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EDITORIAL

Preventive recommendations on the use of valproic acid in pregnant or gestational women to be very present☆

Recomendaciones preventivas sobre el uso de ácido valproico en mujeres embarazadas o con capacidad de gestación para tener muy presentes

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In October 2014, the European Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA/612389/2014)[1] recommended restricting the use of valproic acid for treating epilepsy or bipolar disorder in pregnant women and women of childbearing potential, taking into consideration the risks of developing congenital malformations and neurodevelopment disorders that there were for children exposed to this medication continuously during pregnancy. The recommendations consisted of the following points:

(1) Valproic acid should not be used to treat epilepsy or bipolar disorder in female children and in pregnant women and women of childbearing potential unless other treatments have been ineffective or have not been tolerated.
(2) In women for whom valproic acid is the only possible option after having tried other drugs, effective contraceptive measures must be used, and the commencement and supervision of the treatment must be handled by physicians with experience in treating these disorders.
(3) The physicians that prescribe valproic acid to this population must provide the individuals with complete and understandable information about the risk of congenital malformations and developmental disorders in offspring to facilitate informed decision-making.[2]
(4) Women under treatment with valproic acid must not stop taking it without consulting their physicians.
(5) Valproic acid must not be used in the treatment for preventing migraines.

Likewise, the PRAC recommended carrying out studies at the European level to establish the efficacy of these measures.

Almost 3 years later, on the 15th of March 2017, the Spanish Drug Safety Committee (*Comité de Seguridad de Medicamentos de Uso Humano*, *CSMH*), of the Spanish Agency for Medicines and Healthcare Products (*AEMPS* is the Spanish acronym), convoked the Spanish Society of Neurology (*SEN*), the Spanish Society of Psychiatry (*SEP*), and the

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Spanish Federation of Epilepsy (*FEDE*) to a meeting on the ''Use in Spain of Valproic Acid in Female Children and Women of Childbearing Potential''. The reason for this meeting was to express the concern about the fact that neither had the prescription of valproic acid among women of childbearing potential been significantly reduced nor had its use been accompanied by appropriate birth control measures, in spite of the procedures that the AEMPS or authorised laboratory had implemented since 2014 based on the PRAC recommendations (EMA/612389/2014).[1] Given that the Spanish situation is similar to that of other countries in the European Union and in the United States,[3–5] in March 2017 the PRAC initiated a new review of the use of valproic acid in pregnant women and women of childbearing potential to evaluate the effectiveness of the measures recommended in 2014[1] in the various European countries, and to consider whether the current restrictions needed to be strengthened so that risks to offspring could be minimised (EMA/144306/2017).[3] It is foreseen that this new process will be finished by the end of this year.

The U.S. Food and Drug Administration (FDA) had already issued a warning, in June 2011,[6] about the risk there was that children having prenatal exposure to valproic acid (in addition to the acknowledged congenital malformations) would obtain lower scores on cognitive testing compared with children exposed to other anti-seizure drugs. The FDA also indicated that the benefits and risks should be carefully considered before using valproic acid in women of childbearing potential, recommending that other drugs should be used unless valproic acid was essential for that specific individual (risk of injury or death). If the drug was used, the agency suggested that effective birth control measures should be used. In 2013, the FDA changed valproic acid from Category ''D'' (the potential benefit of the drug to pregnant women is acceptable in spite of the potential risks) to Category ''X'' (the risk of use in pregnant women clearly exceeds any potential benefit of the drug) in the drug list and prohibited its use during pregnancy for the indication of preventing migraines.[7]

Risks to offspring derived from prenatal exposure to valproic acid

It has been known for 3 decades that valproic acid is the most teratogenic anticonvulsant drug, with a significant risk of congenital malformations (neural tube defects, genitourinary and muscle-skeletal anomalies, cleft lip and/or cleft palate, and heart defects) of approximately 10–11% of newborns compared with 2–3% of the general population.[8] In addition, in the last few years various studies have shown that between 30% and 40% of children having prenatal exposure to monotherapy valproic acid during the 2nd and 3rd trimesters of pregnancy will present cognitive and behavioural teratogenicity, as well as a greater risk of presenting neurodevelopmental disorders, principally attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).[9–16] The risk is greater than with other options, including combination drug therapy with antipsychotics plus stabilising drugs other than valproic acid.[17]

Although the studies are relatively few, have been carried out primarily in patients with epilepsy and have methodological limitations, the results are consistent after adjusting for possible confounding effects such as the intellectual quotient (IQ) of the mother, age of the mother, use of folic acid during pregnancy, dosage of valproic acid, type of epilepsy, and, in some studies, the presence of mental disorders in the parents.

With respect to cognitive alterations, there have been descriptions of both delay in language acquisition[11,16] and lower IQ in infancy (from 6 to 10 points), with the verbal scale being the most affected.[9,12,15,18,19] In addition, worse adaptation skills, effects on social function, presence of atypical behaviour, and inattention have all been described.[10,14] The risk of receiving a diagnosis of autism or of ASD is increased; in a Danish study[13] the risk was 2.5% and 4.42%, respectively, compared with 0.48% and 1.53% in the general population: that is, 5 and 3 times more risk than in the general population. As for ADHD, Cohen et al.[14] found that 21% of 6-year-old children were at risk of receiving this diagnosis.

Some studies found a dose-dependent effect, suggesting that valproic acid has a toxic effect on neurodevelopment.[18–20] However, Gerard and Meador[21] conclude that it is currently unclear if there are ''safe doses of valproic acid'' and that prospective studies that incorporate the valproate levels are needed to be able to answer this question.

Important preventative recommendations on the use of valproic acid in pregnant women and women of childbearing potential

The prevalence of antiepileptic drug use during pregnancy is around 2%, with the most common indication being the treatment of mental disorders—principally bipolar disorder—followed by the treatment of disorders for pain and epilepsy.[22] The high prevalence in bipolar disorder would be related, at least in part, with the lack of planning described in approximately 50% of pregnant women.[23] For this reason, the choice of the drug to use in long-term treatment of women of childbearing potential is essential from the time of diagnosis.

In the case of bipolar disorder, shared clinical decision[24] to begin or maintain treatment with valproic acid is based on the result of balancing the benefits (avoiding relapses or flare-ups, with the consequent risks for the mother and the foetus) and the previously indicated risks for the offspring. All of us, the psychiatrists, the patients and their partners, lack sufficient up-to-date information to help us in this decision that is so clinically relevant. On the one hand, the AEMPS has not updated the data on valproic acid in their website—the information contained in the document EMA/144306/2017[3] has either not been incorporated into the website or we have been unable to find it—and it has not published the data on the efficacy in Spain of the measures recommended in 2014, in contrast to countries such as France and the United Kingdom that informed the EMA of the lack of efficacy of these measures based on insufficient knowledge of the risk by both physicians and patients, or on not knowing how to use this information with respect to decisions about prescribing (EMA/144306/2017).[3] Furthermore, the AEMPS has not made the report on the safety of

this drug available for individuals, in the corresponding section of its website, either. On the other hand, the Pharmacy and/or Clinical Pharmacology Services in the hospitals do not remind the psychiatrists about the recommendations of the 2014 PRAC/AEMPS[1] with the same frequency, intensity and insistence that they adopt for the use of other psychotropic drugs. Lastly, the clinical practice guidelines for the treatment of bipolar disorder do not include updated information about this matter; this is probably related to the fact that, except for those of the British Association for Psychopharmacology (BAP),[25] the guidelines were published before 2014 and have not been updated yet.[26–30] For this reason, we have decided to publish this Editorial to give Spanish psychiatrists information on the current state of the official preventative measures on the use of valproic acid in pregnant women or those of childbearing potential.

The BAP guidelines[25] indicate that the fact of being a woman of childbearing potential does not seem to influence the prescription of valproic acid. Consequently, they include 3 items on the treatment with this drug in pregnant women or women of childbearing potential in the battery proposed for auditing the clinical case histories of patients with bipolar disorder: (1) that prescription is justified in writing; (2) the patient has been told about the risks for her offspring and she has understood this information; and (3) effective birth control measures have been offered. With respect to the use of valproic acid in pregnant women or those of childbearing potential for acute mania treatment, the guidelines indicate the recent warnings against its use and the need for informed consent from the patient, providing the web address at which more information can be obtained. For long-term treatment in monotherapy, their recommendation is that, with Level I evidence (maximum), valproic acid generally should not be considered for women of childbearing potential. However, when drug combinations are mentioned, there is no warning about the use of valproic acid. Even more surprising is the fact that in the specific section on ''Neurotoxicity of maternal drug use after birth'' the guidelines make no reference to the abundance of data on the neurotoxicity of valproic acid presented in the preceding section, and that in the section ''Risk of damage associated with drugs'' such neurotoxicity is treated only in passing, being limited to a few lines: ''Valproate has been considered of special concern due to its apparently greater risk of developmental alterations compared to women in treatment with other anti-epileptic agents. The problems described include a lower IQ and developmental disorders''.

Based on the information currently available and previously described, we make the following ''Very Important Preventative Recommendations'' to be remembered when beginning treatment for managing bipolar disorder in pregnant women or those of childbearing potential:

(1) In pregnant women or women of childbearing potential for whom drug treatment for bipolar disorder is to be initiated, a drug other than valproic acid is preferable, both for treatment of acute mania and for long-term treatment.
(2) If, for clinically-justified reasons recorded in the patient's medical history, treatment with valproic acid is started, the following measures should be taken and recorded in the patient history:
   a. Tell the patient and her partner (if applicable) of the risks of congenital malformations and cognitive and behavioural teratogenicity that are involved with this drug.
   b. Make sure that she or they have understood the risks explained.
   c. Obtain written informed consent before prescribing the drug.
   d. Tell and offer the patient and her partner (if applicable) about the need to begin effective birth control measures, and/or joint prescription of folic acid supplements.
   e. Tell the patient about the need to notify her psychiatrist if she wants to get pregnant for proper pregnancy planning at the most appropriate time.
   f. Tell her about the need to let her psychiatrist know she is pregnant as soon as she finds out that this has happened.
   g. Notify the AEMPS of any adverse effects that appear in offspring, regardless of whether they are effects associated with or attributable to prenatal exposure to valproic acid.

In the case of pregnant women or women of childbearing potential who are currently receiving valproic acid for their bipolar disorder, in whom other drugs have not been tried, the steps below should be followed:

(1) Tell the patient and her partner (if applicable) of the risks of congenital malformations and cognitive and behavioural teratogenicity involved with this drug.
(2) Make sure that she or they have understood the risks explained.
(3) With the patient and her partner (if applicable), discuss the possibility of using another drug to replace valproic acid, both for treatment of acute mania and for long-term treatment.
(4) If the shared decision is to continue with valproic acid treatment, the indications (2) c-g of the previous case (commencement of treatment) will be implemented.

These procedures will be applied as soon as possible (preferably in the following visit), unless this is contraindicated by the patient's clinical state, in which case the process of shared decision-making should be postponed until the clinically appropriate time. All the recommendations implemented must be recorded in the clinical case history.

In the case of pregnant women or those of childbearing potential currently in treatment with valproic acid for their bipolar disorder, for whom the other pharmacological options were not effective or were not tolerated, the indications (2) a-g of the first case above (commencement of treatment) should be adopted and recorded.

In conclusion, pending the new EMA report on the need or lack of need to increase the restrictions on the use of valproic acid in pregnant women or women of childbearing potential, Spanish psychiatrists should keep the important preventative measures recommended well in mind, considering the current state of knowledge.

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