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

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Background

- Valproate (VPA) indicated to treat epilepsy and bipolar disorder can be teratogenic to unborn children if taken during pregnancy.
- 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 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 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 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 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.
- Baseline factors associated with successful/unsuccessful clusters were also assessed in SNDS database (not feasible in CPRD database due to small sample size) using a logistic regression model.

Results

❖ Clustering results: anti-epileptic drug (AED) treatment patterns after VPA discontinuation identified by cluster analysis

- In total 7,345 (SNDS) and 358 (CPRD) WCBP with an epilepsy diagnosis were included.
- Median age was 31 years (IQR [20; 41] years) (SNDS) and 30 years (IQR [19; 41] years) (CPRD).
- 67.3% (SNDS, **Figure 1**) and 49.4% (CPRD, **Figure 2**) were in successful clusters (trend to not reintroduce VPA in the follow-up period).

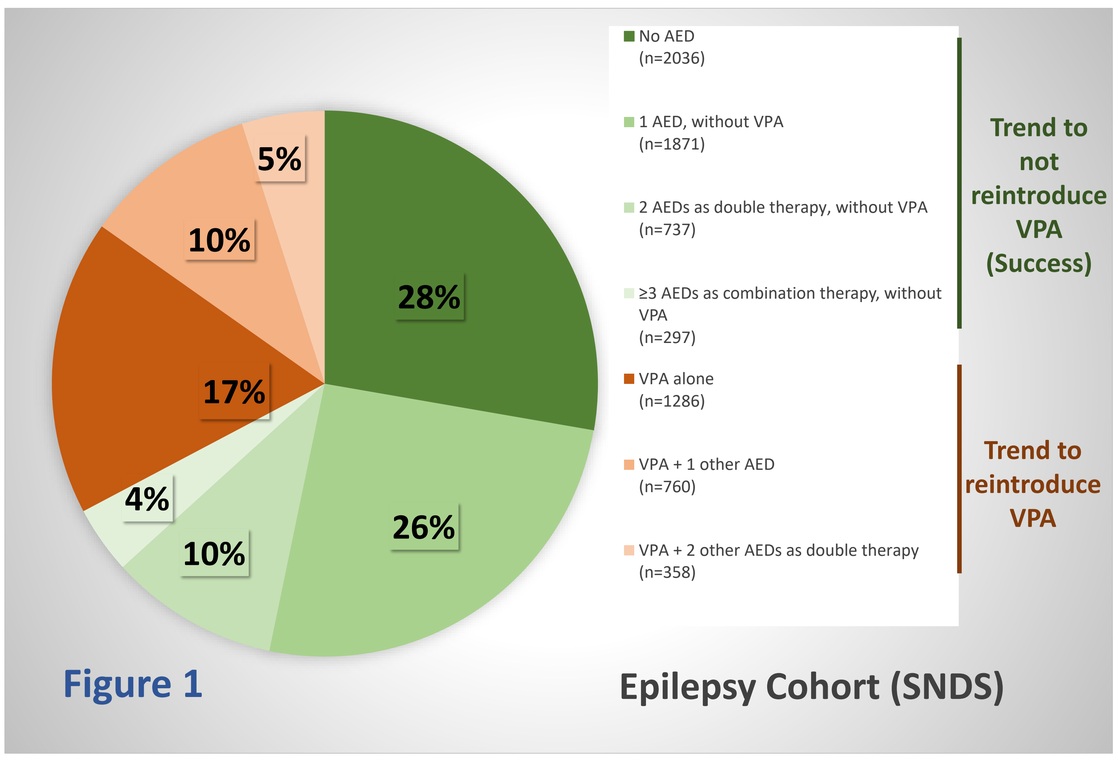

Figure 1 Epilepsy Cohort (SNDS)

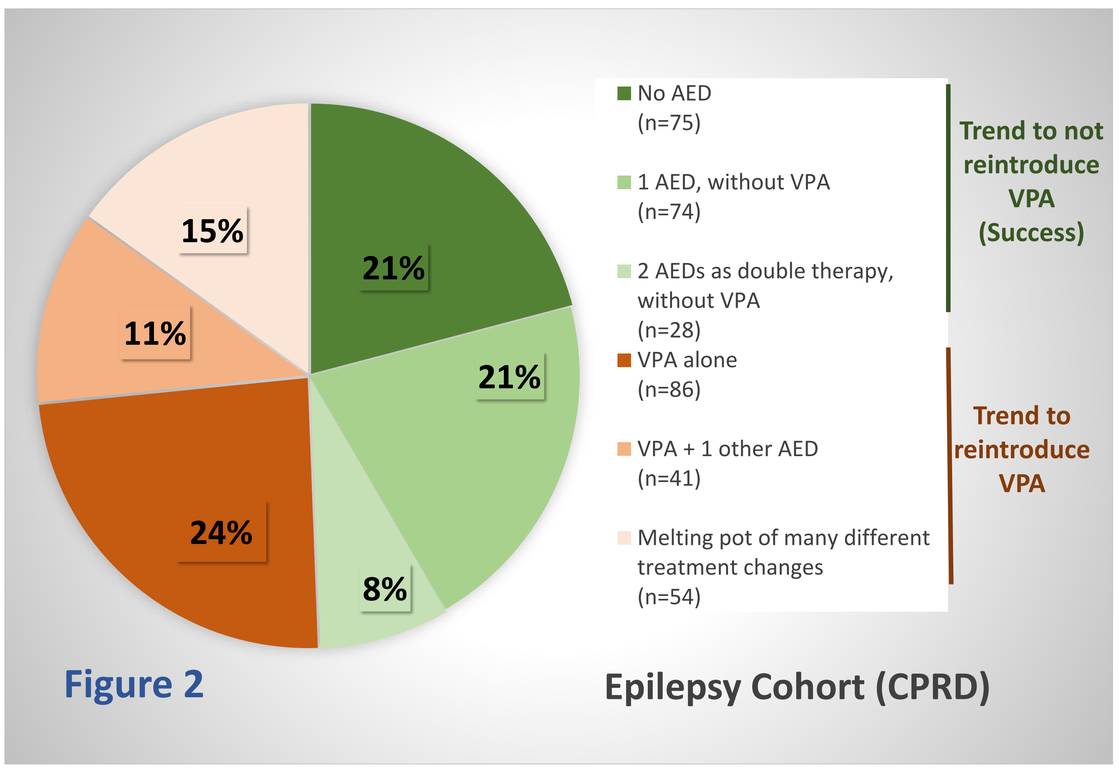

Figure 2 Epilepsy Cohort (CPRD)

❖ Factors associated with successful *vs* unsuccessful VPA discontinuation

Table 1 - Covariates associated with the success of VPA discontinuation in the epilepsy cohort (SNDS)

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

❖ Relapses

- Within the 1-year pre-index period, 12.9% of SNDS cohort and 28.4% of CPRD cohort (among the 109 women with HES-APC linkage available) had a clinical relapse related to epilepsy.
- **For women with a trend to not reintroduce VPA** (SNDS), 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** (SNDS), 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 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, 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 (Table 1) and a resurgence of clinical relapses, probably to control their disease.**

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