Effectiveness of risk minimisation measures for valproate: a drug utilisation study in Europe, analysis of data from Spain

Birgit Ehlken, Irena Stevanovic, Sigal Kaplan, Isabelle Dresco, Denis Granados, Massoud Toussi

Introduction. Risk minimisation measures for valproate were implemented in Spain in 2015.

Objective. The objective of this study is to assess the effectiveness of valproate risk minimisation measures in Spain intended to decrease the use of valproate as a first-line therapy, and to evaluate the prescribing patterns of valproate in women, including women of childbearing potential, in the pre- and post-implementation risk minimisation measures periods.

Materials and methods. The prescribing patterns of valproate in females and women of childbearing potential before and after risk minimisation measures implementation were examined using the longitudinal patient data database, which includes patient information from two panels: primary care physicians and neurologists/psychiatrists. Primary endpoint was the proportion of initial valproate prescriptions with at least one medication related to the valproate indications before the valproate initiation date.

Results. The proportion of incident valproate prescriptions with previous use of medication related to valproate indications was 78.0% (95% CI, 73.9%; 81.5%), and 78.2% (74.5%; 81.4%) in the main pre-and post-implementation periods in the primary care physician panel. The corresponding figures for women of childbearing potential were 79.6% (73.6%; 84.5%) and 75.5% (69.7%; 80.6%), respectively. The incidence rate of pregnancies exposed to valproate (per 1,000 person-years) in women of childbearing potential decreased from 17.4 the entire pre-implementation to 8.5 in the entire post-implementation periods.

Conclusion. After the implementation of risk minimisation measures for valproate in Spain, no meaningful change in prescribing was observed regarding the proportion of valproate initiations preceded by prior medication related to valproate indications. The preventative measures recommended for use of valproate in women of childbearing potential should be considered.

Key words. Bipolar disorder. Drug utilisation study. Epilepsy. Risk minimisation measures. Valproate. Women of childbearing potential.

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Irena Stevanovic, Isabelle Dresco and Denis Granados are employees of Sanofi and may hold shares and/or stock options in the company. Birgit Ehlken and Massoud Toussi are employees of IQVIA, which was paid by a consortium of companies to perform the analyses. Sigal Kaplan is an employee of Teva Pharmaceutical Industries Ltd.

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Introduction

Valproate is an effective drug with indicated benefits for epilepsy and for bipolar disorder [1,2]. In Spain, the recently updated *Diagnostic and Therapeutic Guidelines for Epilepsy* (2019) from the Spanish Society of Neurology (SEN) recommend valproate as the first-line treatment for generalised tonic-clonic crisis and myoclonic or absence seizures, but advise that valproate should be avoided in women of childbearing potential, a population in which the drug is contraindicated due to associated foetal development risks in pregnancy [3]. In addition, the *Clinical Practice Guidelines* (2012) from the Ministry of Health for the treatment of bipolar disorder recommend using valproate as second-line monotherapy for the prevention of new manic episodes but avoiding its use in women of childbearing potential [4]. In women of childbearing potential, it is recommended to change treatment from valproate to any other available alternative before the patient becomes pregnant. In case alternative effective therapies are not available for pregnant patients with epilepsy, valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation [3]. Since 2018, valproate has been contraindicated in pregnant women with bipolar disorder [5]. In Spain, first official diagnosis and treatment initiation for epilepsy or bipolar disorder is given by a specialist; however, primary care physicians are the gatekeepers for most pa-

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Ethical considerations:
All procedures performed in this study involving human participants were in accordance with the ethical standards of the applicable institutional review board and ethics committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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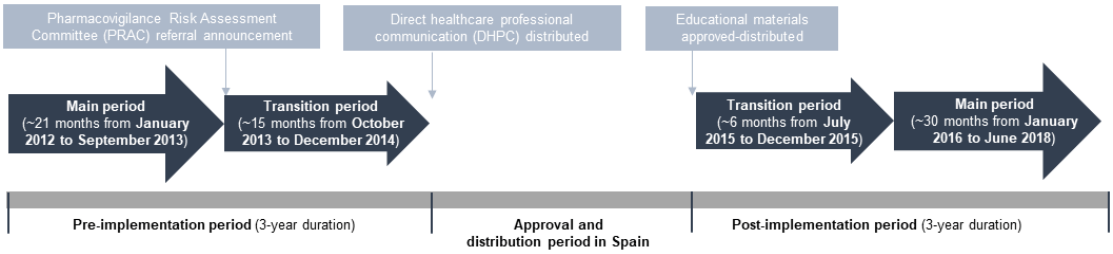
Figure 1. Study periods including entire, main and transition study periods for Spain. Adapted from [10].



tients with bipolar disorder [6], as well as those with epilepsy [7].

In October 2013, the European Medicines Agency (EMA) issued a review of valproate-containing medicines and their use in women of childbearing potential, due to new evidence for the risks of developmental disorders in children following *in utero* exposure to valproate [8]. In October 2014, the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) made recommendations regarding the use of valproate in women of childbearing potential for epilepsy and manic episodes in bipolar disorder, which were that valproate and related substances should not be used in girls, women of childbearing potential or pregnant women, unless alternative treatments are ineffective or not tolerated. Additionally, PRAC determined that further risk minimisation measures were required to appropriately advise patients and healthcare professionals about the potential risks of developmental disorders, along with a drug utilisation study to assess the effectiveness of the proposed risk minimisation measures [9, 10].

The objective of this study is to assess the effectiveness of those risk minimisation measures in Europe which intended to decrease the use of valproate as a first-line therapy, and to evaluate the prescribing patterns of valproate in women, including women of childbearing potential, in the pre- and post-implementation risk minimisation measures periods.

Materials and methods

Study design

This study was a non-interventional, multinational cohort study across five European countries: France, Germany, Spain, Sweden and the United Kingdom. The protocol of the study was approved by the EMA in January 2016 and registered in the European Union electronic Register of Post-Authorisation Studies (EUPAS11379) prior to the start of data collection [11]. For the Spain cohort, the study was based on an existing data source of electronic medical records, the longitudinal patient data database. The study was divided into two periods based on the implementation of risk minimisation measures in 2015: a 36-month pre-implementation period (a 21-month main pre-implementation period, and a 15-month transition pre-implementation period) and a 36-month post-implementation period (a 6-month transition post-implementation period, and a 30-month main post-implementation period) (Fig. 1).

Study population and setting

This study included female patients who were treated with at least one prescription of valproate in oral form in the outpatient setting during the pre- or post-implementation periods. A subgroup of women of childbearing potential, defined as females aged 13-49 years, was identified. Valproate prescriptions were categorised as incident if no prior prescriptions for valproate were recorded in the data source within 12 months before the prescription date, and as first-ever prescriptions, if no prior prescriptions of valproate were recorded within the patient's entire available medical history before the prescription date.

Endpoints

The primary endpoint of this study was the proportion of initial valproate prescriptions with at least one medication related to the valproate indi-

cations before the valproate initiation date. The success of the risk minimisation measures was defined as an increase in this proportion from pre- to post-implementation period. Data on prior medication were obtained from 12 months prior for analysis in incident and from entire medical history for first-ever valproate prescriptions. Secondary endpoints included demographic characteristics, indications for valproate (diagnosis related to the valproate prescription), concomitant medications related to valproate indications, as well as use of hormonal contraceptives or intrauterine devices within 12 months prior to valproate initiation, and pregnancies exposed to valproate.

Data sources and measurement for Spain analysis

The data source included information on written prescriptions, patients' demographics and diagnoses collected from approximately 2,000 prescribers in Spain. The longitudinal patient data database was used to identify patient information from the primary care physician panel and neurologist/psychiatrist panel. Longitudinal patient data database covers approximately 3% of primary care physicians, neurologists and psychiatrists from Spain.

Statistical analysis

Analyses were primarily performed for the main study period using descriptive statistical methods to identify differences between prescribing patterns, including demographics and outcome parameters before and after implementation of risk minimisation measures. All main analyses were performed on prescription-level data, based on incident and first-ever prescriptions. More than 384 incident prescriptions were needed to allow a meaningful comparison of results for the primary endpoints between main periods. Data from the primary care physician panel and neurologist/psychiatrist panel were analysed separately. In addition, a secondary analysis of the primary endpoint interrupted time series was conducted to assess the effectiveness of the risk minimisation measures, comparing the entire 36-month pre- and post-implementation periods. Investigated parameters were period (corresponding to the overall impact of risk minimisation measures and indicating overall change in the post-implementation period compared with the pre-implementation period) and time (indicating trend to change of primary endpoint over time after implementation of risk minimisation measures). Incidence of pregnancy was analysed in both panels together throughout the entire 36-month pre- and post-implementation study periods.

Results

Number of patients and valproate prescriptions

In total, 1,501 female patients (13,663 prescriptions) with at least one prescription record of valproate during the main pre-implementation period and 1,686 patients (20,742 prescriptions) during the main post-implementation period were identified in the primary care physician panel of the longitudinal patient data database. In the neurologist/psychiatrist panel, 182 patients (740 prescriptions) and 153 patients (519 prescriptions) were identified, respectively. Information on all prescriptions in the entire pre- and post-implementation periods is in Table I.

Lower numbers of all incident and first-ever prescriptions were observed in the entire post-implementation period compared with the entire pre-implementation period for the primary care physician panel (incident 652 vs 758 and first-ever 402 vs 577) and the neurologist/psychiatrist panel (177 vs 247 and 153 vs 220).

For all women of childbearing potential, the number of valproate prescriptions in the entire post-implementation period was slightly lower compared with the pre-implementation period for the primary care physician panel (10,092 vs 10,624). It was meaningfully lower for the neurologists/psychiatrists panel (372 vs 767). For incident and first-ever prescriptions, results were similar in the primary care physician panel (incident 286 vs 353 and first-ever 165 vs 252) and the neurologist/psychiatrist panel (99 vs 152 and 85 vs 133) (Table I).

Demographic characteristics

For demographic characteristics, in the primary care physician panel, mean –standard deviation (SD)– age for the overall study population was 46.5 –(SD): 21.4– years in the main pre- and 49.7 (SD: 20.6) years in the main post-implementation period; 47.0% and 41.8% were women of childbearing potential, respectively. Similar findings were captured for the mean age of incident valproate users. In the neurologist/psychiatrist panel, mean age of the overall study population was 46.5 (SD: 17.0) years in the main pre- and 48.4 (SD: 17.0) years in

Table I. Number of valproate prescriptions in the main and entire pre- and post-implementation periods for both study panels in Spain.

	Overall population		Women of childbearing potential (13-49 years of age)	
	Pre-implementation period	Post-implementation period	Pre-implementation period	Post-implementation period
	Main: 21 months (entire: 36 months)	Main: 30 months (entire: 36 months [% change][a])	Main: 21 months (entire: 36 months)	Main: 30 months (entire: 36 months [% change][a])
All prescriptions				
Primary care physician panel	13,663 (23,844)	20,742 (25,014 [+4,9])	6,193 (10,624)	8,305 (10,092 [–5])
Neurologist/psychiatrist panel	740 (1,414)	519 (786 [–44,4])	393 (767)	243 (372 [–51,5])
Incident prescriptions				
Primary care physician panel	449 (758)	554 (652 [–14])	206 (353)	237 (286 [–19])
Neurologist/psychiatrist panel	127 (247)	146 (177 [–28,3])	77 (152)	79 (99 [–34,9])
First-ever prescriptions				
Primary care physician panel	363 (577)	337 (402 [–30,3])	157 (252)	133 (165 [–34,5])
Neurologist/psychiatrist panel	116 (220)	125 (153 [–30,5])	71 (133)	66 (85 [–36,1])

[a] Change of prescription number in the entire post-implementation period compared with the entire pre-implementation period.

the main post-implementation period, and 61.0% and 52.3% were women of childbearing potential, respectively. Similar findings were observed for incident valproate users.

Primary endpoint of prior medication use related to indications of valproate initiation

In the primary care physician panel, the proportion of valproate prescriptions (95% confidence interval [CI]) with previous use of medication related to valproate indications in all incident prescriptions was 78.0% (73.9%; 81.5%) in the main pre-implementation period, and 78.2% (74.5%; 81.4%) in the main post-implementation period; corresponding figures for women of childbearing potential were 79.6% (73.6%; 84.5%) and 75.5% (69.7%; 80.6%), respectively. The corresponding figures of all incident valproate prescriptions in epilepsy were 41.3% (33.8%; 49.3%) and 47.3% (40.6%; 54.1%); and 47.0% (35.4%; 58.8%) and 41.0% (30.8%; 52.1%) in women of childbearing potential, respectively. For all incident prescriptions for bipolar disorder, they were 93.3% (87.4%; 96.6%) and 90.7% (85.8%; 94.1%), and in women of childbearing potential, 89.5% (78.9%; 95.1%) and 92.3% (84.2%; 96.4%) (Table II).

In the neurologist/psychiatrist panel, the proportion of valproate initiations with medication related to valproate indications in all incident prescriptions was 87.4% (80.5%; 92.1%) in the main pre-implementation period and 85.6% (79.0%; 90.4%) in the main post-implementation period; for women of childbearing potential, results were 83.1% (73.2%; 89.9%) and 82.3% (72.4%; 89.1%), respectively. The corresponding figures for all incident valproate prescriptions for epilepsy were 40.0% (19.8%; 64.3%) and 69.6% (49.1%; 84.4%); for bipolar disorder, corresponding figures were 95.0% (83.5%; 98.6%) and 85.5% (74.7%; 92.2%) (Table III).

Regarding first-ever prescriptions, in the primary care physician panel, the proportion of valproate prescriptions with previous use of medication related to valproate indications in the overall population was 80.4% (76.1%; 84.2%) in the main pre-implementation period, and 86.4% (82.3%; 89.6%) in the main post-implementation period; in women of childbearing potential, results were 84.1% (77.5%; 89.0%) and 88.0% (81.4%; 92.5%), respec-

Table II. Prior medication use related to the indication of valproate initiation (primary outcome parameter) in indication subgroups 'epilepsy' and 'bipolar disorder': summary for the main study periods (in all incident prescriptions; first-ever valproate use) in primary care physician panel in Spain.

Primary care physician panel								
	Prescriptions for epilepsy				Prescriptions for bipolar disorder			
	Overall population		Women of childbearing potential (13-49 years of age)		Overall population		Women of childbearing potential (aged 13-49 years)	
	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)
Incident prescriptions *(n)*	150 (100)	205 (100)	66 (100)	78 (100)	120 (100)	194 (100)	57 (100)	78 (100)
Prescriptions with prior medication related to valproate indications: *n* (%) [95% CI of %]	62 (41.3) (33.8-49.3)	97 (47.3) (40.6-54.1)	31 (47) (35.4-58.8)	32 (41) (30.8-52.1)	112 (93.3) (87.4-96.6)	176 (90.7) (85.8-94.1)	51 (89.5) (78.9-95.1)	72 (92.3) (84.2-96.4)
n first-ever prescriptions	114 (100)	123 (100)	42 (100)	32 (100)	94 (100)	101 (100)	45 (100)	39 (100)
Prescriptions with prior medication related to valproate indications[a] *n* (%) [95% CI of %]	51 (44.7) (35.9-53.9)	76 (61.8) (53.0-69.9)	24 (57.1) (42.2-70.9)	21 (65.6) (48.3-79.6)	90 (95.7) (89.6-98.3)	100 (99) (94.6-99.8)	43 (95.6) (85.2-98.8)	39 (100) (91-100)

CI: confidence interval. [a] Analysis in first-ever prescriptions: medications related to epilepsy or bipolar disorder – any time in the patient's entire history, prior to initiation of valproate.

tively. The corresponding figures for all first-ever valproate prescriptions for epilepsy were 44.7% (35.9%; 53.9%) and 61.8% (53.0%; 69.9%). For bipolar disorder, corresponding figures in all first-ever prescriptions were 95.7% (89.6%; 98.3%) and 99.0% (94.6%; 99.8%) (Table II).

In the neurologist/psychiatrist panel, the corresponding proportion in all first-ever prescriptions was 90.5% (83.8%; 94.6%) and 92.8% (86.9%; 96.2%), and 88.7% (79.3%; 94.2%) and 90.9% (81.6%; 95.8%) for women of childbearing potential, respectively. Corresponding figures for all first-ever valproate prescriptions for epilepsy were 46.2% (23.2%; 70.9%) and 80.0% (58.4%; 91.9%). For bipolar disorder, corresponding figures were 97.2% (85.8%; 99.5%) and 98.1% (89.9%; 99.7%) (Table III).

Indication for valproate prescription

For the primary care physician panel, any indication of interest, including epilepsy and bipolar disorder, was reported in 76.9% and 85.0% of all valproate prescriptions in the main pre- and post-implementation periods. Indication for epilepsy was observed in 44.7% and 45.4% of all prescriptions, respectively. Corresponding proportions for epilepsy in the women of childbearing potential population were 48.1% and 51.5%. Bipolar disorder was the indication for 30.3% and 36.7% of all valproate prescriptions, respectively, and the corresponding proportions in the women of childbearing potential population were 26.5% and 28.7%.

For the neurologist/psychiatrist panel, any indication of interest was identified in 75.0% and 77.5% of all valproate prescriptions in the main pre- and post-implementation study periods, respectively. Epilepsy was the indication for 22.4% and 13.5% of all valproate prescriptions, corresponding to 6.9% and 8.2% in women of childbearing potential, respectively. Bipolar disorder indication was recorded at 47.4% and 55.3% in all valproate prescriptions in the main study periods, corresponding to variations between 49.4% and 56.4% in women of childbearing potential across the two study periods.

Table III. Prior medication use related to the indication of valproate initiation (primary outcome parameter) in indication subgroups 'epilepsy' and 'bipolar disorder': summary for the main study periods (in all incident prescriptions; first-ever valproate use) in neurologist/psychiatrist panel in Spain.

Neurologist/psychiatrist panel								
	Prescriptions for epilepsy				Prescriptions for bipolar disorder			
	Overall population		Women of childbearing potential (aged 13-49 years)		Overall population		Women of childbearing potential (aged 13-49 years)	
	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)	Main pre-implementation period (21 months)	Main post-implementation period (30 months)
n incident prescriptions	15 (100)	23 (100)	8 (100)	6 (100)	40 (100)	62 (100)	21 (100)	35 (100)
Prescriptions with prior medication related to valproate indications: *n* (%) [95% CI of %]	6 (40) (19.8-64.3)	16 (69.6) (49.1-84.4)	1 (12.5) (2.2-47.1)	6 (100) (61-100)	38 (95) (83.5-98.6)	53 (85.5) (74.7-92.2)	20 (95.2) (77.3-99.2)	29 (82.9) (67.3-91.9)
n first-ever prescriptions	13 (100)	20 (100)	6 (100)	5 (100)	36 (100)	52 (100)	20 (100)	28 (100)
Prescriptions with prior medication related to valproate indications[a] *n* (%) [95% CI of %]	6 (46.2) (23.2-70.9)	16 (80) (58.4-91.9)	1 (16.7) (3-56.4)	5 (100) (56.6-100)	35 (97.2) (85.8-99.5)	51 (98.1) (89.9-99.7)	20 (100) (83.9-100)	27 (96.4) (82.3-99.4)

CI: confidence interval. [a] Analysis in first-ever prescriptions: medications related to epilepsy or bipolar disorder – any time in the patient's entire history, prior to initiation of valproate.

Concomitant medication related to valproate indication and contraception use

In all panels, the percentage of concomitant use of relevant medications in all valproate prescriptions was high (> 70%) in both the main pre- and post-implementation periods and in all the populations studied.

In the primary care physician panel, the proportion of incident valproate prescriptions with recorded use of hormonal contraceptives within 12 months prior to initiation of valproate in women of childbearing potential was 4.9% in the pre-implementation period and 8.4% in the post-implementation period. Corresponding results in the neurologist/psychiatrist panel were 10.4% and 7.6% in all incident valproate prescriptions, respectively. No records of intrauterine device use within 12 months prior to initiation of valproate were identified in both study periods.

Pregnancies exposed to valproate in women of childbearing potential

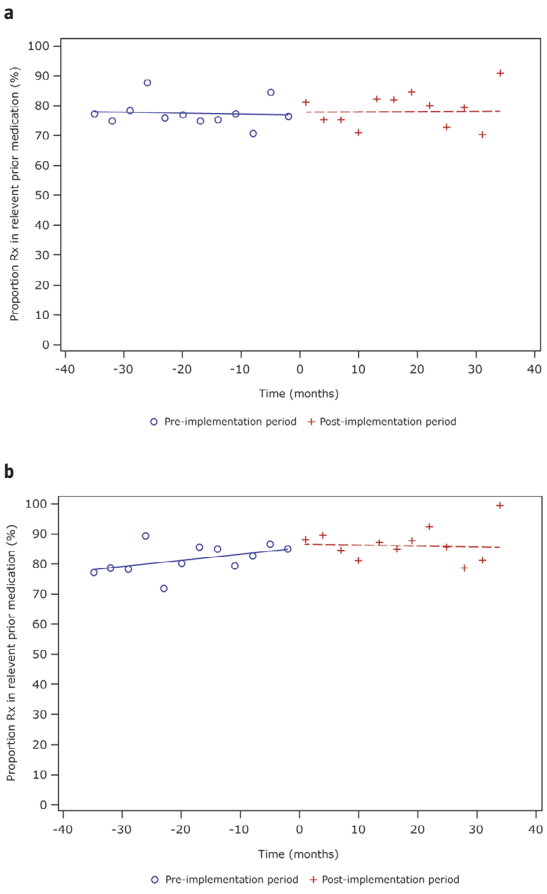
For both panels, overall, 50 pregnancies in women of childbearing potential were identified in the entire pre-implementation period, of which 37 were exposed to valproate. In the entire post-implementation period, 28 pregnancies in women of childbearing potential were identified, 16 of which were exposed to valproate. The incidence rate for pregnancies (per 1,000 person-years) in the women of childbearing potential population was lower in the entire post-implementation period versus the entire pre-implementation period (14.9 vs 23.4 for all pregnancies and 8.5 vs 17.4 for pregnancies exposed to valproate).

Interrupted time series analysis

Interrupted time series analysis of the primary end-

point was performed based on data from the primary care physician panel for all incident and all first-ever valproate prescriptions (Fig. 2a and b). The results for the subgroups of epilepsy and bipolar disorder, and those from the neurologist/psychiatrist panel, were not presented because the quarterly number of valproate prescriptions for these analyses was very low and the analyses have not provided statistically meaningful information. A segmented regression analysis of interrupted time series data (based on Poisson regression) was performed. In both interrupted time series analyses in the primary care physician panel, no statistically significant changes of investigated parameters (period and time) were detected (p-values > 0.05 in the full models in analyses of incident and first-ever prescriptions).

Figure 2. Interrupted time series analysis of primary endpoint. Primary care physician panel. Full model plots. a) All incident valproate prescriptions; b) All first-ever valproate prescriptions (p-values > 0.05 for both parameters in the full models in analyses of incident and first-ever prescriptions).



Rx: valproate prescriptions.

Discussion

The primary objective of this study was to assess risk minimisation measures effectiveness in the outpatient setting in Spain, comparing the proportion of prior medication use related to valproate indications in females initiating valproate treatment during pre- and post-implementation periods. Primary outcome results showed that there was no meaningful difference in the percentage of prior medication use for valproate indications in all incident prescriptions and in women of childbearing potential before and after risk minimisation measures implementation. Among first-ever users however, this percentage was slightly higher in all incident valproate prescriptions and women of childbearing potential groups, in the post-implementation period compared with the pre-implementation period.

For women of childbearing potential, the percentage of prior medication use for valproate indications for epilepsy in first-ever users was higher in the post- compared with the pre-implementation period for both primary care physician and neurologist/psychiatrist panels. Similar results were observed for bipolar disorder. The updated 2019 SEN guidelines are more restrictive regarding valproate prescriptions for epilepsy and bipolar disorder and recommend avoiding the use of valproate in any women of childbearing potential, based on clinical evidence from several studies [3]. An observational study conducted with Spanish neurologists to assess treatments prescribed during neurology consultations found that valproate (48.2%) and levetiracetam (43.2%) were the most frequently prescribed drugs for generalised and partial seizures (n = 559), but the percentage of patients receiving valproate was statistically higher in men than in women: 31.1% vs 20.7%, respectively (p = 0.005) [12].

Results on primary endpoint demonstrate variation across populations and indication subgroups. The proportion of incident valproate prescriptions preceded by other medications related to valproate indications was lower in women of childbearing potential in the primary care physician panel following risk minimisation measures implementation for the epilepsy subgroup and slightly higher for the bipolar disorder subgroup. While in the op-

posite neurologist/psychiatrist panel, the proportion of incident valproate prescriptions for bipolar disorder preceded by relevant medication was slightly lower in the main post- compared with the main pre-implementation period. The results for the epilepsy subgroup in the neurologists/psychiatrists panel were based on very low number of prescriptions and do not provide statistically meaningful information. The interrupted time series analyses performed for all incident and all first-ever prescriptions from the primary care physician panel have also not shown any statistically significant difference regarding the primary endpoint. A greater percentage of prior medication use was recorded in bipolar disorder compared with epilepsy in both study periods, which may reflect the indication of valproate for bipolar disorder when lithium is not effective or tolerated [4].

In this study, reductions in the overall number of incident and first-ever prescriptions from the pre- to post-implementation period suggest that healthcare professionals partially incorporate the recommendations and reduced the number of valproate initiations, specifically after implementation of risk minimisation measures. Indeed, there is evidence to suggest that while valproate was one of the most widely used drugs to treat epilepsy between 1992 and 2004 in Spain [13], a slight decline in use of valproate has been noted over the years [14].

The incidence rate for pregnancies in women of childbearing potential was lower in the entire post- versus the entire pre-implementation period, but due to limited sample sizes, results should be interpreted with caution.

Overall, there seems to be variation in the prescribing behaviour across subgroups relating to the effectiveness of risk minimisation measures in Spain, that supports the need for further monitoring of risk minimisation measures. This prompted the Spanish Drug Safety Committee alongside other European states, to express concern that prescriptions of valproate had not been adequately reduced in women of childbearing potential. The risk minimisation measures implemented for the use of valproate have shown limited impact [15], despite procedures implemented based upon the 2014 PRAC recommendation [9]. Healthcare professionals and patients need up-to-date information to support clinical decision-making to manage valproate treatment, balancing benefits with risks. Despite no observed meaningful difference in the percentage of prior medication use for valproate indications, reductions in the absolute number of prescriptions suggest an increase in compliance with risk minimisation measures in both primary care physician and neurologist/psychiatrist panels in Spain. However, the updated measures in late 2018 [16] lead to the need for further assessment of these risk minimisation measures. A more recent study by Puig-Molto M, *et al*. (2020) evaluated the impact of the EMA alerts on effective contraception in women of childbearing potential undergoing valproate treatment. Results concluded that 31.6% of women of childbearing potential on valproate treatment used a contraceptive method before 2014, and up to 60% of these patients used effective contraception after the updated 2018 EMA alerts [17].

There are few limitations for this study. For Spain, the prescription data issued by primary care physicians and specialists are available on the selected IMS© longitudinal patient data source. Patients cannot be tracked across practices in the longitudinal patient data and can only be partially tracked across specialities; therefore, under-reporting to an unknown extent may be present. Misclassification of incident prescriptions cannot be ruled out in the case of prescriptions issued by both panels. Also, all results in the epilepsy subgroup, as well as the women of childbearing potential subgroup for bipolar disorder in the neurologist/psychiatrist panel, are based on low numbers of observations in both study periods and cannot be considered statistically meaningful.

Conclusion

After the implementation of risk minimisation measures for valproate in Spain, no significant change in prescriptions was observed regarding the proportion of valproate initiations preceded by relevant prior medication for incident prescriptions. However, data for first-ever prescriptions suggest a trend towards increased compliance. Results varied between different populations and indication subgroups. In 2017, the EMA expressed concern about the prescription of valproate and the need to strengthen the risk minimisation measures to accompany its use in clinical practice.

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Eficacia de las medidas de minimización de riesgos del ácido valproico: estudio de utilización del fármaco en Europa, análisis de datos de España

Introducción. En 2015 se aplicaron en España distintas medidas para la minimización de los riesgos (MMR) del ácido valproico.

Objetivo. El objetivo de este estudio es evaluar la eficacia de las MMR del ácido valproico en España, con el fin de reducir el uso de ácido valproico como terapia de primera línea y evaluar los patrones de prescripción de ácido valproico en las mujeres, incluidas las mujeres en edad fértil (MEF), en los períodos previos y posteriores a la implementación de las MMR.

Materiales y métodos. Los patrones de prescripción del ácido valproico en mujeres y MEF antes y después de la implementación de las MMR se examinaron utilizando la base de datos longitudinales de pacientes (*longitudinal patient data*, LPD por sus siglas en inglés), que incluye información de pacientes de dos paneles: médicos de atención primaria (MAP) y neurólogos/psiquiatras. El criterio principal de valoración fue la proporción de prescripciones iniciales de ácido valproico con al menos un medicamento relacionado con indicaciones de ácido valproico antes de la fecha de inicio del ácido valproico.

Resultados. La proporción de prescripciones de ácido valproico secundarias con uso previo de medicamentos relacionados con indicaciones de ácido valproico fue del 78% –intervalo de confianza (IC) al 95%: 73,9-81,5%– y del 78,2% (IC al 95%: 74,5-81,4%) en los períodos principales previo y posterior a la implementación en el panel de MAP. Las cifras correspondientes a MEF fueron del 79,6% (IC al 95%: 73,6-84,5%) y del 75,5% (IC al 95%: 69,7-80,6%), respectivamente. La tasa de incidencia de embarazos expuestos al ácido valproico (por 1.000 personas-años) en MEF disminuyó de 17,4 en el período completo previo a la implementación a 8,5 en el período completo posterior a la implementación.

Conclusión. Tras la implementación de las MMR del ácido valproico en España no se observó ningún cambio significativo en las prescripciones respecto a la proporción de iniciaciones de ácido valproico precedidas por medicación previa relacionada con indicaciones de ácido valproico. Se deben tener en cuenta las medidas preventivas recomendadas para el uso de ácido valproico en MEF.

Palabras clave. Ácido valproico. Epilepsia. Estudio de utilización de medicamentos. Medidas de minimización de riesgos. Mujeres en edad fértil. Trastorno bipolar.