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## **Evolution and characteristics of the use of valproate in women of childbearing age with bipolar disorder: results from the FACE-BD cohort**

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## Abstract

**Background:** Valproate is associated with teratogenic and neurodevelopmental effects. Several agencies have restricted the conditions of its prescription in bipolar disorders (BD). We aimed to assess the evolution of valproate prescription and the clinical profile of BD women of childbearing age receiving valproate.

**Methods:** Based on a large national cohort, we included all BD women 16-50 years old. Sociodemographic, clinical and pharmacological data were recorded. Logistic regression analyses were used to describe variables associated with valproate prescription.

**Results:** Of the 1018 included women 16-50 years old, 26.9% were treated with valproate with a mean daily dosage of 968 mg. The prevalence of BD women using valproate was 32.6% before May 2015 and 17.3% after May 2015 ( $p<0.001$ ), the date of French regulatory publication of restriction of valproate prescription. The multivariate analysis revealed that the inclusion period after May 2015 (OR=0.54, CI 95% 0.37-0.78,  $p=0.001$ ), the age lower than 40 years (OR=0.65, CI 95% 0.43-0.98,  $p=0.040$ ) and the number of lifetime mood episodes (OR=0.98, CI 95% 0.95-0.99,  $p=0.040$ ) were the variables negatively associated with the use of valproate.

**Limitations:** Study could be underpowered to determine a clinical profile associated with valproate prescription.

**Conclusions:** The regulatory change in BD women of childbearing age had a significant impact on valproate prescription, even if the prescription rate remains high. Important efforts are needed to help clinicians and patients to improve quality of care in BD women of childbearing age.

**Keywords:** valproate, anticonvulsant, women of childbearing age, pregnancy, bipolar disorder.

## **1. Introduction**

Bipolar Disorder (BD) is a severe and chronic psychiatric disorder associated with disability, functional impairment and negative impact on quality of life (Grande et al., 2016; Samalin et al., 2016a).

Mood stabilizers, defined as a heterogeneous class including lithium, anticonvulsants and dopamine antagonist/partial agonists (or second-generation antipsychotics), are the cornerstone treatments for the acute phase and long-term management of BD either as monotherapy or in combination (Vieta et al., 2018).

Valproate is recommended by the international guidelines as a first-line or second-line treatment for the treatment of mania and for the prevention of relapse in BD (Fountoulakis et al., 2017; Samalin et al., 2016b). There is also some evidence for its efficacy versus placebo in the treatment of bipolar depression (Taylor et al., 2014).

For childbearing age women with BD, the use of valproate is problematic during pregnancy due to its teratogenic effects and potential neurodevelopmental impact on children being exposed in utero. Risk of congenital malformations with neural tube effects, cardiac malformations, cleft palate and lip has been reported in approximately 11% of children exposed to valproate in utero (compared to a 2%-3% risk for children in the general population) (Meador et al., 2009; Weston et al., 2016). This risk appears dose-related and increases with the number of anticonvulsants (Tomson et al., 2011). Other studies have shown a risk of developmental problems such as delayed walking and talking, memory problems and lower intellectual ability in 30%-40% of pre-school children exposed to valproate in utero (Bromley et al., 2010; Cohen et al., 2019; Cummings et al., 2011; Meador et al., 2009; Thomas et al., 2008). In addition, exposure to valproate in utero has been found to increase the risk of autism spectrum disorder threefold (Christensen et al., 2013).

As a consequence, in October 2014, the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee has recommended to strengthen the restrictions on the use of valproate: *"it should not be used to treat epilepsy or BD in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated"* (European Medicines Agency, 2014). In May 2015, following the European Medicines Agency recommendations, the French National Agency for the Safety of Medicines and Health Products has changed the conditions of prescription of valproate (ANSM, 2015). It cannot be prescribed in women of childbearing age unless other mood stabilizers have been tried without efficacy and/or adequate tolerance and only with efficient contraception. Psychiatrists or neurologists can only initiate treatment and have to reassess patients once a year. Educational materials have also been provided to healthcare professionals and to women using valproate to inform them about the risks. A yearly consent form has to be signed by each BD women treated by valproate. Moreover, more recently, a specific pregnancy prevention plan has been required for these patients. Similarly, in 2018, very comparable recommendations have also been established in United Kingdom and other European countries (Owens, 2019).

As expected, a decrease of prescribing valproate among women of childbearing age has been described in several European countries (Charlton et al., 2019) but the use of valproate in epilepsy as well as in BD remains significant. Based on general population study, the prevalence of women of childbearing age being prescribed valproate varied from 0.27% to 0.66% in different European countries (Charlton et al., 2019). Based on specific population, Paton et al. report that 24% of women of childbearing age with BD still received valproate in UK despite the recent restriction of prescription (Paton et al., 2018).

As a consequence, based on a large well-described French national cohort (FondaMental Academic Centers of Expertise for Bipolar Disorders, FACE BD) (Henry et al., 2015), it

appears of great interest to explore the evolution of prescription of valproate in women of childbearing age with BD before and after the French regulatory change to the conditions for its use (May 2015). It is also of interest to describe the clinical profile of women of childbearing age for whom valproate is still prescribed in order to better understand the reasons for continuing this medication.

## **2. Methods**

### **2.1. Study design and recruiting network characteristics**

This multicenter, cross-sectional study included patients recruited into the FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders) cohort between June 2009 and June 2018. The FACE-BD cohort is based on a French national network of 12 BD Expert Centers (Besançon, Bordeaux, Clermont-Ferrand, Créteil, Colombes, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris and Versailles). This network was set up by the FondaMental Foundation ([www.fondation-fondamental.org](http://www.fondation-fondamental.org)) and funded by the French Ministry of Research and the French Ministry of Health to build an infrastructure and to provide resources to follow clinical cohorts and comparative-effectiveness research on a patient population. This cohort and the clinical variables have been extensively described in a previous paper (Henry et al., 2015).

### **2.2. Participants**

Inclusion criteria were: women 16-50 years old who met DSM-IV-TR criteria for BD, outpatients with stable medication for more than 4 weeks. Similarly to Paton et al. (Paton et al., 2018), women of childbearing age were defined pragmatically as being 50 years of age or



younger. Exclusion criteria included any other DSM-IV-TR diagnosis of psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder and other psychotic disorder) and inpatients at the time of the evaluation.

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18<sup>th</sup>, 2010). Although the committee waived the requirement for written informed consent, the patients received a letter informing them of the study and asking whether they agreed to participate.

All data were collected anonymously.

### **2.3. Measures**

Sociodemographic and clinical data were collected through patient interview and clinical records: age, educational level, number of pregnancy, number of child, BD type, age at BD onset, post-partum onset, illness duration, number of lifetime mood episodes, predominant polarity of BD (defined as 2/3 of total number of episodes having the same polarity (Colom et al., 2006)), lifetime history of suicide attempt, presence of current rapid cycling, psychiatric comorbidities. Diagnoses interviews were carried out by trained psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0, (First et al., 2002)).

Pharmacological treatment was also recorded. We used the “yes/no” format for recording whether the patient was taking lithium, anticonvulsants, second-generation antipsychotics, antidepressants, or anxiolytics at the time of the evaluation. We specifically recorded the daily dose of valproate.

Current depressive and manic symptoms were assessed by clinicians using the Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (Young et al., 1978) respectively.

Psychosocial functioning was assessed using the Functional Assessment Short Test (FAST) (Rosa et al., 2007). The FAST scale consists of 24 items that assess disability over the last 15 days in six specific areas (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). The overall FAST score ranges from 0 to 72 points and higher scores indicate greater disability.

Medication adherence was measured using the Medication Adherence Rating Scale (MARS). The total score ranges from 0 to 10 with higher score indicating better adherence (Thompson et al., 2000).

## **2.4. Statistical analysis**

Sociodemographic, clinical and treatment data are presented as the mean (SD) for continuous variables and frequency distribution for categorical variables.

Statistical comparisons between groups of individuals were performed using Chi-square test for categorical variables and Student t test or Mann-Whitney test for continuous variables.

Subgroup analysis in childbearing BD women younger than 40 years old were also performed according to age-related fertility rates in western countries (GBD 2017 Population and Fertility Collaborators, 2018).

Binary logistic regression analyses were used to explore demographic and clinical variables associated with prescription of valproate in BD women of 50 years of age or younger.

Variables were selected for inclusion in multivariable logistic regression model when significant at  $p < 0.15$  in the univariate analysis. The results were presented as odds ratios (OR) with 95% confidence intervals (CI).

Analyses were conducted using SAS 9.3 (SAS Statistical Institute, Cary, North Carolina). All statistical tests were 2-tailed, with the  $\alpha$  level set at .05. For univariate analysis, no correction for multiple testing was used.

### 3. Results

We included in a national observational cohort, 1018 women of childbearing age ( $\leq 50$  years of age) with BD according to DSM-IV-TR criteria. The mean  $\pm$  SD age was 35.4 ( $\pm 8.5$ ). Of the included women, 274 (26.9%) were treated with valproate. The mean daily dosage of valproate was 968.0 mg (SD =399.6) ( $\leq 600$  mg,  $n=45$ , 23.4%; 601-1000 mg,  $n=100$ , 52.1%;  $>1000$  mg,  $n=47$ , 24.5%).

The demographic, clinical and treatment characteristics of the sample are presented in Table 1.

The prevalence of BD women of 50 years of age or younger was 32.6% before May 2015 and 17.3% after May 2015 ( $p < 0.001$ , Table 1), has decreased since the new conditions of prescription by the French National Agency for Medicines and Health Products Safety. This reduction remained significant for the BD women younger than 40 years old from 30.9% to 14.3% ( $p < 0.001$ ) but was not significant in BD women of 40 years old or older from 35.2% to 26.7% ( $p = 0.139$ ).

BD women currently using valproate were more likely to be 40 years of age or older ( $p = 0.002$ ) and had higher number of children ( $p = 0.009$ ), lower number of lifetime mood

episodes ( $p=0.014$ ) and lower MADRS score ( $p=0.031$ ) in comparison with BD women not currently using valproate (Table 1). Groups did not differ with respect to illness duration, history of suicide attempt, rapid cycling and psychiatric comorbidities. BD women using valproate were less likely to receive lithium as a co-prescription ( $p<0.001$ ) but had higher number of psychotropic medication ( $p<0.001$ ).

The multivariate analysis revealed that the inclusion period after May 2015 (OR=0.54, CI 95% 0.37-0.78,  $p=0.001$ ), the age lower than 40 years (OR=0.65, CI 95% 0.43-0.98,  $p=0.040$ ) and the number of lifetime mood episodes (OR=0.98, CI 95% 0.95-0.99,  $p=0.040$ ) were the variables negatively associated with the use of valproate.

#### **4. Discussion**

Based on a large and clinically well-described national-wide cohort of BD patients, we found an evolution of the prescription rate of valproate from 32.6% before May 2015 to 17.3% after May 2015, i.e. a two-fold decrease of prescription in BD women of childbearing age.

This decrease is consistent with previous European studies conducted in general population as well as specifically in BD patient population (Charlton et al., 2019). Only one study from Germany found a smaller decrease in BD but it is worth noting that the prescription rate was initially low (from 9.3% in 2004 to 8.0% in 2016) (Wentzell et al., 2018). Interestingly, our prescription rate of valproate after 2015 is comparable with the prescription rate observed in other European countries such as described in a UK clinical audit (Paton et al., 2018) in 2016 (i.e. 24%).

Our study confirms that national and European regulatory agencies recommendations have a significant and quick impact on valproate prescription. However, despite these

recommendations and the demonstration of a high teratogenic risk associated with valproate, the prescription rate of valproate remains high in BD women of childbearing age.

In their analyses of this high prescription rate of valproate in UK, Paton et al. have suggested that it was associated with higher age, more comorbidities or presence of rapid cycling (Paton et al., 2018). This may lead to the hypothesis that the continuation of valproate despite recommendations could be associated with severity of BD. If our analysis also supported the association of prescription of valproate with age (specifically in BD women of 40 years old or older), by contrast, we only found that the date of prescription before the restrictions from French agency and the lower number of lifetime mood episodes were associated with valproate prescription.

As a matter of fact, it is possible that some other factors associated with valproate prescription have important effect on prescription such as beliefs about medication. Although the personal choice of the patient about valproate is not taken into account in European as well in French recommendations, one could hypothesize that some women would prefer valproate according to their personal past experience and expectations, despite explanation received about teratogenic risks. We could expect that some women refuse valproate withdrawal. Accordingly, a polish study in patients with epilepsy demonstrate that only 40% of women of childbearing age with persistent valproate use were in accordance to recommendation while 60% simply do not agree to withdraw valproate treatment (Bosak et al., 2019). We found that women of childbearing age using valproate had more frequently 40 years of age or older as previously described (Paton et al., 2018) and tend to have higher number of children. That could be interpreted as a permissive effect for valproate prescription in BD women of childbearing age that already have built their family or have a lower age-related fertility. For these patients, lack of agreement of withdrawal, and the absence of pregnancy plan, in women who already have children as well as the lack of consideration of the long-term effects of

valproate exposure in utero (neurodevelopmental disorders, cognitive impairments, growth restriction, behavioral abnormalities, mental disorders) could probably drive clinicians to maintain valproate instead of following treatment recommendation.

In the same vein, concerns associated to other mood stabilizers may explain the prescription of valproate. This hypothesis is consistent with Paton et al. results that reported “switch from lithium due to tolerability or safety issue” as a specific clinical reason to initiate valproate in BD women of childbearing age, which was never reported by men (Paton et al., 2018). Nevertheless, recent data in the literature suggested that the risks of cardiotoxicity and Ebstein’s anomaly associated with maternal use of lithium during the first trimester were dose-dependent and have been probably overestimated in the past (Belzeaux et al., 2019).

In our cohort, although women using valproate had higher number of psychotropic medications, they had less frequently lithium co-prescription suggesting that valproate is prescribed as a potential alternative strategy to lithium in this population.

Interestingly, a very recent expert advice on the management of valproate in BD women considered that a valproate maintenance could be possible in stable patients with monotherapy, with high risk of relapse and poor experience of alternative treatment, reluctance of therapeutic alternatives or wish to continue valproate (Anmella et al., 2019).

Beyond clinical profile and patients’ attitudes and choices, we could not exclude that adhesion of psychiatrists to recommendations could be variable according to their personal knowledge and beliefs. That could explain the persistence of valproate prescription despite no specific evidence of eligible clinical profile. One could argue that national and international agencies and scientific societies should develop repeated educational materials and programs about risk associated to prescription of valproate in women of childbearing age to maintain knowledge and information.

Up to now, the recommendations from international treatment guidelines for BD women of childbearing age are not unequivocal (Belzeaux et al., 2019). Although treatment guidelines may be of significant help for clinicians, more consensual recommendations contraindicated the use of valproate not only during pregnancy but also for BD women of childbearing age are needed. Moreover, unlike with epilepsy where some patients achieve a therapeutic response only with valproate, there are alternatives including not just lithium but antipsychotics in the management of BD.

### ***Limitations***

Our result could be biased by some limitations. First of all, our study could be underpowered to determine a specific clinical profile associated with valproate prescription. However, we included a large number of subjects of more than 1,000 women of childbearing age using or not using valproate. It is worth noting that Paton et al. included a larger cohort (n=2364) in their analyses but the authors compared clinical profiles of all patients with and without valproate prescription including both men and women, leading to other bias that could explain the differences.

Moreover, we did not conduct our study in a random sample of patients suffering from BD but in a tertiary center where selection bias could happen. Indeed, Paton et al. found that tertiary affective disorders services were more associated with the prescription of valproate than adult community service (Paton et al., 2018). In the same vein, one could expect that more severe and more complicated clinical situations be referred to specialized care system. As a consequence, we are confident in our ability to test the hypothesis of a higher severity profile in women with valproate prescription.

Finally, the study is based on a pre-existing cohort of BD patients and some interesting data were not available, such as the level of awareness of teratogenic risk in women who continued to use valproate.

## **5. Conclusion**

Important research efforts are needed to better help clinicians, patients and family to improve quality of care when BD women wishing to become pregnant, during pregnancy and post-partum periods, that are specific and high-risk periods of relapse (Wesseloo et al., 2016). Further studies to increase knowledge of efficacy and safety of treatment during perinatal period are required. These studies would need to include clinical evaluation but also evaluation of attitudes and beliefs about medication both in patients and clinicians. Based on evidence-based knowledge, specific shared decision-making process need to be implemented to manage treatment of BD women.



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Table 1. Sociodemographic, clinical and treatment characteristics of BD women  $\leq 50$  years of age using vs not using valproate (N=1018)

	Valproate			P value
	Total (n=1018)	No (n=744)	Yes (n=274)	
Age, years: mean (SD)	35.4 (8.5)	35.1 (8.2)	36.0 (9.1)	0.089
Age, n (%)				
< 40 years of age	681 (66.9)	518 (76.1)	163 (23.9%)	<b>0.002</b>
$\geq 40$ years of age	337 (33.1)	226 (67.1)	111 (32.9%)	
High Education level, n (%)	742 (83.4)	543 (84.3)	199 (80.9)	0.220
Number of pregnancy, mean (SD)	1.4 (1.6)	1.4 (1.6)	1.4 (1.6)	0.856
Number of Child, mean (SD)	0.9 (1.1)	0.9 (1.1)	1.1 (1.2)	<b>0.009</b>
Inclusion period, n (%)				
Before may 31 <sup>th</sup> 2015	642 (63.1)	433 (67.5)	209 (32.6)	<b>&lt;0.001</b>
After may 31 <sup>th</sup> 2015	376 (36.9)	311 (82.7)	65 (17.3)	
BD type, n (%)				
Type I	490 (48.1)	346 (46.5)	144 (52.6)	0.229
Type II	424 (41.7)	320 (43.0)	104 (38.0)	
Type NOS	104 (10.2)	78 (10.5)	26 (9.5)	
Age of BD onset, years: mean (SD)	21.3 (6.8)	21.0 (6.6)	22.0 (7.3)	0.059
BD with Post-Partum onset, n (%)	56 (5.7)	37 (5.2)	19 (7.3)	0.218
Illness duration, years: mean (SD)	14.0 (7.9)	14.1 (7.8)	13.9 (8.3)	0.552
Number of lifetime mood episodes: mean (SD)	8.1 (8.3)	8.5 (8.9)	7.0 (6.0)	<b>0.014</b>
Predominant polarity of BD, n (%)				
Depressive	466 (53.1)	341 (53.2)	125 (52.7)	0.653
Manic	224 (25.5)	159 (24.8)	65 (27.4)	
Undetermined	188 (21.4)	141 (22.0)	47 (19.8)	
Suicide attempt, n (%)	462 (46.3)	346 (47.3)	116 (43.5)	0.276
Rapid cycling, n (%)	157 (17.8)	125 (19.0)	32 (13.9)	0.076
MADRS score, mean (SD)	10.6 (9.3)	11.0 (9.4)	9.6 (8.9)	<b>0.031</b>
YMRS score, mean (SD)	2.1 (3.4)	2.2 (3.5)	2.0 (3.0)	0.447
FAST score, mean (SD)	21.6 (14.8)	21.8 (14.8)	20.9 (14.6)	0.402
Comorbidities, n (%)		346 (47.3)	116 (43.5)	0.284
Current daily tobacco smoking	475 (48.5)	344 (48.0)	131 (50.0)	0.575
Lifetime substance use disorder	325 (34.2)	244 (34.9)	81 (32.1)	0.428
Lifetime anxiety disorder	509 (54.0)	378 (54.6)	131 (52.4)	0.559
Adherence to medication (MARS): mean (SD)	6.9 (2.0)	6.9 (2.0)	6.9 (1.9)	0.929
Medications, n (%)				
Lithium	323 (31.7)	291 (39.1)	32 (11.7)	<b>&lt;0.001</b>
Second-generation antipsychotics	254 (25.0)	197 (26.5)	57 (20.8)	0.064
Antidepressants	408 (40.1)	292 (39.3)	116 (42.3)	0.372
Anxiolytics	319 (31.3)	227 (30.5)	92 (33.6)	0.349
Number of psychotropic medication: mean (SD)	2.4 (1.3)	2.1 (1.2)	2.5 (1.3)	<b>&lt;0.001</b>

Values are given as mean (SD) or as n (%) of patients.

Bold values are  $p < 0.05$ .

BD, bipolar disorder; FAST, functioning assessment short test; MADRS, Montgomery Asberg depression rating scale; MARS, medication adherence rating scale; NOS, unspecified; SD, standard deviation; YMRS, Young mania rating scale