Therapeutic strategies after discontinuation of valproate in clinical practice in women with 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.
- 2018: European authorities recommended strong restrictions on the use of VPA in women of childbearing potential (WCBP) and set-up a pregnancy prevention program. Identifying and evaluating the real-life practices for 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 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 to treat 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 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. Baseline factors associated with successful/unsuccessful clusters were also assessed in SNDS database (not feasible in CPRD due to small sample size) using a logistic regression model.

Results

❖ Clustering results: specific BD treatment* patterns after VPA discontinuation identified by cluster analysis

- In total 9,943 (SNDS) and 144 (CPRD) WCBP with a BD diagnosis were included.
- Median age was 42 years (IQR [35; 46] years) (SNDS) and 40 years (IQR [33; 45.5] years) (CPRD).
- 66.9% (SNDS, **Figure 1**) and 63.2% (CPRD, **Figure 2**) were in successful clusters (trend to not reintroduce VPA in the follow-up period).

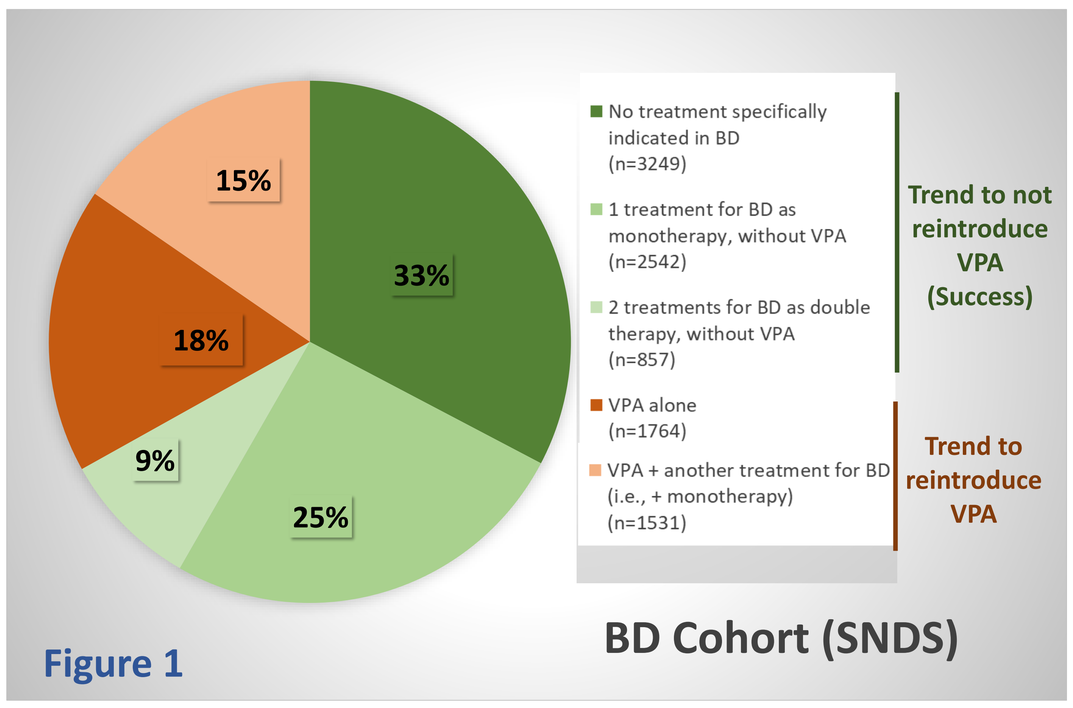

Figure 1

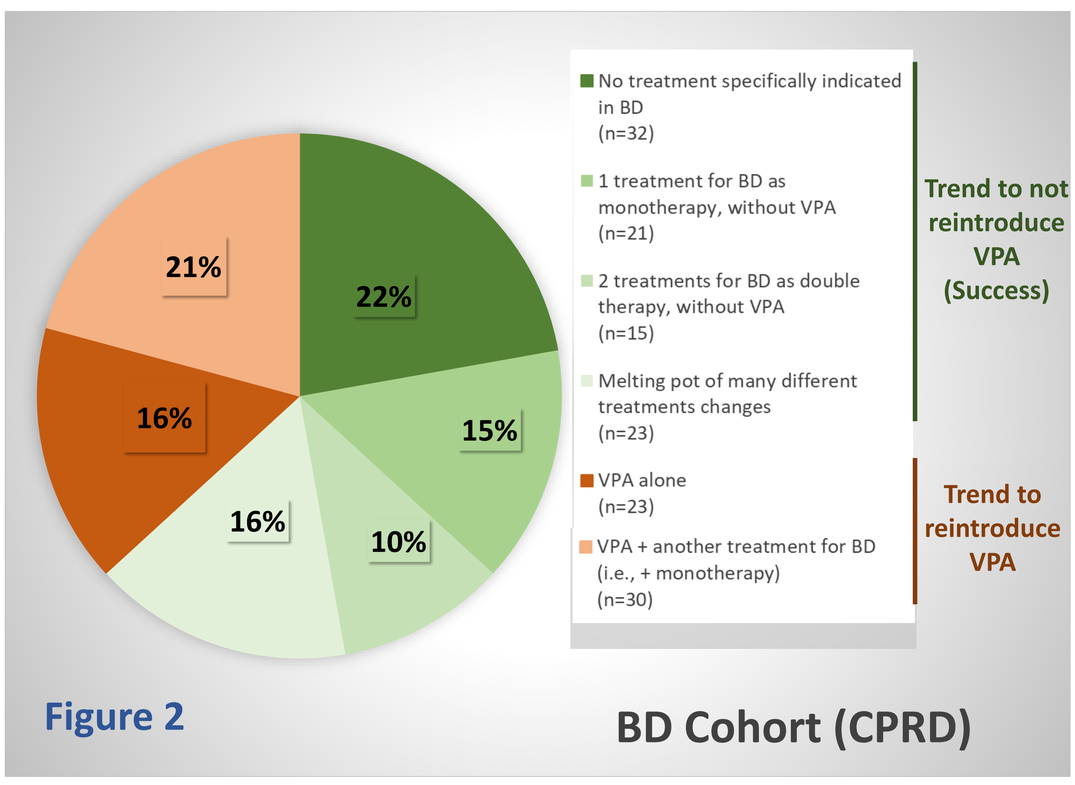

Figure 2

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

❖ Factors associated with successful *vs* unsuccessful VPA discontinuation

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

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

❖ Relapses

- Within the 1-year pre-index period, 27.8% (SNDS) and 23.1% (CPRD, among 52 women with HES-APC linkage) had a clinical relapse related to BD.
- **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 (2.7 *vs*. 2.2 in the no specific BD 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** (SNDS), 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).
- 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.

Conclusion

- **Discontinuing VPA was maintained in half of the WCBP with 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 (Table 1) and a resurgence of clinical relapses, probably to control their disease.**

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