the 55 patients who continued on step 2 analgesics, 37 were treated with tramadol, 14 with codeine and 9 with opium. Pain intensity and the impact of pain on daily activities remained stable.
Conclusion DXP market withdrawal had no consequences on the intensity or impact of chronic pain in elderly patients.

Keywords Dextropropoxyphene · Safety-based drug withdrawals · Chronic pain · Elderly patients

Introduction

With the ageing of the population in the developed world and the resultant increase in the frequency of degenerative joint disorders, the use of analgesic medications is ever more widespread. When pain is not relieved by step 1 analgesics (according to the WHO analgesic ladder) such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), a step 2 analgesic, mainly comprising the three weak opioids codeine, tramadol and dextropropoxyphene (DXP), is usually used in combination with paracetamol.

Until its market withdrawal in France in March 2011, DXP was the second most prescribed analgesic drug after paracetamol [1]. Among the other step 2 analgesics, DXP was the most hepatotoxic [2] and, compared with paracetamol alone, was found to provide only a small added benefit [3]. In England, DXP was withdrawn between 2005 and 2008 due to its hepatotoxicity and its widespread use for suicidal poisoning. After 2005, there was a dramatic reduction in deaths due to DXP [4] as well as in suicidal drug poisonings [5], although there was little change in the annual number of fatal poisonings in England and Wales during the same period [6]. In 2009, the European Medicines Agency (EMA) recommended the withdrawal of DXP throughout the European Union.

While the consequences of DXP market withdrawal on suicidal deaths have been studied, the same cannot be said for its consequences on analgesic prescriptions or the quality of therapeutic management of chronic pain [1, 7].

This study, carried out in a non-institutionalised elderly cohort with chronic pain recruited by general practitioners, aimed to evaluate the consequences of DXP market withdrawal on analgesic prescriptions and the quality of pain management as assessed by pain intensity and impact on daily activities.

Patients and methods

The S.AGE study is a multicenter prospective cohort study conducted in France [8, 9]. The primary objective of the S.AGES cohort is to describe the real-life therapeutic management of non-institutionalised elderly patients. This cohort consists of 3,434 non-institutionalised patients aged 65 years and over with either chronic pain (CP) (n=1379), type 2 diabetes mellitus (T2DM) (n=983) or atrial fibrillation (AF) (n=1072). The inclusion criteria were as follows: men or women aged 65 years or over living in France, who were able to understand the goal of the study, agreed to participate therein and signed the informed consent. Patients included in the study also had one of the following three conditions that defined three sub-cohorts:

- CP present for more than 3 months and requiring care.
- T2DM treated at baseline with any hypoglycemic drug.
- AF (by ECG or Holter ECG).

Patients could not participate if they were residents of a nursing home at the time of inclusion, could not be followed after inclusion (planned move, homeless) or had a short life expectancy (less than 3 months).

Patients were recruited by their general practitioners (GP) throughout France. Seven hundred sixty GPs responded favourably and were randomised into one of the three S.AGE sub-cohorts. Inclusion of patients began in June 2009 and ended in September 2011 [8]. Patients returned to their GP every 6 months (planned follow-up visits) for a 3-year period.

To be eligible for the present study, patients had to be treated every day with DXP for chronic pain for at least 6 months before March 2011 (DXP withdrawal) and to have extensive pain assessment before and at the first follow-up visit after DXP withdrawal.

Study variables

Physical function was assessed using the Activity of Daily Living scale [ADL scale [10]] which includes six dimensions: feeding, bathing, dressing, going to toilet, transferring and continence. Patients with a score of 6 are considered to be independent, while 0 indicates that the patient is totally dependent. Pain intensity was evaluated using auto (patient) and hetero (GP) visual analogue scales (VAS) ranging from 0 to 10. The impact of pain on mood, relationships, walking, daily activities and sleep was assessed by the patients using a VAS scale from 0 to 4.

Treatments: The GP recorded all prescribed drugs at each visit, indicating when the drug was started, stopped and the reason for the prescription.

The study was approved by the Ethics Committee and by the French Medicines Agency. The clinical trial reference of this study is NCT01065909. Further details about the study have been provided in previously published papers [8, 9].

All data are presented as mean±standard deviation or percentage and 95 % confidence intervals.

DXP market withdrawal in France began in September 2010 and was final on 1st March 2011.

Results

Before DXP withdrawal

Of the 3,434 patients enrolled in the S.AGE study between June 2009 and September 2011, 154 were treated every day with DXP for chronic pain for at least 6 months before the final withdrawal of DXP in March 2011. Among these latter patients, 103 had a visit in the 6 months after March 2011 that included clinical data to assess pain intensity and impact. Table 1 shows the characteristics of these 103 patients at their last visit before DXP withdrawal. There were 75, 15 and 13 patients in the chronic pain, type 2 diabetes mellitus and atrial fibrillation sub-cohorts, respectively. The visit before was performed 2.49±1.92 months before DXP withdrawal and the visit after, 9.19±6.75 months after DXP withdrawal. This longer time interval between DXP withdrawal and the second visit was related to the fact that patients had stock up on DXP at home and therefore continued their DXP treatment until the end of their personal stock.

The population consisted of a majority of women with a mean age identical to that of the S.AGE chronic pain sub-cohort and almost half of whom lived alone at home. Pain was mainly common back pain. All were treated with a step 2 analgesic (Table 2), but one patient also received a step 3 drug and another 4 patients received a combination of DXP and tramadol (Table 3). The mean VAS scores for pain intensity during the visit were 4.4±1.6 evaluated by the GP and 4.3±2.3 evaluated by the patient (supplementary figure 1 and figure 1A). The VAS score for pain intensity evaluated by the patient during the 8 days preceding the visit was 5.2±1.7. Figure 1b shows the impact of pain on daily activities. It should be noted that the % of women among the 28 patients included in the atrial fibrillation, and type 2 diabetes mellitus sub-cohorts was lower compared to the 75 patients included in the chronic pain sub-cohort (50 vs 85 %, p=0,001). Baseline pain intensity was also significantly higher in patients originating from the chronic pain sub-cohort compared to those included in the 2 other sub-cohorts (data not shown).

Table 1 Characteristics of the population and description of pain

	n=103
Women	78 (75.7 %)
Age	77±6
Occupational activity	
Working	2 (1.9 %)
No longer works	84 (81.6 %)
Never worked	17 (16.5 %)
Socioprofessional category[a]	
Farmer operator	7 (6.8 %)
Craftsman, shopkeeper, entrepreneur	9 (8.7 %)
White collar worker	9 (8.7 %)
Middle management	10 (9.7 %)
Employee	34 (33.0 %)
Factory worker	17 (16.5 %)
Residence	
Alone at home	46 (44.7 %)
At home but not alone	57 (54.4 %)
Home help	24 (23.3 %)
Type of pain[b]	
Mechanical	67 (65.1 %)
Inflammatory	5 (4.9 %)
Neuropathic	2 (1.9 %)
Mechanical+inflammatory	13 (12.6 %)
Mechanical+neuropathic	10 (9.7 %)
Mechanical+inflammatory+neuropathic	1 (1.0 %)
Site of pain[c]	
Upper limbs	1 (1.0 %)
Lower limbs	23 (22.3 %)
Back	70 (68 %)
Other	4 (3.9 %)
Diagnosis[d]	
Osteoarthritis	15 (14.6 %)
Common back pain	44 (42.7 %)
Vertebral fracture /compression	18 (17.5 %)
Inflammatory arthropathies	7 (6.8 %)
Peripheral neuropathy	7 (6.8 %)
Other	7 (6.8 %)

[a] 17 missing values

[b] 5 missing values

[c] 5 missing value

[d] 5 missing values

After DXP market withdrawal

At the first visit after DXP withdrawal, after the patients had finish their personal DXP stock, 40.8 % of patients were treated only with a step 1 analgesic, 53.4 % remained on a step 2 drug, 2.9 % received a step 3 analgesic and 2.9 % did not receive any analgesic medication (Table 2).

Table 2 Treatment strategy

Treatment strategy	Before 01/03/2011 (number of patients)	After 01/03/2011 (number of patients)
Step 1 analgesics	103	42 (40.8 %)
Step 2 analgesics	102 (99.0 %)	55 (53.4 %)
Step 3 analgesics	1 (1.0 %)	3 (2.9 %)
No step 1 to 3 analgesic	0	3 (2.9 %)

None of the patients were still treated with DXP. The step 2 analgesics prescribed, in decreasing order, were tramadol, codeine and opium (Table 3). NSAID prescriptions remained stable. Patients who started tramadol after DXP withdrawal did not differ from the other patients on baseline values (data not shown). Thirteen patients were treated with drugs specific for neuropathic pain versus only five patients before DXP withdrawal. Four patients received a combination of two opioids.

VAS pain scores evaluated by the GP remained unchanged (supplementary figure 1 and figure 1A) as did the impact of pain on daily activities (Fig. 1b).

Discussion

In this study in elderly patients with chronic pain living at home, recruited by their general practitioners, DXP prescriptions were switched mainly to paracetamol alone or tramadol after DXP market withdrawal.

To our knowledge, only one study, conducted in a teaching hospital, has focused on changes in analgesic prescriptions following DXP withdrawal [1]. The authors found a 28 % decrease in consumption of step 2 analgesics. Our findings are similar although the observed decrease was even larger, reaching almost 50 %. The authors also found an increase in tramadol prescriptions, which is in agreement with our findings since three patients were treated with tramadol before DXP withdrawal compared with 37 patients after DXP withdrawal. These authors also reported an increase in consumption of step 1 analgesics, mainly paracetamol. In our study, all the patients were taking paracetamol before and almost all after March 2011, so we cannot demonstrate an increase in paracetamol prescriptions. This takes into account the fact that DXP was only available as a dextropropoxyphene/paracetamol combination. On the other hand, after DXP withdrawal, 40.8 % of patients were treated with only a step 1 analgesic, mainly paracetamol, and NSAID prescriptions remained low and stable.

Table 3 Pharmacologic class prescribed

Pharmacologic class	Before January 03, 2011 (number of patients)	After January 03, 2011 (number of patients)
NSAIDs	16	17
Paracetamol	103	94
Dextropropoxyphene	103	0
Tramadol	4	37
Codeine	0	14
Opium	0	9
Morphine	1	2
Fentanyl	0	1
Anti-neuropathic drugs	5	13

The sum of each column is greater than the total cohort because each patient received a combination of analgesics.

Lastly, there was no increase in step 3 analgesic prescriptions in either the hospital study [1] or in our study. Surprisingly, DXP was mainly switched to tramadol, another step 2 analgesic, even though in France, this drug has been implicated as the cause of serious adverse drug reactions between 1987 and 2006 [2]. In contrast, codeine, the step 2 analgesic which appears to be best tolerated and which is prescribed first-line in many countries, was used in only 14 patients, or 27 % of those treated with a step 2 analgesic. Also noteworthy was the finding that a non-negligible number of patients in our study were treated with opium, which is available in France as an oral or rectal formulation at unit doses of 10 or 15 mg, with a maximum daily dose of 100 mg. After DXP withdrawal, nine patients (17 %) receiving a step 2 analgesic were treated with opium every day. This switch from DXP to opium was not observed in the hospital study [1] because opium is not available in hospital pharmacies, but like tramadol and codeine, it can be obtained by prescription for ambulatory patients.

We also noted that some prescriptions, such as combinations of step 2 or step 2+3 analgesics, did not comply with international guidelines. Although these inappropriate combinations were infrequent, they nonetheless reflect real-life prescribing practices. After DXP withdrawal, 13 patients were treated with anti-neuropatic pain drugs, vs only five before withdrawal. This might suggest that some elderly with neuropathic pain might have been wrongly treated with an opioid before DXP withdrawal. Apart from these few deviations, we observed that the recommendations of the French Medicines Agency (ANSM) relating to DXP market withdrawal [11] were closely followed. These recommendations propose that chronic pain should be re-assessed after discontinuation of DXP and that patients on low or intermediate DXP doses should be switched to paracetamol alone, while those on high DXP doses should be offered another step 2 analgesic. The recommendation does not propose a hierarchy for the choice of step 2 analgesic and advises against the use of NSAIDs in the elderly.

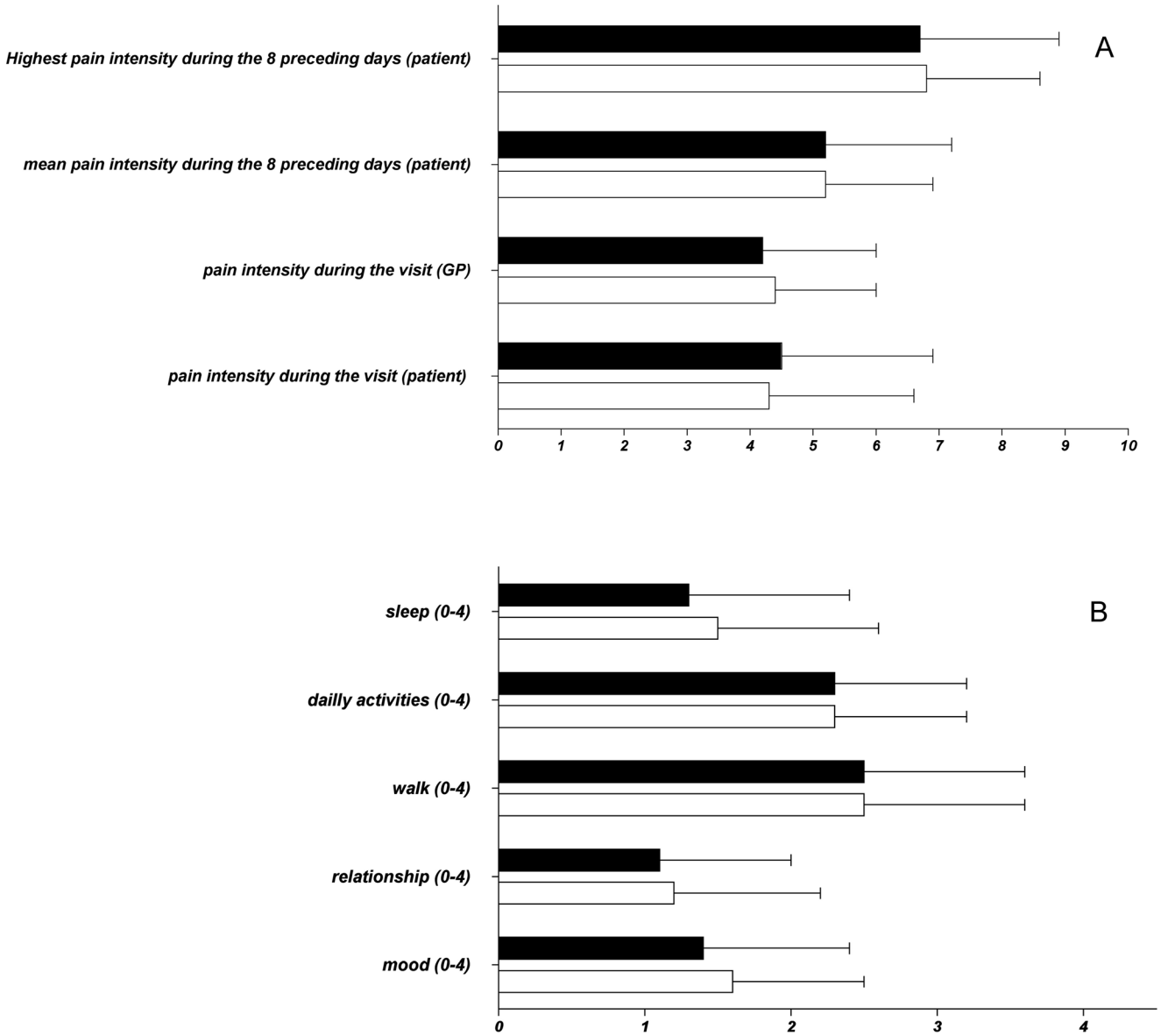

Fig. 1 Pain assessments. **a** Chronic pain assessments based on patients' or GPs' evaluation using a visual analogue scale ranging from 0 (no pain) to 10 (the highest imaginable pain). **b** Impact of chronic pain on different daily activities, assessed by the patient using a visual analogue scale ranging from 0 (no impact) to 4 (dramatic impact). *Black* before DXP withdrawal. *White* after DXP withdrawal. Data are presented as mean± SD

This study presents several limits: (a) study patients were non-institutionalised with relatively preserved cognitive functions. Among more fragile institutionalised patients, the consequences of analgesic drug modifications might have been more pronounced and less well tolerated. (b) One-third of the patients came from two other sub-cohorts (type 2 diabetes mellitus and atrial fibrillation) that differed mainly from the chronic pain sub-cohort by their sex ratio (more men) and baseline pain intensity (lower). This heterogeneity may introduce a bias, although pain assessment had been similar in the three sub-cohorts. (c) One-third of the patients chronically treated by DXP before its withdrawal, were not included in the present study due to absence of pain evaluation after DXP withdrawal. This might introduce a selection bias.

Several analgesics before DXP have been withdrawn from the market because of toxicity, including phenacetin, glafenine and noramydopyrine. To our knowledge, there have been no studies of the consequences of these withdrawals on the quality of pain management. The main finding of our study is that DXP market withdrawal had no deleterious consequences on the management of elderly patients with chronic pain. The mean pain intensity scores during the visit evaluated by both the general practitioner and the patient remained stable at around 4/10 before and after DXP market

withdrawal. The same was true for pain intensity in the 8 days preceding the visit. Also, the impact of pain on mood, relationships, walking, daily activities and sleep remained unchanged.

In conclusion, in elderly patients living at home and treated for chronic pain by their general practitioner, DXP market withdrawal had no effect on pain intensity or the impact of pain on daily activities. DXP prescriptions were switched to paracetamol, tramadol, codeine and opium.

Conflict of interest Lazkani A, Delespierre T, Benattar-Zibi L, Sophie Bucher, Ourabah R and Piedvache C have no conflict of interest. Becquemont L received consulting fees from Sanofi-Aventis, Pfizer, Servier and lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp and Dohme. Close family member working at Sanofi France. Bauduceau B received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, Novo Nordisk. Bertin P received consulting fees from Sanofi-Aventis, Pfizer, Ethypharm, Reckitt-Benkiser and speaking fees from Genevrier, Roche, Bristol-Myers Squibb, Merck Sharp and Dohme. Berrut G received fees from Sanofi, Lundbeck, Eisai, Novartis, Merck Sharp and Dohme, Amgen, Boehringer-Ingelheim, Bayer. Corruble E received consulting fees from Servier, Lundbeck, Sanofi-Aventis, Bristol Myers Squibb, Eisai. Danchin N received consulting or speaking fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, MSD-Schering Plough, Novartis, Novo Nordisk, Pierre Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, and The Medicines Company. Derumeaux G received consulting or speaking fees from Actelion, Boehringer-Ingelheim, Pfizer, Sanofi-Aventis, and Servier, Research grant from Actelion and Astra Zeneca. Doucet J received speaking fees from Novo Nordisk, consulting fees from Sanofi-Aventis, Novo Nordisk, Merck-Serono and research partnership with Lilly. Falissard B received consulting fees from Sanofi-Aventis, Servier, Roche, AstraZeneca, Grünenthal, Lilly, HRA, Boeringher-Ingelheim, Bayer, Novartis, Genzyme, Stallergenes, Daiichi, Otsuka, Bristol-Myers Squibb. Forette F received speaking and consulting fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Eisai, Exonit Fabre, Ipsen, Janssen-Cilag, Lilly, Lundbeck, Novartis, Merck Sharp and Dohme, Merz, Pfizer, Roche, Sanofi-Aventis, Servier, Schwarz Pharma, Specia, Warner-Lambert, Wyeth. Hanon O received speaking and consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer, Eisai, Exonit, Janssen-Cilag, Lundbeck, Novartis, Pfizer, Sanofi-Aventis, Servier. Pasquier F: investigator for Eisai, ExonHit, Novartis, Ipsen, Medivation, Pfizer, Bayer, Noscira, Sanofi, Roche, GE Healthcare. Consulting fees from Lilly, Bayer, Janssen, Sanofi. Pinget M received speaking and consulting fees from Asdia, AstraZeneca, Bristol-Myers Squibb, Medtronic, Merck Sharp and Dohme, Novo Nordisk, Novartis, Roche Diagnostics, Ypsomed.

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