Therapeutic strategies after discontinuation of valproate in clinical practice in women with epilepsy or bipolar disorder: a cohort study in UK and France databases

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Background

- Valproate (VPA) is indicated to treat epilepsy and bipolar disorder (BD) and can be teratogenic to unborn children if taken during pregnancy. VPA is contraindicated in pregnant women with BD.
- In 2018, European authorities recommended strong restrictions on the use of VPA in women of childbearing potential (WCBP) and pregnant women, and set-up a pregnancy prevention program. Identifying and evaluating the real-life practices for epilepsy and BD therapeutic management leading to a successful switch after VPA discontinuation were therefore needed.
- **Objective: To determine the clusters of patients most likely to reflect a success in epilepsy or BD management after VPA discontinuation, and to identify their associated factors.**

Methods

- **Study design**: Retrospective non-interventional longitudinal population cohort based on secondary data use (French SNDS and UK CPRD databases).
- **Inclusion:** WCBP who had been using VPA for epilepsy or BD and discontinued its use between 1 Jan. 2014 and 31 Dec. 2017 (index date) were identified in the SNDS and CPRD databases and followed-up for 1 year.
- Clusters of women that most likely reflected a success in epilepsy or BD management after VPA discontinuation were identified using a **partition-around-medoids clustering algorithm** based on treatment patterns. **Success was defined based on "No VPA reintroduction" in the follow-up period, contextualized according to clinical relapse, hospitalization, polypharmacy.**
- Factors associated with success were assessed in SNDS using a logistic regression model.

Results

❖ Clustering results: treatment (ttt) patterns (anti seizure medication, ASM, or ttt for BD#) after VPA discontinuation identified by cluster analysis

Table 1: SNDS	Epilepsy diagnosis	BD diagnosis
Total of WCBP, n	7,345	9,943
Median age [IQR], y	31 [20;41]	42 [35;46]
Successful clusters (trend to not reintroduce VPA in the follow-up period)	67.3%	66.9%

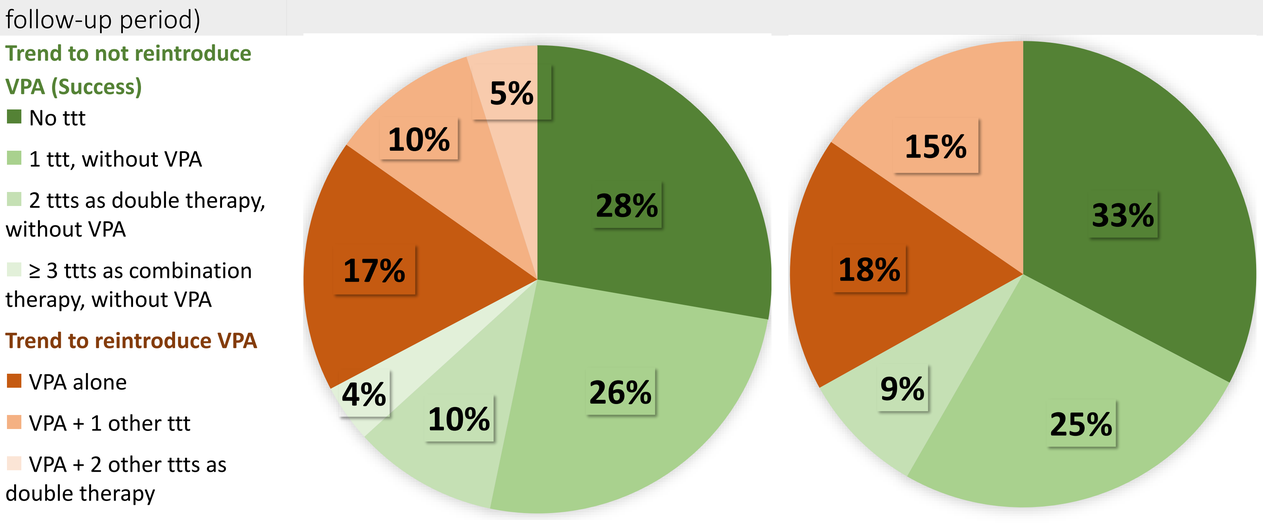
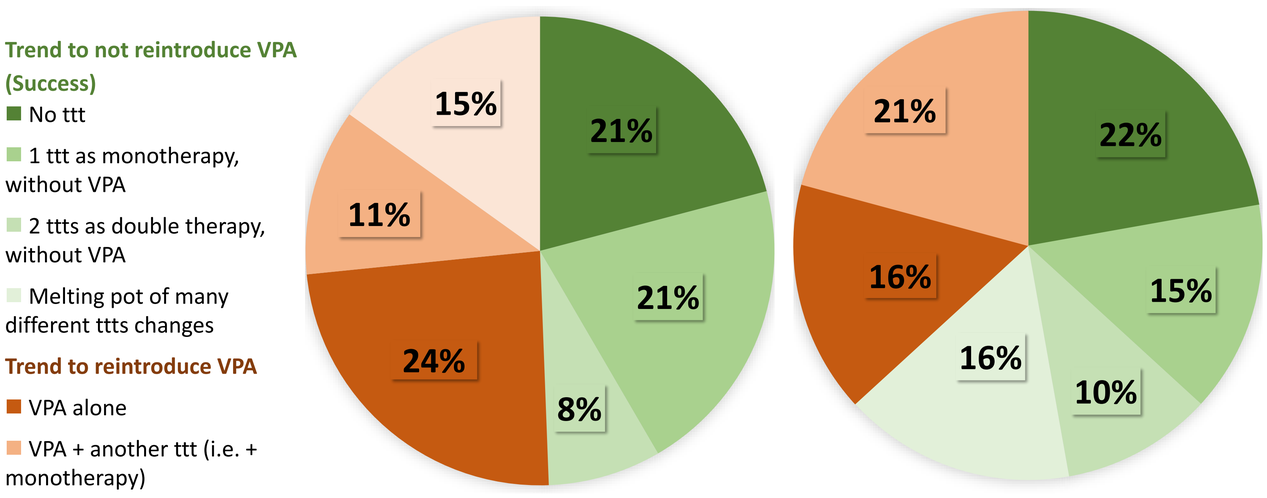


Table 2: CPRD	Epilepsy diagnosis	BD diagnosis
Total of WCBP, n	358	144
Median age [IQR], y	30 [19;41]	40 [33;45.5]
Successful clusters (trend to not reintroduce VPA in the follow-up period)	49.4%	63.2%



 # Specific BD ttt: mood stabilisers [carbamazepine, lamotrigine and lithium], atypical antipsychotics [aripiprazole, olanzapine, quetiapine, risperidone, paliperidone, clozapine], asenapine and lurasidone hydrochloride.

❖ Table3: For epilepsy, factors associated with successful *vs* unsuccessful VPA discontinuation, in SNDS cohort

Factors associated with successful switch	Odds-Ratio, [95% confidence interval]
More specific care (neurology imaging exam, neurologist visits) in the 90 days prior to index date	**2.30** [1.83; 2.90]
VPA dose-tapering phase in the 1-year pre-index	**2.40** [2.08; 2.77]
Pregnancy at index date	**1.96** [1.22, 3.12]
Specific ASM dispensing within the 90 days prior to index date (*vs* 'No dispensing' for each ASM)	
+ Levetiracetam	**1.81** [1.53; 2.15]
+ Lamotrigine	**1.54** [1.32; 1.81]
Factors associated with unsuccessful switch	**Odds-Ratio,** [95% confidence interval]
Older age. [13-19] year old (reference)	
[20-29] year old	**0.82** [0.69; 0.97]
[30-39] year old	**0.68** [0.57; 0.80]
[40-49] year old	**0.49** [0.42; 0.58]
No exposure to an ASM within 3 months after index	**0.59** [0.51; 0.69]
More dispensing of other nervous system treatments during the 90-days prior to index *vs* <4 ttts	
For >5	**0.58** [0.48; 0.69]
For [4-5]	**0.73** [0.62; 0.86]
Longer history of epilepsy vs <1 year of history	
For >5	**0.63** [0.51; 0.78]
For [4-5]	**0.71** [0.56; 0.89]

❖ Table 4: For BD, factors associated with successful switch *vs* unsuccessful VPA discontinuation, in SNDS cohort

Factors associated with successful switch	Odds-Ratio, [95% confidence interval]
Lamotrigine or lithium dispensing in the 90 days prior to index date	
+ Lamotrigine	**4.32** [3.15; 5.93]
+ Lithium	**2.26** [1.86; 2.76]
VPA dose-tapering phase in the 1-year pre-index	**1.84** [1.63; 2.08]
Previous pregnancy starting in the 1-year pre-index	**1.79** [1.22; 2.61]
Factors associated with unsuccessful switch	**Odds-Ratio,** [95% confidence interval]
[13-29] year old (reference)	
For [30-39] year old	**0.70** [0.59; 0.83]
For [40-49] year old	**0.46** [0.39; 0.54]
No exposure to a BD treatment in the 3 months after index date	**0.54** [0.48; 0.62]
Longer history of BD *vs* <1 year of history	
For ≥5	**0.60** [0.51; 0.71]
For [4-5]	**0.62** [0.52; 0.74]
For [1-4]	**0.84** [0.71; 0.98]
Same BD treatment in the month prior to and after index date	**0.63** [0.55; 0.74]

❖ Table 5: Relapses

	Epilepsy diagnosis		BD diagnosis	
	SNDS	CPRD*	SNDS	CPRD*
Clinical relapse (re. epilepsy or BD) within the 1-year pre-index period	12.9%	28.4%	27.8%	23.1%
For women with a trend to not reintroduce VPA, mean number of clinical relapses per woman during the follow-up compared to in the pre-index period for all clusters:				
- In the no specific treatment of the pathology (epilepsy or BD) cluster	2.2 vs. 1.7		2.7 vs. 2.2	
- In the monotherapy cluster	1.5 vs. 1.4	x	2.2. vs. 2.0	x
- In the double therapy cluster	1.8 vs. 1.6		2.5 vs. 2.2	
- For the combination therapy cluster	2.3 vs. 2.5		x	
For women with a trend to reintroduce VPA, mean number of clinical relapses per woman during the year of follow-up compared to the observed in the previous year:				
- In the VPA cluster alone	1.4 vs. 1.2		2.0 vs. 1.8	
- In the CPA + double therapy cluster	2.6 vs. 2.5	x	x	x
- in the VPA + monotherapy cluster	1.5 vs. 1.5		2.3 vs. 2.1	

** 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.*

Conclusions

- Discontinuing VPA was maintained in half of the WCBP with epilepsy or BD, especially if young, with a stabilized disease.
- Treatments used after discontinuation were consistent with the experts' consensus.
- VPA was mostly reintroduced in older women with a more advanced disease and a resurgence of clinical relapses, probably to control their disease.

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Access to the Study Abstract