



Compliance with Prescribing and Dispensing Conditions for Valproate and Related Substances in Girls and Women of Childbearing Potential: A Survey of Community Pharmacists in France

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Abstract

Introduction Prenatal exposure to valproate and related substances is associated with a risk of malformations and/or neurodevelopmental disorders. In France, prescription and dispensing conditions of oral valproate forms are subject to risk minimization measures for girls and women of childbearing potential with the aim to limit pregnancy under this treatment. These risk minimization measures were issued in 2015 and were strengthened in 2018.

Objective We aimed to evaluate compliance with prescription and dispensing conditions of valproate for oral administration: an annual prescription from a specialist and a signed risk acknowledgment form.

Methods Two prospective observational surveys were carried out between 2018 and 2020 on a representative sample of French community pharmacies. Data were collected from female patients aged 2–49 years presenting to one of the participating pharmacies with a valproate prescription.

Results In total, 1067 and 824 valproate prescriptions were analyzed in 2018 and 2020, respectively, the majority of which were for girls and women of childbearing potential ($\geq 92\%$). The prescription and dispensing conditions for valproate were met in 42% of cases (95% confidence interval 39–45) in 2018 and in 47% of cases (95% confidence interval 43–50) in 2020. Compliance levels were higher for prescriptions from neurologists ($\geq 60\%$) than from other prescribers ($\leq 45\%$).

Conclusions In France, the implementation of specific risk minimization measures for girls and women of childbearing potential with respect to oral valproate forms and related substances requires a stronger involvement of stakeholders. Increased awareness and compliance among healthcare professionals regarding risk minimization measures could limit prenatal exposure to valproate.

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1 Introduction

Valproate and relative substances (sodium valproate/valproic acid, sodium divalproate, and valpromide), hereafter called “valproate,” are molecules with anti-seizure and mood regulation properties, which are indicated in the treatment of epilepsy and bipolar disorders [1–3]. Their use during pregnancy is known to be associated with

Key Points

In France, valproate and related substances are subject to measures governing prescription and dispensing to girls and women of childbearing potential, which were introduced in 2015 and strengthened in 2018.

Five years after first being introduced and 2 years after the measures were last strengthened, compliance with these measures among valproate prescribers remained stable, with no significant improvement since 2017.

All stakeholders, including health authorities, should increase and diversify their communication efforts with healthcare professionals to raise awareness of risk minimization measures to limit prenatal exposure to valproate.

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teratogenic and fetotoxic risks [4, 5]. A meta-analysis reported that the incidence rate of congenital malformations in newborns exposed in utero to valproate was approximately 11%, while it was 3.3% in newborns of healthy women [6]. Another meta-analysis showed that newborns exposed in utero to valproate monotherapy had a six-fold higher risk of malformations than newborns of non-epileptic mothers and a three-fold higher risk than newborns of untreated epileptic mothers [7]. In addition, there is evidence of an increased risk of neurodevelopmental disorders, such as psychomotor or cognitive developmental delays, in children exposed in utero to valproate and related substances, with studies reporting different frequencies of occurrence up to 30–40% in preschool children [5, 8–13]. The evidence of an increased risk of congenital malformations and neurodevelopmental disorders after valproate in utero exposure led the European Medicines Agency in 2014 to strengthen warnings and measures to prevent valproate exposure during pregnancy [14].

Following these recommendations, in France, risk minimization measures (RMMs) have been implemented in 2015, which included educational materials for both healthcare professionals and patients and the introduction of specific prescribing and dispensing conditions (PDCs) for the use of valproate in girls and women of childbearing potential. The PDCs include: (1) mandatory annual prescription from a specialist in neurology, pediatrics, or psychiatry; (2) prescription renewal carried out by any physician, within the limit of 1 year; and (3) an annual risk acknowledgment form, signed by both the specialist and the patient. The annual prescription and the annual risk acknowledgment form must be presented to the pharmacist each time valproate is dispensed to girls and women of childbearing potential or to those who are pregnant. Additionally, since 2017, a patient card is provided by the pharmacist to the patients at each dispensation. Moreover, a visual warning about the risk of valproate use during pregnancy is also affixed on the outer packaging of valproate medicines.

As utilization studies had previously shown that the patterns of the use of valproate in women of childbearing potential had not changed significantly from 2014 to 2016, a second referral procedure was triggered in March 2017 to assess the impact of the RMMs in the current pregnancy exposure to medicines containing valproate and their impact on the benefit–risk balance. These measures were subsequently strengthened in 2018 with the introduction of a pregnancy prevention program (PPP) [15]. Valproate must not be prescribed to girls and women of childbearing potential, unless they are enrolled in a PPP and other treatments are ineffective or not tolerated. The PPP ensures that patients

use effective contraception and undergo regular pregnancy tests (once a month). It also ensures that patients get their treatment reviewed by their prescriber annually to reassess the need for valproate therapy or alternative treatment options [16, 17]. For pregnant women, valproate-based treatments are fully contraindicated for bipolar disorders while for epilepsy, valproate-based treatments are contraindicated unless there is no suitable therapeutic alternative [16, 17]. Finally, since December 2019, a detachable card from the outer box containing essential safety information has been available for distribution at the time of dispensing the drug. Moreover, since 2020, a quick response code has been made available on the outer packaging of medicine that can direct the patient to educational materials and a patient leaflet from the health authority's website.

To assess the implementation of these RMMs by healthcare professionals in France (i.e., the level of compliance with valproate PDCs), four surveys were undertaken by Sanofi, France since 2016 on the request of the health authorities. Evaluation focused solely on compliance with the two PDCs (mandatory annual prescription by a specialist and a signed annual risk acknowledgment form) to ensure comparability between the different surveys. The first two surveys conducted in 2016 and 2017 showed a 31 and 47% compliance to PDCs, respectively [18]. In the context of strengthened measures in 2018 with the introduction of the PPP, we describe the results of the third (at the time of the strengthening in 2018) and fourth (after the strengthening in 2020) surveys and the overall evolution of the rate of compliance with the valproate PDCs by healthcare professionals in France since 2016.

2 Methodology

2.1 Survey Design and Plan

The two surveys were methodologically identical: national observational prospective surveys of pharmacies in mainland France. The surveys were conducted in accordance with the ethical recommendations of the Declaration of Helsinki, the recommendations on Ethics and Best Practice in Epidemiology [19], and applicable French and European regulations. Verbal consent was requested before including participants in the surveys.

Participating pharmacies were selected by centralized dynamic allocation and stratified by region, size of town, and pharmacy sales. From the second survey in 2017 onward, pharmacies that had already participated in one of the previous surveys were selected as a priority.

2.2 Inclusion Criteria and Data Collection

A paper questionnaire on the PDCs applicable to valproate-based treatments was sent to each pharmacy. All female patients aged 2–49 years presenting to the pharmacy with a prescription for an oral form of valproate or relative substances were included in the study, and a questionnaire was completed for each prescription dispensed. Patients were included from June and August 2018 for the third survey and from February and June 2020 for the fourth survey. A longer recruitment period was necessary for the fourth survey because of the coronavirus disease 2019 pandemic.

2.3 Primary and Secondary Evaluation Criteria

The primary evaluation criterion was the percentage of patients who met both PDCs for valproate defined as follows: a prescription from a specialist and a signed risk acknowledgment form, both established and/or signed within 1 year prior to the study date. The primary evaluation criterion (percentage and 95% confidence interval [CI]) was described overall and for the following two subgroups: girls aged 2–12 years and girls and women of childbearing potential aged 13–49 years.

The secondary evaluation criteria included compliance with PDCs by the type of prescriber (general practitioner vs specialist) and indication for valproate (epilepsy vs bipolar disorder). The frequency and characteristics of dispensing in cases of non-compliance with PDCs were also analyzed.

2.4 Procedure

The survey questionnaire was completed by participating pharmacists for any prescription of valproate to a female patient aged 2–49 years (Electronic Supplementary Material [ESM]). Questionnaires were completed in the presence of the patient (or their legal representative) at the time of dispensing.

2.5 Sample Size

For each survey, the inclusion of 1000 patients was estimated to describe the primary evaluation criterion with an accuracy of 2–3% in the overall population, as well as in the subgroup of girls/women of childbearing potential, assuming a PDC compliance rate of between 40 and 90%.

2.6 Statistical Analysis

The statistical analysis was descriptive and was conducted using IBM SPSS Statistics version 17.0 (IBM, Armonk, NY, USA). Categorical variables were described using number, percentage, and 95% CI.

3 Results

3.1 Description of the Population

For the 2018 survey, 1097 questionnaires were completed by pharmacies during the 3-month inclusion period, of which 1067 (97.3%) were analyzable (questionnaires for which the age range and the primary evaluation criteria [Questions 7a and 7b; see ESM] were completed). For the 2020 survey, 833 questionnaires were completed during the 5 months of inclusion, of which 824 (98.9%) were analyzable.

The characteristics of valproate prescriptions for the 2018 and 2020 surveys are summarized in Table 1. In both surveys, most prescriptions concerned women of childbearing potential, with a slight decrease recorded between 2018 and 2020: 96% of women of childbearing potential in 2018 versus 92% in 2020. Most of the patients were treated for epilepsy; this proportion slightly increased between 2018 and 2020: from 60 to 69%. In approximately half of the cases, the prescription came from a general practitioner. Among patients aged 2–12 years, around 20% of the prescriptions came from a general practitioner in both surveys. In this age group, the majority of the prescriptions came from a neurologist or pediatrician in the 2018 survey and from a pediatrician in the 2020 survey (Table 1).

The majority of the analyzed prescriptions concerned renewals and < 5% of the prescriptions were valproate initiations in both surveys. Most of these treatment initiations (74% in 2018 and 94% in 2020) were prescribed by a specialist and were in compliance with the prescribing guidelines. A decrease in treatment initiations by a general practitioner was observed in the 2020 survey: of the 35 initial treatments in 2020, only two (6%) were prescribed by a general practitioner, compared with ten (26%) of 39 in 2018.

3.2 Compliance with the PDCs for Valproate

The analysis of the primary evaluation criterion for the 2018 and 2020 surveys is presented in Table 2. All PDCs were met in 42% of cases (95% CI 39–45) in 2018 and in 47% of cases (95% CI 43–50) in 2020. Compliance with PDCs can be broken down as follows: a valid annual risk acknowledgment submitted in 46 and 49% of cases and a valid prescription from a specialist in 77 and 80% of cases in 2018 and 2020, respectively.

In patients aged 2–12 years, PDCs were met in only 17% of cases (95% CI 8–26) in 2020, compared with 25% of cases (95% CI 13–37) in 2018. In this age group, a decrease in the presentation of prescriptions written by a specialist was observed from the previous year (92% in 2018 vs 78% in 2020). Within the 2–12 years of age group, there was also a lower proportion of signed risk acknowledgment forms

Table 1 Characteristics of valproate prescriptions in girls and women of childbearing potential

	Survey 2018			Survey 2020		
	Total (<i>N</i> = 1067) ^a	Girls (aged 2–12 years) (<i>N</i> = 48)	Girls and women of childbearing potential (aged 13–49 years) (<i>N</i> = 1019)	Total (<i>N</i> = 824)	Girls (aged 2–12 years) (<i>N</i> = 65)	Girls and women of childbearing potential (aged 13–49 years) (<i>N</i> = 759)
Products pre-scribed, <i>n</i> (%)	(<i>N</i> = 1067)	(<i>N</i> = 48)	(<i>N</i> = 1019)	(<i>N</i> = 821)	(<i>N</i> = 65)	(<i>N</i> = 756)
For epilepsy						
Originator ^b	537 (50%)	48 (100%)	489 (48%)	469 (57%)	65 (100%)	404 (53%)
Generics	109 (10%)	0	109 (11%)	96 (12%)	0	96 (13%)
For bipolar disorder ^c	421 (40%)	NA	421 (41%)	256 (31%)	NA	256 (34%)
Prescriber, <i>n</i> (%)	(<i>N</i> = 1053)	(<i>N</i> = 46)	(<i>N</i> = 1007)	(<i>N</i> = 818)	(<i>N</i> = 64)	(<i>N</i> = 754)
General practitioner	505 (48%)	9 (20%)	496 (49%)	370 (45%)	13 (20%)	357 (47%)
Specialist						
Neurologist	205 (19%)	17 (37%)	188 (19%)	181 (22%)	13 (20%)	168 (22%)
Psychiatrist	301 (29%)	NA	301 (30%)	194 (24%)	1 (2%)	193 (26%)
Pediatrician	26 (2%)	15 (33%)	11 (1%)	55 (7%)	32 (50%)	23 (3%)
Other ^{d,e}	16 (2%)	5 (11%)	11 (1%)	18 (2%)	5 (8%)	13 (2%)
Type of prescription, <i>n</i> (%)	(<i>N</i> = 1059)	(<i>N</i> = 47)	(<i>N</i> = 1012)	(<i>N</i> = 818)	(<i>N</i> = 65)	(<i>N</i> = 753)
Initial	39 (4%)	2 (4%)	37 (4%)	35 (4%)	2 (3%)	33 (4%)
Renewal	1020 (96%)	45 (96%)	975 (96%)	783 (96%)	63 (97%)	720 (96%)

NA not applicable because not indicated for this age group

^aThere were some missing data while reporting information

^bSodium valproate (Depakine[®]) and sodium valproate/valproic acid (Depakine Chrono[®], Micropakine[®])

^cSodium divalproate (Depakote[®]) and valpromide (Depamide[®])

^dHospital prescriber (6), neuropsychiatrist (3), neuropsychiatrist (2), or other specialty (5) for the 2018 survey

^eHospital prescriber (2), neuropsychiatrist (9), or other specialty (7) for the 2020 survey

compared with that observed in the total study population. For girls and women of childbearing potential, PDC compliance findings were similar to that of the whole study population (Table 2).

For both surveys, the level of compliance with the PDCs was broadly similar depending upon whether the prescription was for an originator product indicated for epilepsy or bipolar disorder (Table 3). The level of compliance with the PDCs also varied according to the type of prescriber (Table 3): for both surveys, the compliance was higher for neurologists followed by psychiatrists and pediatricians. While the level of compliance with PDCs was stable between 2018 and 2020 for all these specialist physicians, it increased among general practitioners.

About 55% of patients in 2018 and 61% in 2020 received the patient card. The increase in patient card utilization between 2018 and 2020 was observed not only among women of childbearing potential (from 56 to 62%) but also among patients aged 2–12 years (from 33 to 48%).

3.3 Frequency and Characteristics of Dispensing That Did Not Comply with the Prescribing Conditions

When the prescribing conditions were not met, pharmacists rarely contacted the prescribing physicians (only 22–23% of the time in both surveys). However, they contacted the prescribing physicians more often when an initial prescription did not meet the prescribing conditions (40% of cases in 2018 and in 54% of cases in 2020).

Despite not meeting the prescribing conditions, valproate was still dispensed in most cases (98% of non-compliant prescriptions in both surveys). The main reason (65–68% of cases in both surveys) given for dispensing was to avoid the abrupt discontinuation of treatment.

In 2020, at the time of dispensing, in 85% of cases (vs 94% in 2018), pharmacy staff ensured that the patient (or her legal representative) knew and understood the risks associated with the treatment and in 81% of cases (vs 87% in 2018), pharmacy staff ensured that the patient was aware of the requirement for an annual specialist consultation.

Table 2 Compliance with prescribing and dispensing conditions for valproate in girls and women of childbearing age

	Survey 2018			Survey 2020		
	Total (<i>N</i> = 1067)	Girls (aged 2–12 years) (<i>N</i> = 48)	Girls and women of childbearing age (aged 13–49 years) (<i>N</i> = 1019)	Total (<i>N</i> = 824)	Girls (aged 2–12 years) (<i>N</i> = 65)	Girls and women of childbearing age (aged 13–49 years) (<i>N</i> = 759)
Compliance with prescribing and dispensing conditions^a						
<i>n</i> (%)	451 (42%)	12 (25%)	439 (43%)	385 (47%)	11 (17%)	374 (49%)
95% confidence interval	39–45	13–37	40–46	43–50	8–26	46–53
Presentation of the annual risk acknowledgment form dated < 1 year ago						
<i>n</i> (%)	496 (46%)	12 (25%)	484 (47%)	400 (49%)	13 (20%)	387 (51%)
Presentation of a specialist's prescription dated < 1 year ago						
<i>n</i> (%)	818 (77%)	44 (92%)	774 (76%)	658 (80%)	51 (78%)	607 (80%)

^aComposite primary evaluation criteria: submission of a signed risk acknowledgment form and a prescription from a licensed specialist, both <1 year old

Table 3 Compliance with prescribing and dispensing conditions for valproate by product prescribed and type of prescriber

	Survey 2018		Survey 2020	
	<i>N</i>	Compliance with prescribing and dispensing conditions ^a <i>n</i> (%)	<i>N</i>	Compliance with prescribing and dispensing conditions ^a <i>n</i> (%)
Prescribed products				
For epilepsy				
Originator ^b	537	220 (41%)	469	210 (45%)
Generics	109	41 (38%)	96	55 (57%)
For bipolar disorder ^c	421	190 (45%)	256	118 (46%)
Type of prescriber				
General practitioner				
	505	180 (36%)	370	168 (45%)
Specialist				
Neurologist	205	123 (60%)	181	113 (62%)
Psychiatrist	301	128 (43%)	194	82 (42%)
Pediatrician	26	8 (31%)	55	16 (29%)

^aPresentation of a signed risk acknowledgment form and a specialist prescription, both < 1 year old

^bSodium valproate (Depakine[®]) and sodium valproate/valproic acid (Depakine Chrono[®], Micropakine[®])

^cSodium divalproate (Depakote[®]) and valpromide (Depamide[®])

3.4 Evolution of Compliance with PDCs Between 2016 and 2020

The results of the survey over the past 4 years are presented in Fig. 1. The overall compliance rate was 31% (95% CI 28–33) in 2016, 47% (95% CI 44–50) in 2017 [22], 42% (95% CI 39–45) in 2018, and 47% (95% CI 43–50) in 2020.

It should be noted that in pharmacies that participated in at least one of the three previous surveys (21 pharmacies that dispensed a total of 544 prescriptions), the compliance rate observed in 2020 was slightly higher, reaching 51% (95% CI 47–55).

4 Discussion

Prescribing and dispensing conditions for valproate products in girls and women of childbearing potential in France were implemented in 2015 and warnings and measures were strengthened in 2018. In this analysis, we found that health-care professionals complied with the PDCs in 42% of cases in 2018 and in 47% of cases in 2020. For patients aged 2–12 years, the rate of compliant prescriptions was 25% and 17% in 2018 and in 2020, respectively. For girls and women of childbearing potential, PDC compliance findings were similar to that of the whole study population.

This low overall compliance rate was due to the non-presentation of the signed annual risk acknowledgment form at the time of dispensing in half of cases. This form, to be completed and signed jointly at least once a year by both the specialist physician and the patient or legal representative, was introduced following the first evaluation of valproate prescribing guidelines for girls and women of childbearing potential by the European Medicines Agency in 2014 [14]. It ensures that patients (or the legal representatives of minors or adults under safeguard measures) are fully aware of the risks associated with the use of valproate during pregnancy. It also enables the physician to confirm the specific circumstances that led to the prescription of valproate (i.e., resistance/ineffectiveness or intolerance to other treatments).

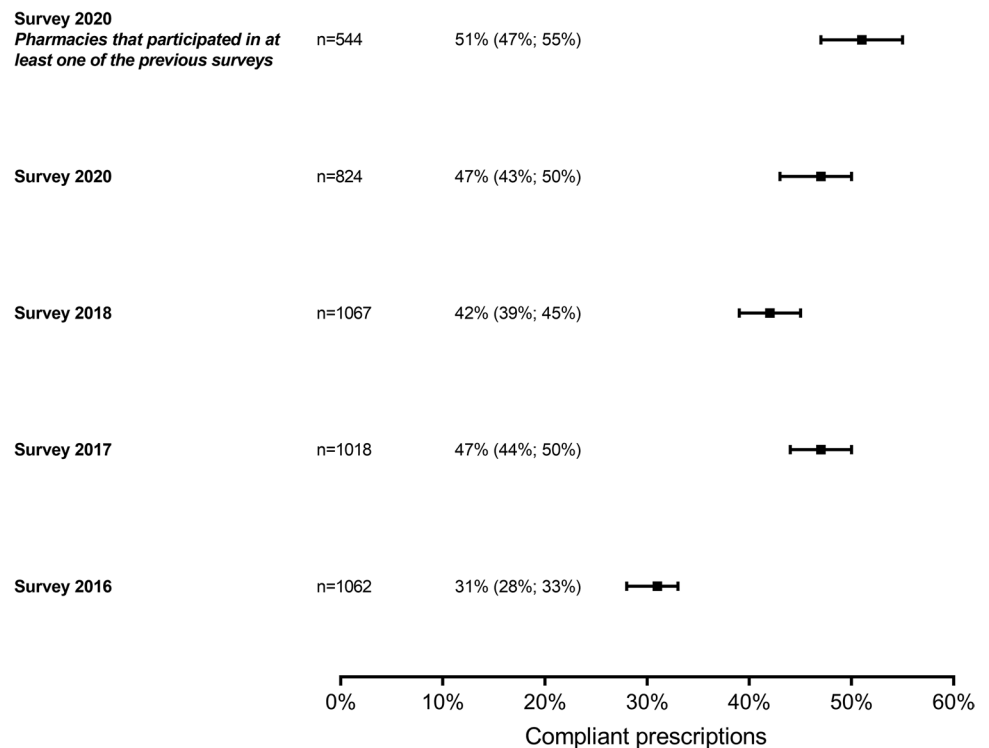
In addition to the annual risk acknowledgment form, dispensing of valproate to girls and women of childbearing potential also requires an annual prescription from a specialist. This measure is well respected, with compliant prescriptions in at least 80% of cases among patients of both groups: girls aged 2–12 years and girls and women of childbearing potential. Between 2018 and 2020, compliance with this measure remained stable for girls and women of childbearing potential (from 76 to 80%) but decreased for girls aged 2–12 years (from 92 to 78%). This may be explained by the fact that girls aged 2–12 years are not of childbearing potential, even though they, or their caregivers/legal representatives, should sign the annual risk acknowledgment form. This mandatory annual prescription by a specialist is an essential part of the PPP for female patients treated with

valproate. In particular, it requires regular reassessment of the individualized benefit–risk balance of treatment. While a general practitioner can renew the prescription during the year, it is essential that they refer the patient to a specialist to re-evaluate her treatment each year.

In addition to the need for a routine yearly assessment, reassessing the benefit–risk balance of valproate is particularly important when the female patient reaches puberty or is considering pregnancy. In these situations, the prescriber must evaluate the therapeutic alternatives to valproate [20].

The results reported here are from the third (2018) and fourth (2020) surveys conducted after the introduction of valproate prescribing guidelines in girls and women of childbearing potential in 2015, which were strengthened in 2018. The first two surveys had shown an improvement, from 31 to 47%, in the compliance rate between 2016 and 2017 [18]. However, the data from the third survey, conducted in 2018, showed an overall stabilization or even a slight decline in the compliance level, with a compliance rate of 42%. Similarly, the 2020 survey results showed the level of compliance returning to the levels found in 2017 (compliance rate: 47%). In the UK, a survey conducted in 2017, 2 years after initial measures were introduced, revealed that 64% of women of childbearing potential treated with valproate reported that they had been informed and understood the risks associated with their treatment [21]. The analysis of the French National Health Insurance Database from 2011 to 2017 considering 114,936 female patients with epilepsy aged under 50 years found that prevalent use of valproate

Fig. 1 Percentage of prescriptions complying with valproate prescribing conditions between 2016 and 2020. Horizontal error bars and numbers in parentheses indicate 95% confidence intervals. ^aPharmacies that participated in at least one of the previous surveys



among girls and women of childbearing potential with epilepsy had decreased significantly after the implementation of RMMs, after the first referral in 2015. This analysis also reported that there was a significant change in valproate incident use, although there were still 317 women and 206 girls who started treatment with valproate in 2017.

In addition to the Direct Healthcare Professional Communication, health authorities could intensify national television and/or online campaigns, targeting general practitioners who are more frequently consulted by girls and women of childbearing potential for treatment initiation with valproate or for its renewal. A similar approach can be followed for raising awareness among the specialists as well. Improved information from healthcare professionals to patients is also essential to ensure that patients are aware of the risks and take an active part in reducing them, such as by using effective contraception and undergoing regular pregnancy tests. Pharmacists, specialists, and general practitioners have a key role to play in this public health mission. Our survey reveals that in approximately nine out of ten cases, pharmacists who dispensed the product made sure that the patient was informed of the risks associated with valproate during pregnancy despite non-compliance with the prescription rules.

Although this survey was not designed to collect information about the reasons for not being compliant to PDCs, an online study among 215 clinical specialists in the UK reported that one third of both the patients and the clinicians were “dissatisfied” or “strongly dissatisfied” with the risk acknowledgment form. Clinicians reported that patients found the risk acknowledgment form “time-consuming,” a “tick-box exercise,” “invasive,” “marginalizing,” and “weighted toward the patient in terms of accountability” [22]. Our data suggest that, despite government information and communication campaigns targeting healthcare professionals in France, the implementation of RMMs for girls and women of childbearing potential receiving valproate remains insufficient. All physicians prescribing a valproate-based product must be properly informed of these measures and apply them in their daily practice. The recent results of the EPI-PHARE study showed that valproate exposure in women of childbearing potential and pregnant women decreased significantly in France between 2013 and 2018, with the decrease accelerating after May 2015 (the date of implementation of the various measures following the first referral) [23]. Despite this drop, the number of women of childbearing potential exposed to valproate remains high, > 30,000 female patients aged 15–49 years received valproate treatment in France during the second quarter of 2019. This finding justifies continued efforts in order to inform healthcare professionals about RMMs via communication campaigns, although reaching zero prescription will not be feasible as valproate remains the only alternative for some girls and women [23].

Findings from this study should be interpreted with caution. This survey was not designed to analyze the 1-year window according to the initial/renewal prescription of valproate to investigate the reasons and factors associated with noncompliance to PDCs by physicians or patients to identify patients undergoing contraception. Because of the longitudinal nature of this study, there could be heterogeneity between the populations and investigators involved in each survey. Variation in observations between different surveys may reflect real variation, heterogeneity between surveys, or a combination of these.

5 Conclusions

The results of these surveys show that, in France, there is still insufficient compliance with the RMMs put in place to limit the use of valproate in girls and women of childbearing potential. Robust and effective interventions, involving all health stakeholders, must be taken to ensure appropriate compliance to the RMMs and PPP and to improve awareness among all valproate prescribers regarding the need to comply with the prescribing guidelines. Only through collective efforts, involving all stakeholders of the healthcare system (e.g., pharmaceutical companies, health authorities, governments, medical and pharmacy schools, pharmacists, and physicians [including their professional associations]), will it be possible to limit the number of women exposed to valproate during pregnancy.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40264-022-01234-8>.

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Declarations

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Conflict of interest Khristina Fauvelle and Jean Joel Bigna are employees of Sanofi, France and may hold shares and/or stock options in the company.

Ethics approval This article does not contain data from any individual. According to the French Public Health code, ethics committee approval or the granting of exemption of ethic committee approval is not a prerequisite for research not involving human subjects.

Consent to participate Data analyzed in this survey were provided by pharmacists and were not collected data from patients. As this study did not include any patient/person, written patient consent was not required. Verbal consent was requested before including participants in the surveys.

Consent for publication Not applicable.

Availability of data and material All data generated by the surveys conducted in 2018 and 2020 are provided in full in this article. The datasets generated by the surveys conducted in 2016 and 2017 are available on the ANSM website at: https://archiveansm.integra.fr/var/ansm_site/storage/original/application/cfc9902b616321c0fc3bc742dc57053b.pdf.

Code availability Codes generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author contributions KF participated in the conception and design of the study, provided data, contributed to data analysis and interpretation, and reviewed several versions of the manuscript. JJB contributed to the interpretation of the data and reviewed several versions of the manuscript. KF and JJB approved the final version of the manuscript and its submission for publication.

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