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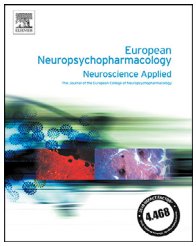

REVIEW

Expert advice on the management of valproate in women with bipolar disorder at childbearing age

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Valproate;
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Abstract
Introduction: The perinatal period is associated with up to 2/3 relapses in untreated bipolar disorder (BD), with important consequences on the clinical BD outcome and on fetal and child development. Valproate (VPA), one of the most effective treatments in BD, is associated with the highest risk of serious neurodevelopmental disorders in exposed children. This has brought to tightened restrictions to its use by regulatory agencies and clinical guidelines.
Methods: A panel of experts on the pharmacological treatment of BD conducted a non-systematic review of the scientific literature and clinical guidelines until March 2019, and provided specific evidence-based and experience-based clinical recommendations for VPA switching/discontinuation in BD women of childbearing potential.

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Results: After the review of the evidence in a face-to-face meeting, the panel concluded that several clinical criteria need to be considered to make a clinical decision about VPA discontinuation and switch. The plateau cross-taper switch may be preferred. Abrupt switching may bear augmented risk of relapse

Conclusions: BD childbearing women treated with VPA must be managed on a personalized basis according to the clinical situation. It is mandatory to stop VPA during pregnancy. The duration of the discontinuation/switch process depends on different clinical variables. Lithium, lamotrigine, quetiapine, olanzapine or aripiprazole are good options for switch in stable BD patients in planned/unplanned pregnancy. In unstable BD patients planning pregnancy, stability is paramount. Prevention of post-partum episodes requires reinstatement of effective treatment before or after birth (in the case of VPA). VPA is still an option in the post-partum period and beyond.

1. Introduction

Bipolar disorders (BD) are chronic and recurrent disorders that affect >1% of the global population (Grande et al., 2016). Relapses occur rather quickly without treatment in most BD patients (Biel et al., 2007) and sharply soon after rapid discontinuing (Baldessarini et al., 1999). However, preventive strategies, including mood stabilizers and adjunctive psychoeducation may reduce significantly relapse rate (Colom et al., 2009; Grande et al., 2013; Vieta et al., 2018).

The perinatal period (from pregnancy to 1 year after delivery) in BD patients is associated with a higher risk of relapse, up to 66% in non-treated patients (Wesseloo et al., 2016), especially after birth delivery (Bergink et al., 2012; Cohen et al., 1995). Time to relapse becomes considerably shorter in case of rapid treatment discontinuation (Baldessarini et al., 1999; Viguera et al., 2007). The risk of suicide constitutes one of the leading causes of maternal perinatal mortality and suicidal ideation is one of the strongest predictors for suicide attempt and completion, thus representing a need for early intervention and treatment (Martini et al., 2019). Suicide risk seems to be higher especially during the final quarter of the first postpartum year, also with more violent methods (Grigoriadis et al., 2017) together with higher rates of residual mood symptom-related dysfunction (Epstein et al., 2014; Yonkers et al., 2011). Consequently, perinatal relapses can directly affect fetal and child development and may have serious consequences on child attachment due to potential maternal separation (Boukakiou et al., 2018; Pawlby et al., 2010). Therefore, discontinuation of treatment during pregnancy in BD may be considered more harmful than continuation in individual cases (Broeks et al., 2017).

Mood stabilizers (MS) are one of the most effective treatments for acute phases and long-term prevention of relapses of BD, thus representing first- or second-line treatments in clinical guidelines (Grande et al., 2016; Murru et al., 2015b; Vieta et al., 2018; Yatham et al., 2018).

Amongst them, valproate (VPA) has proven as an effective and useful treatment for BD, even proving advantages over lithium in treatment of severe mania and benefitting a broader spectrum of bipolar conditions (Bowden, 2003). Despite this, currently VPA use in women of fertile age is strongly discouraged, meaning that it should not be used unless other treatments are ineffective or not tolerated, and in any case, according to the Pregnancy Prevention Program conditions.

Actually, prospective registries and meta-analyses have better defined the risk of major congenital malformations (MCMs) in offspring exposed to individual antiepileptic drugs (AEDs). Although the sensitive VPA exposure period for MCMs induction is limited to the first trimester (organogenesis), exposure throughout pregnancy is likely to impact on fetal growth and neurodevelopment, due to brain maturation throughout the entire duration of pregnancy (Tomson and Battino, 2019). VPA is the AED with the highest risk of MCMs and children exposed in utero to VPA were found to be at very high risk (up to 30–40%) of developing serious neurodevelopmental disorders, including cognitive impairments (higher rates of low IQ, neurodevelopmental deficits, reduced verbal abilities), growth restriction, behavioral abnormalities (attention deficit hyperkinetic disorder) (Cohen et al., 2011; Meador et al., 2013; Tomson et al., 2016b, 2018; Veroniki et al., 2017; Weston et al., 2016; Wlodarczyk et al., 2012) and it has been suggested a link with autistic spectrum disorders(Bromley et al., 2008; Christensen et al., 2013). Moreover, MCMs occur in approximately 10% of cases of VPA-exposed offspring (Andrade, 2018), including spina bifida, cardiovascular malformations, cleft palate, intrauterine growth retardation, hypospadias, hydrocephalus, limb defects, craniosynostosis and pulmonary atresia (Medicines and Healthcare products Regulatory Agency, 2018; The Royal College of Psychiatrists, 2018). The risk appears to be dose-related: the risk exists whatever the dose, with a higher risk with VPA doses >650–1000 mg/day or VPA plasmatic levels >70 μg/mL (Andrade, 2018; Diav-Citrin et al., 2008; Goodwin et al., 2016; Mawhinney et al., 2012), especially for the development of spina bifida and hypospadias (Vajda et al., 2013), and it increases with AED polytherapy. Prevalence of MCMs seems to be the lowest with lamotrigine, levetiracetam, and oxcarbazepine in monotherapy (Giménez et al., 2019).

The awareness of these findings have led to a gradual decrease in VPA prescription in women of childbearing potential (Tomson and Battino, 2019) accompanied by tightened restrictions to its use by regulatory agencies and the Pharmacovigilance Risk Assessment Committee (AEMPS, 2018a; 2018b; European Medicines Agency, 2019, 2018b, 2018c, 2018a, 2017, 2014; NICE, 2014a, 2014b; Rybakowski et al., 2019; Rymaszewska et al., 2019; Samochowiec et al., 2019),

Table 1 US Food and Drug Administration (FDA) classification of teratogenicity for medications commonly used in bipolar disorder.[a]

	Pregnancy risk category[b]	Lactation risk category[c]
Lithium	D	L4
Anticonvulsants		
VPA	Dm	L4
Lamotrigine	Cm	L2
Carbamazepine	Dm	L2
Atypical antipsychotics		
Aripiprazole	Cm	L3
Quetiapine	Cm	L2
Olanzapine	Cm	L2
Risperidone	Cm	L2
Clozapine	Bm	L3
Ziprasidone	Cm	L2
SSRI antidepressants		
Citalopram	Cm	L2
Escitalopram	Cm	L2
Fluoxetine	Cm	
Fluvoxamine	Cm	L2
Paroxetine	Dm	L2
Sertraline	Cm	L2
Other antidepressants		
Bupropion	Bm	L3

[a] FDA replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final Rule (PLLR)(US Food and Drug Administration, 2015).

[b] Adapted from ACOG Committee on Practice Bulletins-Obstetrics(ACOG, 2008): US Food and Drug Administration Rating. A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out (human data lacking, animal studies show positive teratogenic risk or have not been done); D = positive evidence of risk (benefit may outweigh risk). The "m" subscript is for data taken from the manufacturer's package insert.

[c] Hale TW and Rowe HE Lactation risk categories are listed as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated (Hale and Rowe, 2017).

Abbreviations: VPA = valproate-containing drug.

as well as by the most recent clinical guidelines recommendations (Fountoulakis et al., 2016; Goodwin et al., 2016; Grunze et al., 2013; Malhi et al., 2015; Yatham et al., 2018), and by position statements from prestigious influential institutions (The Royal College of Psychiatrists, 2018, 2016). The new regulatory requirements will translate into a significant change in the management of women of childbearing age suffering from epilepsy or BD (Wieck and Jones, 2018).

Due to what mentioned above, currently VPA and also CBZ are classified as category "D" drugs by the US Food and Drug Administration (FDA) and are contraindicated during pregnancy. In Europe, the European Medicines Agency also contraindicated the use of VPA during pregnancy in BD, in all cases, and in epilepsy, unless there is no suitable alternative (European Medicines Agency, 2018a). Table 1 includes a brief overview of medications commonly used in BD and the risk categories (Yatham et al., 2018).

Unplanned pregnancies are among 30–50% in the general population, and may be higher in BD (Heffner et al., 2012), since we often have to deal with severe and highly unstable patients. Faced with this situation, there is a lack of practical recommendations on how to manage VPA use (The Royal College of Psychiatrists, 2016). An effective contraception is strongly recommended during the entire duration of treatment with VPA and at least one effective method of contraception (preferably an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used (The Royal College of Psychiatrists, 2018). Despite these explicit official recommendations in national guidelines and published safety alerts and warnings, the real-world data on currently prescribed drugs show that up to 24% of women with BD below 50 years were prescribed VPA, and in only half a documented evidence on teratogenic risks of exposure had been provided (Paton et al., 2018).

To our knowledge, there is no evidence on VPA switch or discontinuation in BD during pregnancy, being the majority of studies conducted on epileptic populations (Tomson et al., 2016a).

The aim of this work is to provide specific evidence-based clinical recommendations for VPA switching/discontinuation in women of childbearing potential with BD who are planning pregnancy or who have become pregnant.

2. Experimental procedures

We performed a non-systematic review of scientific literature and clinical guidelines until March 2019 on VPA switching/discontinuation in women of childbearing potential with BD who are planning pregnancy or who have become pregnant. Considering this body of evidence and based on the Expert Meeting Report on VPA in BD on the 3rd October, 2018 in Paris, France, attended by several experts in the field from different European countries, we provided specific evidence-based clinical recommendations for VPA switching/discontinuation in BD women of childbearing potential according to patients clinical profiles and specific criteria in order to help physicians to comply with the measures aimed at avoiding VPA exposure in pregnancy and evidence-based management of women with BD at childbearing age. The experts discussed several clinical scenarios in light of the current scientific evidence and their clinical experience and developed, through several rounds of exchange drafts, this document with clinical recommendations.

3. Results

3.1. Criteria to be taken into consideration to make a clinical decision about VPA discontinuation and switch

In order to establish personalized real-world recommendations, specific criteria for the patient profiles were defined. The criteria and their implications are summarized in Table 2, adapted from the Expert Meeting Report.

3.2. Switching and discontinuation techniques

3.2.1. General switching techniques

General switching techniques have been proposed for antipsychotic medications (Mcevoy et al., 1999; Murru et al., 2015a), and they can be resumed into four different strategies (see also Fig. 1):

Table 2 Criteria to be taken into consideration to make a clinical decision about valproate discontinuation and switch.

Criteria (in the order of descending importance)		Examples of patient profiles	Implications
1. **Severity**	**1.1. Current state of the disease** **1.2. Longitudinal course of the disease** - Number and severity of relapses - Predominant polarity - Duration of stable euthymia	Unstable	- Obtain remission / stability acceptable from clinical point of view (advisably at least 9 months) - Prepare adequate healthcare setting - Educate patient
		Stable with history of severe disorders	- Minimize the risk of relapse (pay specific attention to the benefit / risk)
		Stable euthymia with mild disease course	- Taper down valproate and monitor patient without medication
	1.3. Comorbidities - Substance abuse - Anxiety disorders - Personality disorders - Medical comorbidities (obesity, fertility issues, hormonal issues, diabetes, renal system issues, etc.)	Substances abuse	- Target stopping addiction
		Medical comorbidities	- Weight efficacy and potential side effects of different medication to choose the most appropriate alternative treatment - Account for drug–drug interactions
2. **Treatment**	**2.1. Current treatment** (mono vs. polytherapy)	Monotherapy	- Taper down valproate and monitor patient without medication (mild disease severity case) or switch using plateau-cross strategy (delayed descending valproate while introducing and ascending other drug(s))
		Polytherapy	- Use plateau-cross strategy (delayed descending valproate and up-titrate of another medication or introduce and up-titrate other drug(s))
	2.2. Treatment history - Level of response to different drugs - History of relapses on different drugs	No response to certain medications in the past	- Avoid switching to a medication which showed to be inefficient in the patient or was not tolerated
3. **Obstetric history**	**3.1. Age** - Number of fertile years left	Beginning / mid of fertility	- Take time to ensure stability before pregnancy - Educate the patient
		Close to menopause	- Assess the urgency of getting pregnant and adjust the timing of discontinuation and switch
	3.2. History of perinatal episodes - Pregnancies - Abortions - Miscarriages - Type of delivery - Reactions to pregnancy - Post-partum period	Previous perinatal episodes	- Carefully assess benefit/risk profile - Ensure close cooperation with gynecologist
4. **Family & social environment**	**4.1. Level of support from family/partner**	Supportive environment	- Provide psycho-education to the patient (and possibly partner)
		Difficult / troublesome environment	- Provide psycho-education discussing specifically the risk of unplanned pregnancy - Emphasize that pregnancy is not a solution for issues in a couple

(*continued on next page*)

Table 2 (*continued*)

Criteria (in the order of descending importance)		Examples of patient profiles	Implications
5. **Education & attitudes**	**5.1. Level of education** - Comprehension of risk **5.2. Believes and** values - Attitude to pregnancy, strength of will - Attitude to abortion **5.3. Attitudes to treatment** - Adherence to treatment - Preference regarding treatment - Adherence to contraception - Choice of contraception		- Explain the balance between mental and teratogenicity risk - Discuss with the patient contraception, pregnancy, potential abortion, delivery, etc. taking into account her believes - Educate the patient and address her concerns - Document the discussion around attitudes
6. **Access to specialized healthcare**	**6.1. Perinatal unit availability** **6.2. Possibility of collaboration with gynecologist and/or obstetrician** **6.3. Availability of psychological support** **6.4. Stability of patient relations with** psychiatrist		- Cooperate with gynecologist or obstetrician and aim at reaching a consensus on pregnancy preparation and the choice of treatment - Cooperate with pediatrician or GP to ensure the monitoring of the new-born child - Provide materials to patients (card)
7. **Family history with the disease**	**7.1. Members of family with bipolar disorder, predisposition** **7.2. Misbelieves in terms of treatment**		

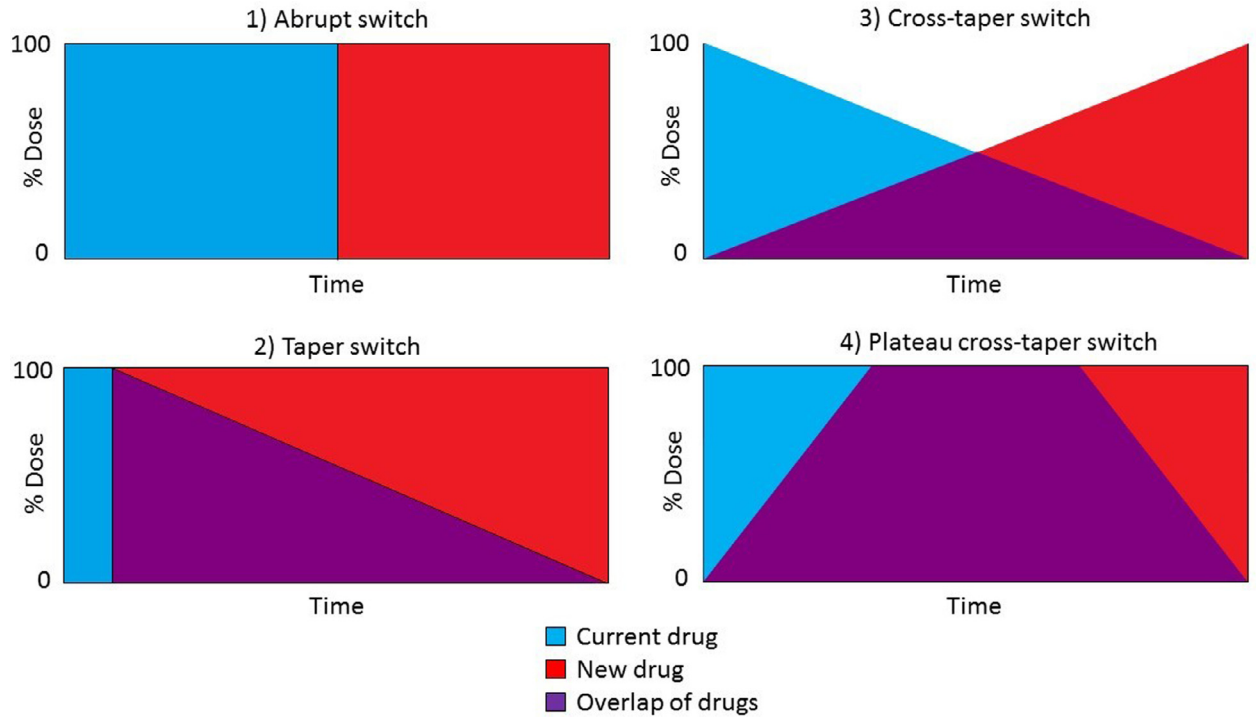


Fig. 1 General switching techniques.
(1) Abrupt switching: discontinuing the current drug immediately and initiating the new drug at full dosage.
(2) Tapering (overlapping and discontinuing): initiating the new drug at full dosage and previous drug is gradually discontinued.
(3) Cross-tapering: gradual increase in dosage of the new drug while, at the same time, gradually discontinuing the current drug.
(4) Plateau cross-tapering: gradual increase in dosage of the new drug and, once an effective dosage of the new drug is reached, gradually discontinuing the previous.

3.2.2. Switching strategies from VPA to other drugs commonly used in BD

Generally, in stabilized BD patients, the plateau cross-taper switch might be preferred. Abrupt switching is only justified in acutely ill patients or for emergency reasons. Clinicians have to consider that it may bear an increased risk for relapses (Grande et al., 2014; Murru et al., 2015a). Withdrawal of VPA should be tapered gradually. Currently, the most recent clinical guidelines and institution recommendations suggest a period of at least 4 weeks (Goodwin et al., 2016; The Royal College of Psychiatrists, 2018). This recommendations are based on evidence inferred from studies on lithium withdrawal, in which relapses are prevented when the dose is tapered down slowly (Baldessarini et al., 1999).

First (FGAs) and Second generation antipsychotics (SGAs) as alternative to VPA. Second generation antipsychotics (SGAs), which can be used as an alternative to MS, have been increasingly used during antepartum period during the last 15 years due to the lack of serious teratogenic effects as highlighted in the most recent studies and clinical guidelines (Einarson and Boskovic, 2009; Epstein et al., 2014, 2013; Malhi et al., 2015; McAllister-Williams et al., 2017; Toh et al., 2013; Yatham et al., 2018). In particular, quetiapine, olanzapine and aripiprazole have found to present the safest profile in comparison with risperidone, which may be associated with a very minor increased risk of overall or cardiac congenital malformations (Huybrechts et al., 2016). No or minimal safety data are available for paliperidone, ziprasidone, amisulpride, asenapine, lurasidone, sertindole, and clozapine (Damkier and Videbech, 2018; Kulkarni et al., 2008).Regarding FGAs, haloperidol performed the best integrated assessment of acute antimanic effectiveness. The better-known reproductive safety profile of haloperidol makes it appealing for the treatment of acute mania during pregnancy (Cipriani et al., 2011).

3.3. Lithium and other mood stabilizers as alternative to VPA

Lithium has proven as the most efficacious treatment for relapse-prevention in stable BD (Miura et al., 2014) as well as during pregnancy (Grof et al., 2000). There is a consensus on the issue that lithium's association with cardiotoxicity and Ebstein's anomaly has been overestimated in the past (Bergink, 2014; McKnight et al., 2012; Patorno et al., 2017). Therefore, lithium has been recommended as first-line treatment during pregnancy in severe BD women by several clinical guidelines (Larsen et al., 2015; Malhi et al., 2015).

Also lamotrigine seems to be safer during pregnancy, with MCMs rates approximate to the general population (Clark et al., 2013; Prakash et al., 2016), specially in doses $<$200 mg/d (Yatham et al., 2018).

Carbamazepine teratogenicity is estimated at 2,01% of MCMs (Tomson et al., 2019) and relatively specific to spina bifida. This percentage is substantially lower than that associated with VPA but higher compared with lamotrigine; thus, the most recent guidelines recommend avoiding during the perinatal period (Fountoulakis et al., 2016; Goodwin et al., 2016). There is a lack of evidence for the use of other MS as alternative to VPA in BD women in childbearing age.

3.4. Evidence-based recommendations in BD women of childbearing age treated with VPA

Specific recommendations by the Royal College of Psychiatrists (The Royal College of Psychiatrists, 2018) have been published for the management of BD young women of childbearing age treated with VPA:

(a) *Non-pregnant BD women with childbearing potential treated with VPA*

In stable BD patients, withdrawal is recommended by slow tapering ($>$4 weeks) in line with clinical recommendations (Yatham et al., 2018).

In non-pregnant but unstable BD patients, much faster cross-tapering while introducing an alternative treatment is needed. During acute manic episodes, haloperidol, olanzapine or quetiapine should be considered.

During acute depressive episodes, olanzapine–fluoxetine combination or olanzapine alone, lithium, quetiapine or lurasidone are possible options. Antidepressant use without MS is disrecommended. Overall, antidepressants use during pregnancy is associated with a small risk of congenital malformations (Gao et al., 2018; Grigoriadis et al., 2013). Guidelines generally support their use, with preferrence for sertraline and disrecommending paroxetine (Molenaar et al., 2018).

(b) *Unplanned pregnancy in BD women treated with VPA*

In the situation of an unplanned pregnancy, patients should be informed not to stop VPA abruptly and should be referred urgently for a specialist review (preferably to a perinatal psychiatric specialized unit ideally within 72 h (Wieck and Jones, 2018)) and to fetal medicine specialist for scanning and counselling.

Unstable pregnant BD patients should be urgently referred to a specialized perinatal community mental health team. The assessment of teratogenic risks and perinatal complications is needed before pharmacological alternative treatments are initiated. In case of a manic relapse, haloperidol, olanzapine or quetiapine should be started. Augmentation by benzodiazepine anxiolytics is recommended if needed.

In case of severe or refractory symptoms electroconvulsive therapy (ECT) has been recommended as a safe and efficacious treatment for BD during pregnancy (Anderson and Reti, 2009; Fountoulakis et al., 2016; Malhi et al., 2015; McAllister-Williams et al., 2017; Nivoli et al., 2012). Clinical guidelines advise the use of monotherapy at the lowest effective dose whenever possible to minimize fetal drug exposure, sparing polytherapy for more complex cases (NICE, 2014b; Sharma, 2011).

Psychiatrists must review patients who are currently prescribed VPA at least once a year. Most women of childbearing potential who are undergoing psychiatric care should be withdrawn from continued treatment with VPA. Specific BD patients that may have poor experience with alternative treatments and they might be reluctant to essay therapeutic alternatives and so wish to continue with VPA. In these exceptional cases, the awareness of potential hazards in case of pregnancy should be provided and an effective Pregnancy risk minimization program must be followed (see Fig. 2.) (European Medicines Agency, 2018a).

3.5. Practical clinical recommendations for VPA switch/discontinuation: clinical cases

Based on the consensus of the expert meeting and the literature reviewed, six real-world clinical situations are presented together with respective schematic flow-chart resolution processes (see Figs. 2–6).

(A) *Stable BD patient with VPA monotherapy who is planning pregnancy (Fig. 2).*
(B) *Stable BD patient with VPA polytherapy who is planning pregnancy (Fig. 3).*
(C) *Unstable BD patient with frequent relapses and VPA polytherapy who is planning pregnancy (Fig. 4).*
(D) *Stable BD patient treated with VPA and unexpected pregnancy (Fig. 5).*
(E) *Unstable BD patient treated with VPA and unexpected pregnancy (Fig. 6).*

4. Discussion

Many factors involving the patient's clinical profile, environment, available resources and acute clinical situation need to be considered for establishing personalized practical recommendations for a safe and effective switching or discontinuation of VPA in women of childbearing potential.

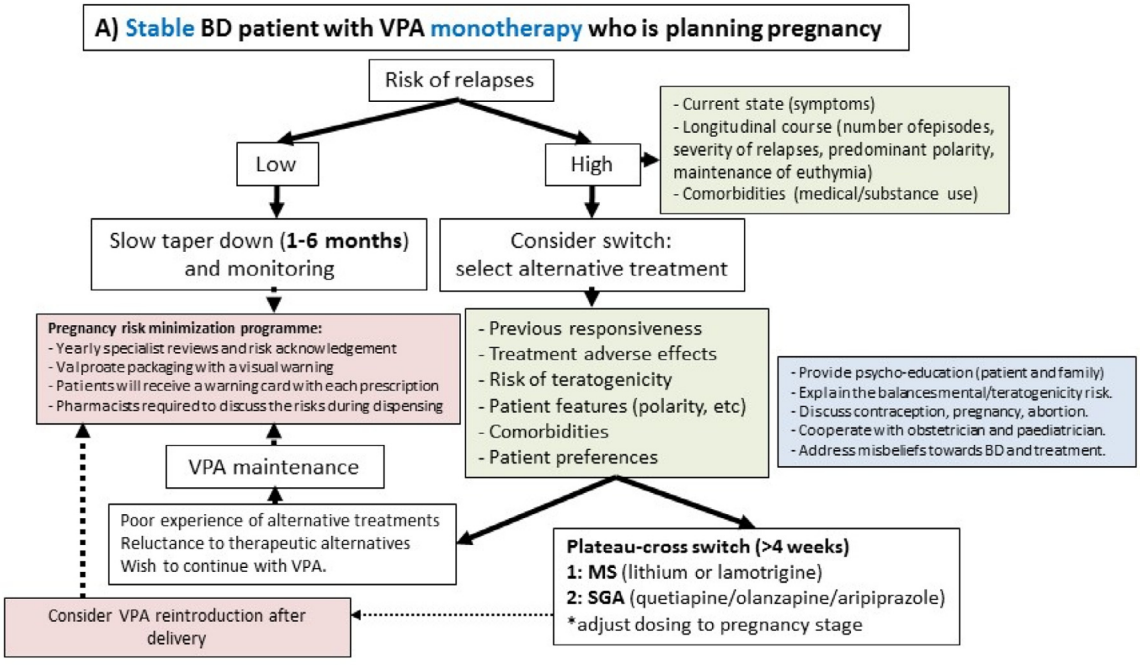
In general, any recommendations to discontinue/switch VPA should consider whether the patient is planning pregnancy or has an unplanned pregnancy, whether the pregnancy is in the early or later stages, and the severity, stability and comorbidities associated with the treated disorder. They should also take into account the current and previous treatment, the attitudes and belief and the social and family situation of the patient, and their access to healthcare. In all cases, patient will have to be fully informed of the risks related to an in-utero exposure to VPA, including the potential risks for the child, and the risks of the discontinuation/switch that is considered.

In the early stages of pregnancy, VPA should be withdrawn immediately, under hospitalization. In the later stages of pregnancy, the switch should take between 1 and 15 days (Figs. 5 and 6). In case of stability, lithium, lamotrigine, quetiapine, olanzapine or aripiprazole should be considered for switch. In unstable patients, indicated treatments vary depending on the episode polarity (Popovic et al., 2012, 2011).

In stable BD patients, planning pregnancy with VPA monotherapy and low risk of relapse, slow tapering of VPA (1–6 months) and monitoring is recommended. In case of risk of relapse, plateau-cross switch (>4 weeks) to lithium, lamotrigine, quetiapine, olanzapine or aripiprazole should be considered (see Fig. 2).

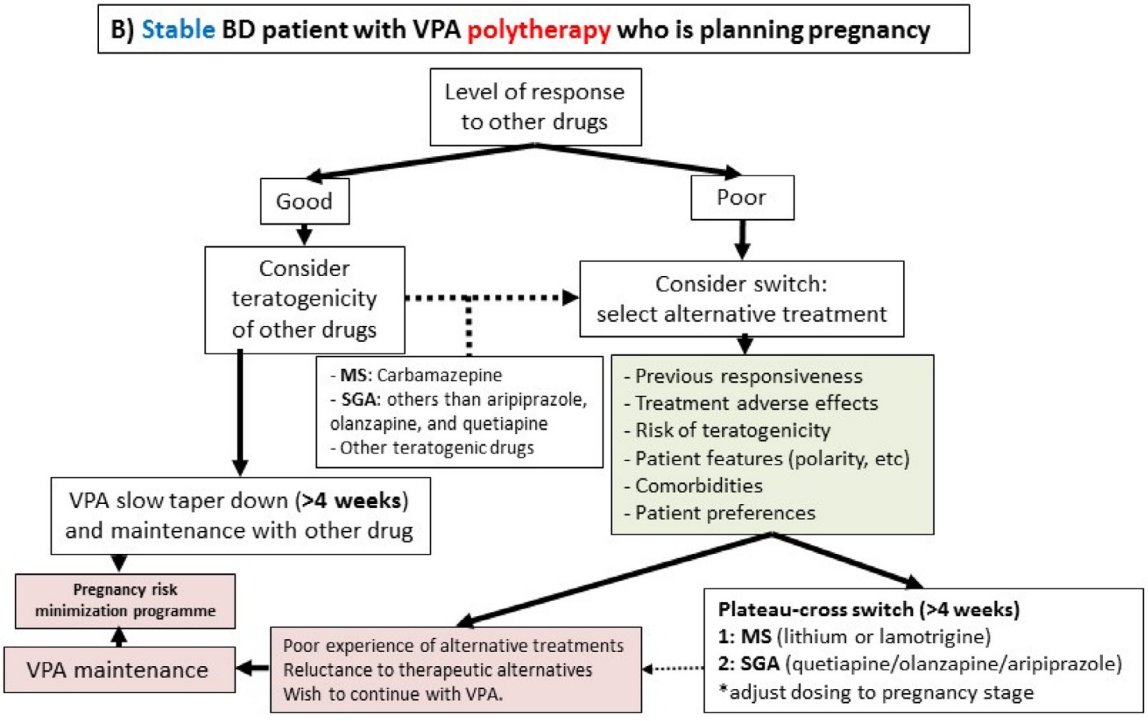
In stable BD patients planning pregnancy with VPA polytherapy and good response to the other drugs for treatment, VPA should be tapered down slowly (>4 weeks) and the other drugs maintained (if not teratogenic). In case of poor response to the other drugs or teratogenicity of the other drug(s), plateau-cross switch (>4 weeks) to lithium, lamotrigine, quetiapine, olanzapine or aripiprazole should be considered (see Fig. 3).

In unstable BD patients planning pregnancy, stability is paramount and urgency of pregnancy determines the stability recommended period (see Fig. 4). In acute manic episodes, plateau-cross switch vs. addition to VPA of haloperidol, aripiprazole, olanzapine, quetiapine or lithium are recommended (see Figs. 4 and 6). In acute depressive episodes, plateau-cross switch vs. addition to VPA of



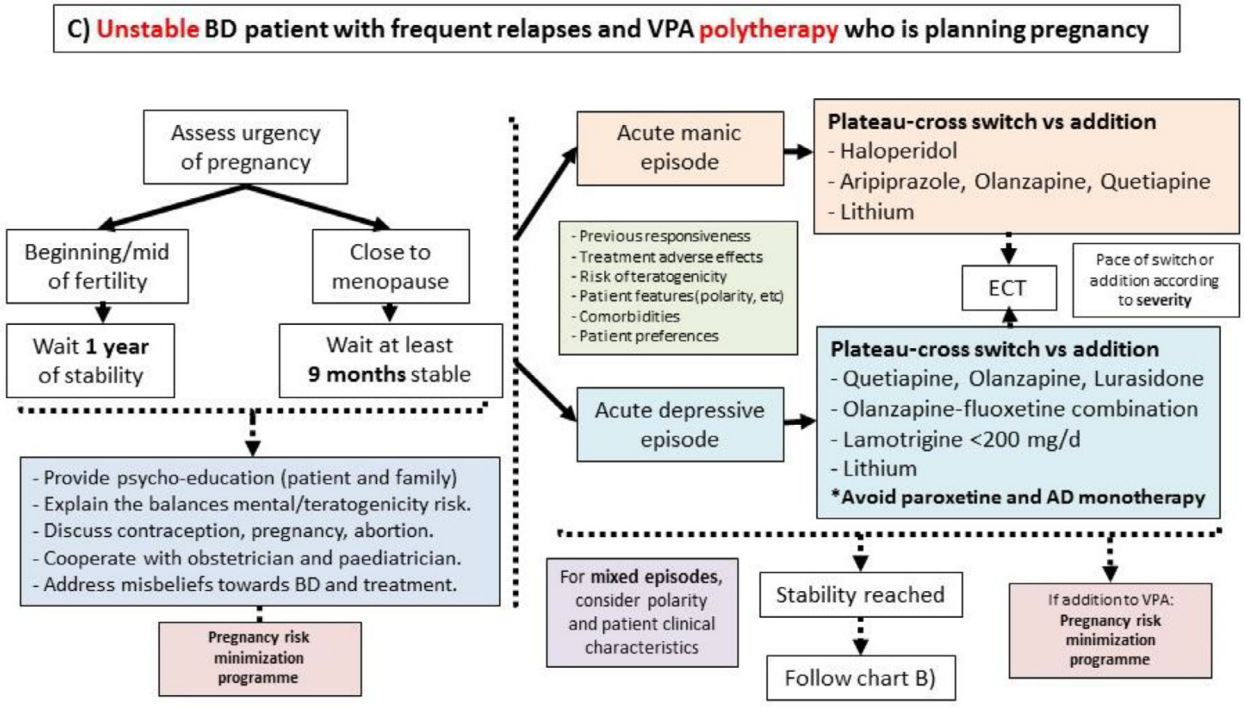
Abbreviations: MS: mood stabilizer; SGA: second generation antipsychotic; VPA: valproate

Fig. 2 (A) Stable BD patient with VPA monotherapy who is planning pregnancy.



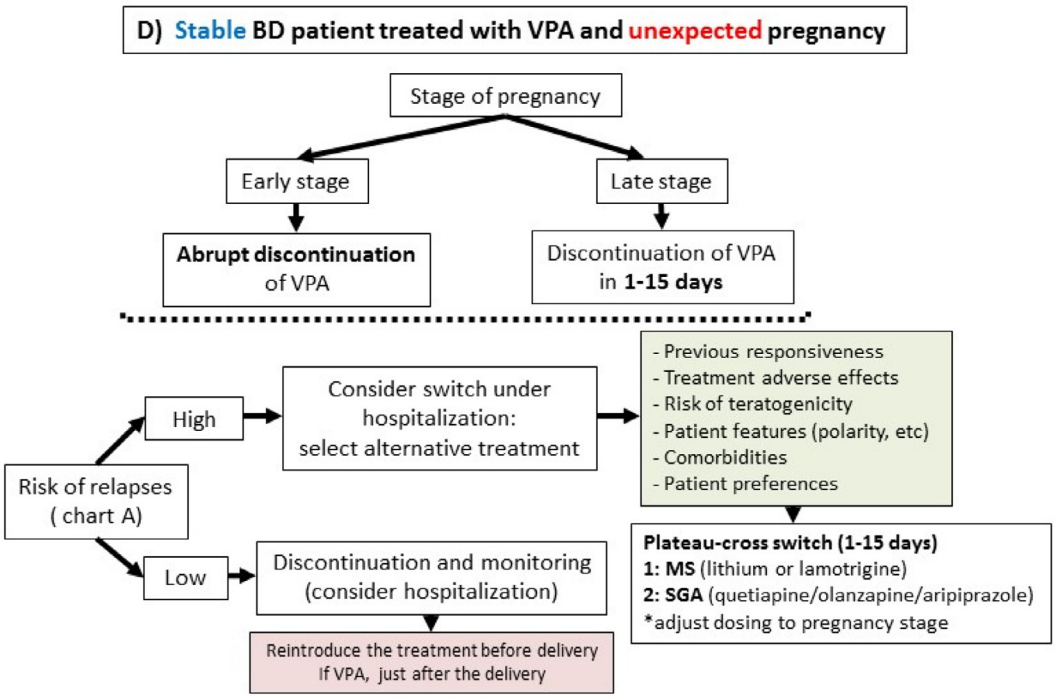
Abbreviations: MS: mood stabilizer; SGA: second generation antipsychotic; VPA: valproate

Fig. 3 (B) Stable BD patient with VPA polytherapy who is planning pregnancy.



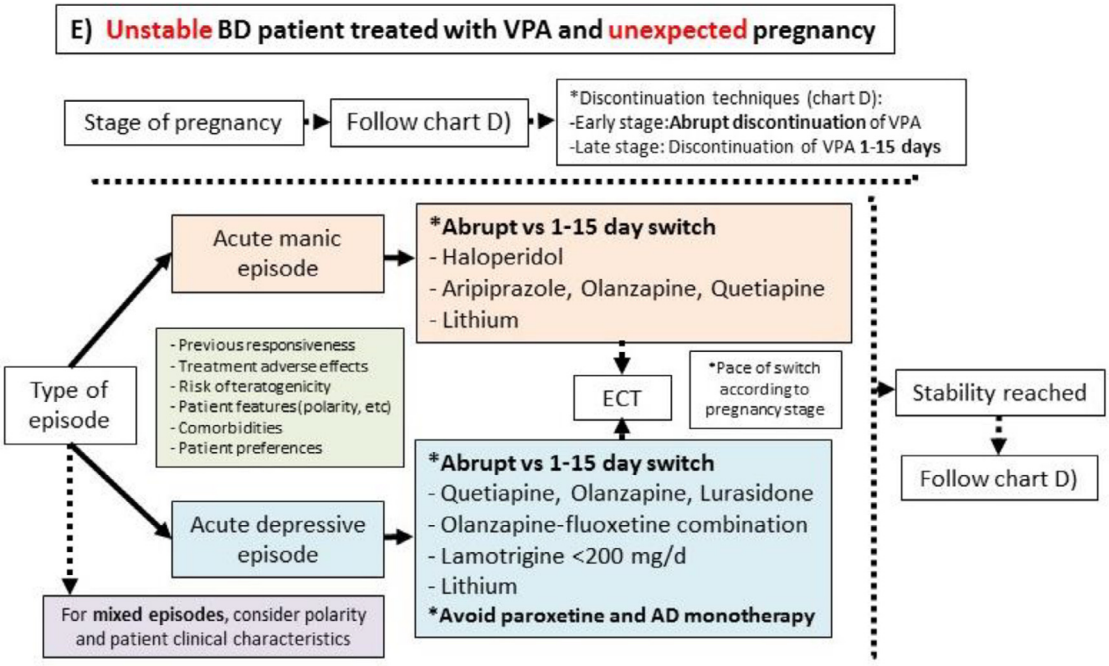
Abbreviations: AD: antidepressant; VPA: valproate

Fig. 4 (C) Unstable BD patient with frequent relapses and VPA polytherapy who is planning pregnancy.



Abbreviations: MS: mood stabilizer; SGA: second generation antipsychotic; VPA: valproate

Fig. 5 (D) Stable BD patient treated with VPA and unexpected pregnancy.



Abbreviations: AD: antidepressant; VPA: valproate

Fig. 6 (E) Unstable BD patient treated with VPA and unexpected pregnancy.

quetiapine, olanzapine, lurasidone, olanzapine-fluoxetine combination, lamotrigine (<200 mg/d) or lithium are recommended. Antidepressant monotherapy and paroxetine should be avoided. ECT in case of refractory episodes can be performed. In acute mixed episodes, the polarity and clinical characteristics of the patients are key to follow the prior treatment recommendations (see Figs. 4 and 6).

Problems can arise when the mother is too ill to care for their child, and some healthcare facilities have dedicated centers to keep mothers with their children.

The prevention of post-partum mania and depression is fundamental and episodes occur rapidly after birth delivery. Therefore, a treatment that was effective before pregnancy should be reinstated before (providing that the treatment is not contraindicated during the 3rd trimester of pregnancy) or after birth (in the case of VPA), depending on how long it takes to become effective. Although all options need to be considered, for this expert group VPA is still an option in the post-partum period and beyond as far as there is strong evidence of a positive benefit-risk ratio for the individual patient (for example, a patient with a history of excellent response to valproate and poor response to other treatments) and that a pregnancy risk minimization program is put in place.

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Contributors

All the authors have been sufficiently involved in the submitted study and have approved the final paper.

Conflict of interest

Dr. Pacchiarotti has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck and reports no financial or other relationship relevant to the subject of this article. **Dr. Anmella** has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini and reports no financial or other relationship relevant to the subject of this article. **Prof. Cubała** has received research support from or served as consultant, adviser or speaker for Adamed, Alkermes, Allergan, Angelini, AstraZeneca, Auspex Pharmaceuticals, Biogen, BMS, Celon, Cephalon, Eli Lilly, Ferrier, Forest Laboratories, GedeonRichter, GlaxoSmithKline, GW Pharmaceuticals, Janssen, KCR, KRKA, Lekam, Lundbeck, Minerva, NIH, NeuroCog, Novartis, Orion, Otsuka, Pfizer, Polfa Tarchomin, Quintiles, Roche, Sanofi, Servier, and Zentiva. **Prof. Dominika Dudek** served as consultant, adviser or speaker for Apotex, Angelini, Gedeon Richter, G-Pharma, Janssen, Lundbeck, Medical Experts, Medforum, Pfizer, Sandoz, Sanofi-Aventis, Servier. **Prof. G. Maina** has received research support from or served as consultant, adviser or speaker for Angelini, Boehringer Ingelheim, Janssen, Lundbeck, Otsuka, Recordati, Sanofi. **Prof. Vieta** has received research support from or served as consultant, adviser or speaker for AB-Biotics, Abbott, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sage pharmaceuticals, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute. All other authors declare no conflict of interests.

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