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REPORT

COMPOUND: VPA and related substances

Non-Interventional retrospective longitudinal study in the United Kingdom and France to investigate the therapeutic strategies after discontinuation of VPA and related substances in clinical practice

VALSE / VALNAC09344

Final Report - Abstract

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TITLE	VALSE (VALNAC09344): Non-Interventional retrospective longitudinal study in the United Kingdom and France to investigate the therapeutic strategies after discontinuation of valproate (VPA) and related substances in clinical practice.
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KEYWORDS	Valproate WCBP chronic users, bipolar disorder, epilepsy, claims multi-database study, cohort study.
RATIONALE AND BACKGROUND	Valproate (VPA) and related substances have been licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorder (BD) in Europe. In March 2017, a referral under Article 31 of Directive 2001/83/European Commission was initiated and the Pharmacovigilance Risk Assessment Committee (PRAC) assessed the impact of the risk minimisation measures in the current pregnancy exposure to the treatment with medicinal products containing substances related to valproate and their impact on the benefit-risk balance. Several consultations including a Public Hearing and two Scientific Advisory Group meetings with Neurologists and Psychiatrists were held in September and October 2017. During these consultations, considerations were discussed with clinicians about the case when a woman of childbearing potential (WCBP) (aged 13 to 49 years) treated with valproate is unable to comply with an effective contraception method or is willing to become pregnant or finds out she is pregnant. It was highlighted that the currently available recommendations regarding switching or discontinuation of valproate are insufficient. The outcome of the Referral procedure was approved on 31 May 2018, recommended new restrictions on the use of valproate and set-up of a pregnancy prevention program. Also, further studies to characterise the nature and extent of the risks posed by valproate are imposed on all Marketing Authorisation Holders (MAHs). Among those, a retrospective study that aims to evaluate and identify the best practices for therapeutic management after valproate discontinuation in clinical practice was proposed. The MAHs conducted two analyses, one in France using the SNDS, a nationwide claims database, and one in UK using the CPRD, a GP electronic medical records database. This final report presents the overall results, in both SNDS and CPRD databases, according to the amended protocol v8.0 approved by the EMA: it presents the results related to the description of the treatment patterns, the identification and characterisation of the different clusters (group of women with similar treatment patterns), at baseline and during follow-up, including determination of clusters that were the most likely to reflect a success in epilepsy/ BD management after VPA discontinuation as well as the identification of covariates associated with the clusters, and those associated with the other studied outcomes.

RESEARCH QUESTION AND OBJECTIVES	The study aimed to investigate the therapeutic strategies implemented when VPA is discontinued in clinical practice for WCBP. The study population was split for each indication of VPA (epilepsy or BD) in the overall population of VPA WCBP chronic users and, in a subpopulation of pregnant women. The **primary study objective** was to determine the clusters of women that are the most likely to reflect a success in epilepsy/ BD management after VPA discontinuation based on: (i) the description of the overall treatment patterns in the year following VPA discontinuation, (ii) the categorisation of women according to their treatment patterns after VPA discontinuation (clusters), and (iii) the description of women's and treatment characteristics at baseline, and clinical relapse occurrence, pregnancy occurrence, and other healthcare resources in the follow-up period in each of these clusters. For each cluster, Success/Failure in epilepsy/BD management after VPA discontinuation was defined based on the absence of VPA reintroduction in the follow-up period. This was contextualised according to several clinical and pharmaceutical parameters such as: clinical relapse, number of hospitalisations and polypharmacy. Results were then discussed with the Scientific Committee to determine which cluster(s) was (were) the most likely to reflect a success in epilepsy/ BD management after VPA discontinuation. The **secondary study objective** was to identify the baseline factors (e.g., women's, Epilepsy/BD treatments, disease characteristics) associated with the potential successful/unsuccessful clusters.
STUDY DESIGN	Cohort study of WCBP chronic users of VPA for either epilepsy or BD, who have discontinued VPA during the inclusion period with a follow-up of up to one year after inclusion, using the French SNDS and UK CPRD databases.
SETTING	The index date was defined as the last supply day of the last VPA prescription/dispensing before discontinuation during the inclusion period from 1 January 2014 to 31 December 31 2017 (4 years). A pre-index period of at least 1 year and until the first data available in the CPRD database and of 5 years before the index date in SNDS database was defined for each woman. Each woman has been followed for 1 year after the index date, or until the date of death or database eligibility lost, whichever came first. Data were extracted from 1 January 1987 to 31 December 31 2018, for women identified in CPRD database and from 1 January 2009 to 31 December 31 2019, for women identified in SNDS database. A supplementary year was extracted in SNDS to ensure a period of 9 months in addition to the 1-year of follow-up, necessary to accurately define all pregnancies as the delivery date is included in the pregnancy identification algorithm.
SUBJECTS AND STUDY SIZE, INCLUDING DROPOUTS	All WCBP, i.e., aged 13 to 49 years, chronic users of VPA for either epilepsy or BD who have discontinued VPA during the inclusion period were included. Women with less than at least1-year of historical data in the database, with both epilepsy and BD, and with less than 3 months of follow-up in the database were excluded. Pregnant subpopulation was all women of the study population who were pregnant at inclusion or during follow-up.

VARIABLES AND DATA SOURCES

Variables

Exposure

- Drugs of interest:
  - VPA and its related substances (ATC code: N03AG01 and N03AG02).
  - Other antiepileptic drugs.
  - Drugs indicated in BD (antidepressants, mood stabilisers and neuroleptic drugs).
- Valproate exposure (before the index date and during follow-up):
  - Index date (i.e., date of last VPA prescription/dispensing plus the number of days supply of the last prescription/dispensing).
  - Chronic use of VPA (i.e., being continuously exposed to VPA during the year before the index date: Medication Possession Ratio (MPR)> 60% and no VPA discontinuation) followed by a VPA discontinuation after a 60-day grace period.
  - VPA dose-tapering phase before valproate discontinuation.
  - VPA discontinuation (i.e., absence of new prescription/dispensing of VPA for at least 60 days after the days supplied by the last prescription/dispensing) assessed before the index date and after VPA reintroduction.

Main outcomes

To describe all situations of therapeutical management after discontinuation that could be observed in clinical practice, 14 different treatment states were defined according to the observed previous “on treatment” state:

- Monotherapy: only 1 drug of interest for epilepsy/BD (excluding VPA).
- Double therapy: 2 distinct drugs of interest for epilepsy/BD (excluding VPA).
- Combination therapy: ≥3 distinct drugs of interest for epilepsy/BD (excluding VPA).
- Different monotherapy: 1 medication that differs from the previous sequence treatment.
- Different double therapy: ≥ 1 of the 2 medications that differ from the previous sequence treatment.
- Different combination therapy: ≥ 1 of the medications of the combination therapy that differ from the previous sequence treatment.
- VPA reintroduction.
- Monotherapy + VPA reintroduction.
- Double therapy + VPA reintroduction.
- Combination therapy + VPA reintroduction.
- Different monotherapy + VPA reintroduction.
- Different double therapy + Valproate reintroduction;
- Different combination therapy + VPA reintroduction.
- Not exposed to any epilepsy/BD medication (including VPA).

These treatment states were identified each month (frequency of dispensing of the drugs of interest in SNDS), from the day after the index date to the end of the follow-up, forming an individual treatment pattern for each woman. The overview of the overall treatment patterns was represented graphically, using a sequence index plot, to illustrate the succession of treatment sequences over time for each woman.

This step was then followed by the determination of clusters defined as groups of women sharing homogeneous treatment patterns of the different predefined sequences according to time periods, using an unsupervised clustering method.

All the identified clusters and their women's characteristics were reviewed by two independent clinical experts (Scientific Committee), each of them being specialist in each studied disease (epilepsy and BD) to determine which ones were the most relevant according to their experience in clinical practice. Relevant clusters that were the most likely to reflect a success in epilepsy/BD management after VPA discontinuation were identified based on the non-reintroduction of VPA, contextualised with clinical and pharmaceutical parameters such as the number of hospitalisations, polypharmacy and other parameters supplemented by Scientific Committee experts with regard to the results and their interpretation.

Secondary outcomes

The following secondary outcomes were assessed to complement the main outcome during the year of follow-up for either epilepsy or BD in the overall cohort and by clusters: first occurrence of VPA reintroduction, occurrence of clinical relapse and occurrence of pregnancy.

Other outcomes were also considered: hospitalisation and discharge diagnoses, emergency room (ER) visits**,** number of office visits to GP, neurologist or psychiatrist or other medical specialty or other relevant health care professionals, overlapping between VPA and pregnancy, death from any cause and sick leave days.

Modelling analyses to identify factors associated with clusters were exploratory conditioned by the size of the clusters and the number of candidate covariates.

Data sources

The study has been based on secondary data collection from the French nationwide claims, the SNDS and a United Kingdom electronic medical records database, the CPRD.

The ***SNDS database*** contains individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires.

The ***CPRD*** is a primary care database containing anonymised patient records for about 6% of the UK population. Its strengths as a research tool include its size, representativeness of patient and practice characteristics, and a virtually complete medical history of patients due to the recording of referral to secondary care. More than 700 participating general practices are required to record (i) each episode of illness, or new occurrence of a symptom, and (ii) all significant morbidity events, e.g., all significant clinical contacts, all significant diagnoses and abnormal test results, all referrals to outpatient clinics and hospital admissions practices.

RESULTS

Epilepsy cohorts

Clusters

Between 2014 and 2017, from the 136,782 women with at least one VPA dispensing identified in the SNDS, 36,057 were WCBP and discontinued VPA (according to protocol definition) after 1-year of chronic use (MPR> 60%). Of these, 7,345 WCBP

with an epilepsy diagnosis and who discontinued VPA after at least 1-year chronic use were included in the epilepsy cohort. According to a clustering method, we found that most of them (67.3%, n=4,941) were included in clusters with a trend to not reintroduce VPA after discontinuation and 32.7% (n=2,404) in clusters with a trend to reintroduce VPA after discontinuation.

In SNDS, for women with a trend to not reintroduce VPA after discontinuation, 27.7% were included in a cluster with a trend to not use any epilepsy treatment (n=2,036), 25.5% in a cluster with a trend to use only one epilepsy treatment as monotherapy (n=1,871), 10% in a cluster with a trend to use two epilepsy treatments as bitherapy (n=737), and 4% in a cluster with a trend to use a combination therapy (n=297).

In SNDS, for women with a trend to reintroduce VPA after discontinuation, the reintroduction was mostly stable and continuous although around 18% of the women discontinued again VPA after reintroduction. Three clusters with a trend to VPA reintroduction were differentiated: reintroduction with VPA alone (17.5% of the women, n=1,286), with one (10.3%, n=760) or with two (4.9%, n=358) other treatments for epilepsy.

Similar patterns of treatment discontinuation were found in the **CPRD data**. From the 4,900 women identified with at least one VPA prescription record in the CPRD, 662 were WCBP and discontinued VPA (according to the protocol definition) after 1 year of chronic use (MPR> 60%). Of these, 358 women were included in the CPRD epilepsy cohort, about half of them (49.4%, n=177) had a trend to not reintroduce VPA after discontinuation and the other half to reintroduce VPA (50.6%, n=181).

In CPRD, for women with a trend to not reintroduce VPA after discontinuation, 20.9% had a trend to not use any epilepsy treatment (n=75), 20.7% to use only one epilepsy treatment as monotherapy (n=74), and 7.8% to use two epilepsy treatments as bitherapy (n=28).

In CPRD, for women who had a trend to reintroduce VPA after discontinuation, the reintroduction seemed stable and continuous although 41.5% of the women discontinued VPA again after reintroduction. Three clusters with a trend to VPA reintroduction were differentiated: with VPA alone (24.0%, n=86) or with one (11.5%, n=41) other treatment for epilepsy, or with a melting pot of many different changes (15.1%, n=54, mix cluster).

Relapses

For women with a trend to not reintroduce VPA in SNDS, the proportion who relapsed during the follow-up period increased with the number of epilepsy treatments, and the figures were generally lower than those observed in the previous year (7.0% vs. 10.6% in the no epilepsy treatment cluster, 11.2% vs. 13.0% in the monotherapy cluster, 18.6% vs. 19.5% in the double therapy cluster) except for the combination therapy cluster (36.7% vs. 31.6%). In contrast, the mean number of clinical relapses per woman was slightly higher during the follow-up than in the pre-index period for all clusters (2.2 vs. 1.7 in the no epilepsy treatment cluster, 1.5 vs. 1.4 in the monotherapy cluster, 1.8 vs. 1.6 in the double therapy cluster), except for the combination therapy cluster (2.3 vs. 2.5).

For women with a trend to reintroduce VPA in SNDS, the proportion who relapsed during the follow-up period increased with the number of treatments, and the figures remained broadly like those observed in the previous year (11.6% in the VPA+monotherapy cluster and 21.5% in the VPA+double therapy cluster). The mean number of clinical relapses per woman in the year of follow-up was slightly higher than that observed in the previous year in the VPA alone cluster (1.4 vs. 1.2) and in

the VPA+double therapy cluster (2.6 vs. 2.5) but remained similar in the VPA+monotherapy cluster (1.5). In CPRD data, the low proportion of women with HES linkage and the low numbers of women in each cluster limited the interpretation of clinical relapses by cluster in the previous and in the follow-up periods.

Associated factors

Considering the SNDS multivariable analysis, comparing clusters with a trend to not reintroduce VPA to clusters that tend to reintroduce VPA (reference), factors associated with not reintroducing VPA were: more specific care during the 90 days before the index date (OR= 2.33, 1.90 and 2.30 for an EEG +/- MRI alone, neurologist/psychiatrist consultations alone, and both, respectively), VPA dose-tapering phase in the 1-year pre-index period (OR=2.40), levetiracetam or lamotrigine dispensed during the 90 days before the index date (OR=1.81 and 1.54, respectively), MPR>80% during the 1-year pre-index period (OR=1.42), pregnancy at index date (OR=1.96), and having other psychiatric disorders (OR=1.37). While factors associated with a more likely reintroduction of VPA were: older ages (OR=0.49, 0.68 and 0.82 for [40-49], [30-39], and [20-29] year old respectively, vs. [13-29]), no exposure to a specific treatment for epilepsy within the 3 months after the index date (OR=0.59), more dispensing of other specific nervous system treatments during the 90-day period before the index date (OR=0.73 and 0.58 for [4-5] treatments and >5 treatments, respectively, vs <4 treatments), a longer history of epilepsy (OR=0.71 and 0.63 for]4-5[years of history and ≥5 years, respectively, vs. <1 year), or having paraplegia (OR=0.59). In CPRD, the small size of the clusters did not allow modelling analyses in the epilepsy cohort. Nevertheless, the same trends seemed to be observed.

Subgroup of pregnant women

In the SNDS database, among the 7,345 women of the epilepsy cohort, 513 (7.0%) were identified as being pregnant over the study period: most of them (85.8%, n=440) had a trend to not reintroduce VPA after discontinuation. Same trends of clustering as in the overall cohort were observed in pregnant women. In the CPRD database, of the 358 women of the epilepsy cohort, 24 (6.7%) were identified as being pregnant over the study period, an insufficient number to use a clustering method.

Bipolar disorder cohorts

Clusters

Between 2014 and 2017, from the 136,782 women with at least one valproate dispensing identified in the SNDS, 36,057 were WCBP and discontinued valproate (according to protocol definition) after 1 year of chronic use (MPR> 60%). Of these, 9,943 WCBP with a BD diagnosis and who discontinued VPA after at least one year of continuous treatment were identified in the SNDS and included in the BD cohort. According to a clustering method, we found that most of them (66.9%, n=6,648) were in clusters with a trend to not reintroduce VPA after discontinuation, and 33.1% (n=3,295) in clusters with a trend to reintroduce VPA after discontinuation.

In SNDS, for women with a trend to not reintroduce VPA after discontinuation, 32.7% were included in a cluster with a trend to not use any treatment specifically indicated in BD (n=3,249), 25.6% in a cluster with a trend to use only one treatment specifically indicated in BD as monotherapy (n=2,542), and 8.6% in a cluster with a trend to use two treatments as bitherapy (n=857).

In SNDS, for women with a trend to reintroduce VPA after discontinuation, the reintroduction seemed stable and continuous although around 23% discontinued VPA again after reintroduction. Two clusters with a trend to VPA reintroduction were

differentiated: with VPA alone (17.7% of women, n=1,764) or with one other treatment for BD (15.4%, n=1,531).

Similar patterns of treatment discontinuation were found in the **CPRD data**. From the 4,900 women identified with at least one valproate prescription record in the CPRD, 662 were WCBP and discontinued valproate (according to the protocol definition) after 1 year of chronic use (MPR> 60%).

In CPRD, for women with a trend to not reintroduce VPA after discontinuation, 22.2% had a trend to not use any specific BD treatment (n=32), 14.6% to use only one specific BD treatment as monotherapy (n=21), 10.4% to use two specific BD treatments as bitherapy (n=15), and 16% to use a melting pot of many different changes (mix BD cluster, n=23).

In CPRD, for women with a trend to reintroduce VPA after discontinuation, the reintroduction seemed stable and continuous although 39.6% discontinued VPA after reintroduction. Two clusters with a trend to VPA reintroduction were differentiated: with VPA alone (16.0%, n=23) or with one other treatment for BD (20.8%, n=30).

Relapses

For women with a trend to not reintroduce VPA in SNDS, the proportion who relapsed during the follow-up period increased with the number of BD treatments, and the figures were lower than those observed in the previous year in all clusters (20.6% vs. 24.4% in the no specific treatment cluster, 27.0% vs. 31.8% in the monotherapy cluster, 38.5% vs. 43.4% in the double therapy cluster). In contrast, the mean number of clinical relapses per woman was slightly higher during the follow-up than in the pre-index period for all clusters (2.7 vs. 2.2 in the no epilepsy treatment cluster, 2.2 vs. 2.0 in the monotherapy cluster, 2.5 vs. 2.2 in the double therapy cluster).

For women with a trend to reintroduce VPA, the proportion of women who relapsed during the follow-up period was slightly lower than that observed in the previous year (16.4% vs. 19.0% in the VPA alone cluster and 28.2% vs. 29.5% in the VPA+monotherapy cluster). In contrast, the mean number of clinical relapses per woman during the year of follow-up was slightly higher than that observed in the previous year (2.0 vs. 1.8 in the VPA alone cluster and 2.3 vs. 2.1 in the VPA+monotherapy cluster). The proportion of women who relapsed decreased after VPA reintroduction and remained stable afterwards. In CPRD data, the low proportion of women with HES linkage and the low numbers in each cluster limited the interpretation of clinical relapse by cluster in the previous and the follow-up periods.

Associated factors

In the SNDS multivariable analysis, comparing clusters with a trend to not reintroduce VPA to clusters that tend to reintroduce VPA (reference), the main factors associated with not reintroducing VPA were: lamotrigine or lithium dispensed during the 90 days before the index date (OR=4.32 and 2.26, respectively), dose-tapering phase within the 1-year pre-index period (OR=1.84), MPR>80% during the 1-year pre-index period (OR=1.55), and previous pregnancy starting during the 1-year pre-index period (OR=1.79). While the main factors associated with a more likely reintroduction of VPA were: older ages (OR=0.70 and 0.46 for [30-39] and [40-49] years old, respectively, vs. [13-29]), a longer history of BD (OR=0.84, 0.62 and 0.60 for [1-4],]4-5[and ≥5 years, respectively, vs. less than one year), no exposure to a specific treatment for BD within the 3 months after the index date (OR=0.54), or same specific BD treatment within the month before and after the index date (OR=0.63). Other factors were also associated with more or less VPA successful discontinuation (use, during the 90 days pre-index period, of specific neuroleptic treatment, of specific nervous system

treatment, of non-specific nervous system treatment, of treatment other than those for the nervous system, number of psychiatrist/neurologist consultations; within the year before the index date, other cancer under surveillance and addictive disorders, duration of sick leave allowance over 90 days) but with a lower strength of association. According to the SNDS stratified analyses, similar factors and odds ratios were observed for women using VPA alone or in combination with one or more other specific epilepsy treatments before VPA discontinuation.

In CPRD, the small size of the clusters did not allow to perform modelling analyses in the BD cohort. Nevertheless, some similar trends seemed to be observed.

Subgroup of pregnant women

In the SNDS database, among the 9,943 women of the BD cohort, 452 (4.5%) were identified as being pregnant over the study period; all of these women had a trend to not reintroduce VPA. Same trends of clustering as in the overall cohort were observed in pregnant women.

In the CPRD database, of the 144 women of the BD cohort, only 9 (6.3%) were identified as being pregnant over the study period, an insufficient number to use a clustering method.

DISCUSSION

Limitations

A main limitation inherent in the SNDS claims database, is the lack of information regarding the severity and the specific type of the disease (type of BD, previous course of the disorder), the justification of treatment prescriptions, and the reasons for discontinuing or reintroducing VPA, which can impact the results interpretation. This limitation led us to exclude a large number of women without mention of epilepsy or BD diagnosis in the database. A selection bias by considering more severe cases than in the overall population may be thus induced. In CPRD data, selection bias could have been introduced as only women followed by general practitioners (GP) and drugs prescribed by GP were entered in the CPRD database. A misclassification bias may have been introduced if the GP entered an inaccurate or not precise diagnosis resulting in a wrong cohort assignment.

Another limitation of both SNDS and CPRD databases is that drug identification was based on drugs dispensing (SNDS) and prescription (CPRD) but not on consumption. Misclassification of exposure for some women may thus be possible and slightly overestimate the proportion of women with VPA reintroduction, but should have a limited impact on factors of success for VPA discontinuation.

For clinical relapses, data available in the SNDS only allows the identification of events requiring hospitalisation and events with emergency room visits without hospitalisation, as well as events managed in outpatient settings such as in partial epilepsy, were not captured. Consequently, the actual clinical relapses incidence is probably underestimated by taking into account only the more severe cases.

Finally, we recognise that residual confounding may remain in multivariate analyses designed to identify factors associated with successful VPA discontinuation. Numerous variables that could influence the decision to stop VPA and its success are missing from the claim database used in this study.

Interpretation

To our knowledge, this study is the first to investigate the therapeutic strategies that are implemented when VPA is discontinued in clinical practice for WCBP in two large population-based studies.

Clusters

Using similar clustering methods in SNDS and CPRD cohorts of women who discontinued VPA after at least one year of continuous use for epilepsy or BD (MPR>60%), we found 5 to 7 very similar clusters in both datasets based on epilepsy or BD specific treatments patterns in the year following VPA discontinuation. Two main groups of clusters may be distinguished, those with a trend to reintroduce VPA, and those with a trend to not reintroduce VPA.

In the light of the overall results, and further to the advice of clinical experts in neurology and psychiatry, clusters with a trend to not reintroduce VPA may truly reflect a success in VPA discontinuation. The rate of full discontinuation (defined as no reintroduction at all during the one-year follow-up) was of 49.5% and 47.9% in the SNDS epilepsy and BD cohorts, respectively. Because of methodological choices (sample biased towards more severe cases, definition of VPA discontinuation, time of follow-up), these rates of discontinuation may neither reflect the true rate of successful VPA discontinuation in real life.

The “successful clusters”, with a trend to use one treatment for epilepsy or BD or to use two or more treatments after VPA discontinuation are homogeneous and show very little VPA reintroduction. These clusters probably truly reflect women who tend not to reintroduce VPA. On the other hand, clusters with a trend to not use any specific treatment appear more heterogeneous; half of the women having sporadic reintroductions of VPA without information of other sporadic reintroductions over the one-year follow-up of the study design. Characteristics of these women were not particularly different from those of the same cluster who did not reintroduce VPA at all. This could be that VPA was actually not interrupted and that this ad-hoc VPA reintroduction was an artefact due to VPA stockpiling, poor compliance and/or use of lower doses.

In the clusters with a trend to not use any specific treatment, another issue relies on the interruption of VPA without replacing it with another treatment which is against any recommendations. It is important to note that recommendations published in 2019 and 2020 could not have had a beneficial impact on switching behaviours captured in the present report as the inclusion period was prior to the recommendations. According to the experts, this does not seem surprising in the context of pregnancy project according to their real-life clinical expertise. In cases with low severity disease, the non-prescription of a specific treatment after VPA discontinuation is an option although it is against treatment guidelines, especially given the large heterogeneity of patients’ profile. As these two databases are completely independent and designed in different ways, this finding is consistent with a correct construction of clusters and the actual existence of this specific subgroup of women.

Clinical relapses

Women with epilepsy

In clusters with a trend of “successful” VPA discontinuation, findings suggest that VPA discontinuation was maintained in women with stable epilepsy. In these women, VPA discontinuation kept over the 1 year of follow-up did not result in increasing the number of epilepsy treatments. In accordance with the national guidelines, the epilepsy treatments frequently dispensed after VPA discontinuation in these clusters were lamotrigine and levetiracetam, alone or in combination. This observation further corresponds to published experts’ consensus where it is noted that levetiracetam is the best option in case of urgent switching. However, it should be noted that in SNDS data clobazam was also an alternative treatment used alone or in combination after

VPA discontinuation. This is surprising as clobazam is not a recommended treatment option in women who discontinue VPA. One explanation could be that clobazam was initiated occasionally in women with more severe epilepsy to stabilise their disease. In clusters with a trend of "unsuccessful" VPA discontinuation, findings suggest that VPA reintroduction was probably motivated by the resurgence of clinical relapses in order to control epilepsy and highlight the risk of switch for people with more unstable epilepsy.

Women with bipolar disorder

In clusters with a trend of "successful" VPA discontinuation, findings suggest that VPA discontinuation was maintained in women with stable BD condition. VPA discontinuation maintained over the 1 year of follow-up did not result in increasing the number of treatments for BD. However, in the monotherapy and double therapy clusters, VPA discontinuation was made at the expense of antidepressant initiation in almost 5% of women, while some of the antidepressants are also suspected to have teratogenic effects or to be at risk of autism. In accordance with the national guidelines, the treatment for BD most frequently dispensed after VPA discontinuation in the clusters with a trend to not reintroduce VPA are atypical neuroleptics (olanzapine, aripiprazole, and quetiapine), but also lithium and lamotrigine. Published expert consensus in BD management are to switch VPA to lithium, lamotrigine, quetiapine, olanzapine, aripiprazole but with a preference for the lithium. In clusters with a trend of "unsuccessful" VPA discontinuation, findings suggest that VPA reintroduction was probably motivated by the resurgence of clinical relapses to control symptoms of BD.

Factors associated with successful VPA discontinuation

Overall, in women with epilepsy and BD, three main factors have been identified as factors associated with a successful VPA discontinuation: a better management of these women (specific care, dose-tapering phase, and better compliance to VPA, use of other specific treatments), less severity of the disease (number of specific nervous system treatments, older history of diseases and older age), and pregnancy and planned pregnancy with dose-tapering. Regarding the use of specific treatment, findings are in line with published results that found that antiseizure medicine resistance was associated with unsuccessful VPA withdrawal in women with epilepsy. Findings regarding severity are consistent with those from two small observational studies using a review of medical records of WCBA with epilepsy where the number of seizures and the history of the disease was consistently associated with unsuccessful switching. Similarly, various studies reported that the use of VPA in WCBA was associated with older age, the number of children, and the absence of pregnancy prospect. Finally, some important comorbidities such as paraplegia, mental impairment, and some cancer under surveillance were associated with less successful VPA discontinuation probably because being pregnant is a less possible or reasonable choice for these women. Regarding mental impairment, other studies suggested that VPA withdrawal might be a challenge for these women, especially due to destabilising for seizure control.

Other factors were associated with VPA successful discontinuation, including high duration of sick leave during the 1-year pre-index period and addictive disorders in women with BD, and other psychiatric disorders in women with epilepsy. Positive associations with addictive disorders in women with BD and with other psychiatric disorders in women with epilepsy could reflect the sometimes significant difficulty in making an accurate diagnosis and thus treating mental illness.

	Conclusion Results of this study highlighted that, in WCBP with epilepsy or bipolar disorder, the discontinuation of VPA after chronic use was maintained in half of the cases, especially in young women with a stabilised disease. VPA was mostly reintroduced in older women with a more advanced disease, and with a resurgence of clinical relapses, probably to control the symptoms of their disease. Treatments used after discontinuation to control symptoms of the disease were consistent with the treatment options recommended by the French Health Authorities published during the study. In women with bipolar disorder, the benefit of maintaining VPA withdrawal needs to be weighed against the initiation of antidepressants for some women, knowing that these treatments may also have harmful effects on newborns. Factors independently associated with successful VPA discontinuation were younger age, shorter history of the disease, better woman management with more clinical and medical examinations, dose-tapering phase before VPA discontinuation, and continued use of previous specific drugs. Finally, planned pregnancy associated with a dose-tapering phase was a strong positive factor for successful VPA discontinuation.
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