A Joint Drug Utilisation Study (DUS) of valproate and related substances, in Europe, using databases

Final study report:

Abstract

Title
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Keywords
Drug utilisation study, valproate, treatment characteristics, effect of Risk Minimization Measures (RMM)

Rationale and background
The PRAC review of valproate medicines and their use in pregnant women started in October 2013, following the publication of new data on the risks of malformations and developmental problems in children exposed to valproate in the womb.

CMDh endorsed the PRAC's recommendations in November 2014. Risk minimisation measures (RMM) included the Direct Healthcare Professional Communication (DHPC) and educational materials as approved by national competent authorities.

Following the implementation of RMM, marketing authorisation holders (MAHs) of valproate had to perform a drug utilisation study (DUS) to assess the effectiveness of the measures and to further characterise the prescribing patterns for valproate.

Research question and objectives
To describe the prescribing practices, before and after the dissemination of RMM (i.e. educational materials and DHPC), and to assess the effectiveness of these measures.

Study design
Multinational cohort study based on existing data sources using a pre- and post- design to examine the changes in the prescribing patterns of valproate.

Setting
The study was conducted in the outpatient setting in five European countries (France, Germany, Spain, Sweden and the United Kingdom).

The study considered a 36-month period before the implementation of RMM (pre-implementation period) and a 36-month period after the implementation of RMM (post-implementation period). The pre-implementation period started in January 2012 and ended in December 2014 in all countries; the start date of the post-implementation period varied (depending on date of distribution of DHPC and educational materials) between January 2015 (Germany), February 2015 (Sweden and UK), June 2015 (France) and July 2015 (Spain); the end date varied between December 2017 in Germany and Sweden, January 2018 in UK, May 2018 in France and June 2018 in Spain.

The final study report contains results for the entire 36-month pre-implementation period and entire 36-month post-implementation period in four countries, France, Germany, Spain and the United Kingdom: the two main study periods (for the primary analysis) were a 21-month pre-implementation period and a 30-month post-implementation period. In the fifth country, Sweden, the entire post-implementation period (35 months) and the main post-implementation period (29 months) are both one month shorter. The reason is that following the implementation of RMM in Sweden, a 36-month post-implementation period would end in January, but the annual update schedule of national registries is done for calendar years.

Subjects and study size, including dropouts

The study population included all female patients receiving valproate prescriptions during the pre-defined pre- and post- implementation periods in the selected databases of target countries.

Variables and data sources

Longitudinal patient-level Electronic Medical Records databases were used for the final report: IMS® Disease Analyzer for France and Germany, IMS® LPD for Spain and CPRD for UK. In France and UK, selected databases include primary care physicians (PCPs); in Germany and Spain, PCPs and neurologists/psychiatrists were considered for the DUS. In Sweden, three National Health Registries were used.

The primary endpoint was defined as proportion of valproate prescriptions with at least one medication used prior the valproate initiation and related to the valproate indication (epilepsy, bipolar disorder, migraine headaches)[1] within 12 months before the valproate initiation date. The main analysis was performed in incident valproate prescriptions and in addition in first ever valproate users. Incident use was defined as valproate prescriptions issued during the pre- or post-implementation study period without prior prescription for valproate *within 12 months* before the prescription date; first ever use was defined as valproate prescriptions issued during the pre- or post-implementation study period without prior prescription for valproate *within entire available patient's medical history* before the prescription date.

Results

The number of patients included in the analysis for the main 21-month pre-implementation period ranged from 1,683 patients with 14,403 valproate prescriptions in Spain to 14,287 patients with 184,606 valproate prescriptions in Sweden. The corresponding figures for the main post-implementation period were 1,839 patients with 21,261 prescriptions in Spain to 14,444 patients with 257,573 prescriptions in Sweden. In both main study periods the majority of prescriptions were prevalent. In the 21-month main pre-implementation period the number of incident valproate prescriptions ranged from 576 in Spain to 4,424 in Sweden. In the main post-implementation period the number of incident prescriptions ranged from 700 in Spain to 5,065 in Sweden. The number of first ever valproate users varied in the main pre-implementation period between 479 (Spain) and 3,676 (Sweden) and in the main post-implementation period between 462 (Spain) and 3,972 (Sweden).

Proportion of prior medications - related to valproate indications - within 12 months before valproate initiation - the primary endpoint - was 48.7% of all incident prescriptions in the main pre- and 40.6% in the main post-implementation period in France; the corresponding figures in Sweden were 81.1% and 84.5%, in UK - 66.4% and 72.4%. In Germany, prior medication was recorded in 47.9% and 47.0% in the PCP panel, 49.4% and 49.1% in the neurologists/psychiatrists panel. The corresponding figures in Spain were 78.0% and 78.2% in the PCP panel, 87.4% and 85.6% in the neurologists/psychiatrists panel. The results in entire pre- and post-implementation periods were in line with the main analysis. In first ever valproate users, when prior medication for epilepsy and bipolar disorder from entire patients' history was considered, the proportions in the main pre- and main post-implementation periods were 75.1% and 72.7% in France, 86.0% and 89.0% in Sweden, 77.8% and 83.2% in UK. The corresponding figures in Germany were 57.9% and 63.6% (PCP panel) and 78.5% and 77.9% (neurologists/psychiatrists panel); the proportions in Spain were 80.4% and 86.4% in the PCP panel and 90.5% and 93.0% in the neurologists/psychiatrists panel.

Overall, information on indication of interest (epilepsy, bipolar disorder, migraine headaches) was available for over 65% of all valproate prescriptions in Germany, Spain, Sweden and UK in the main pre- and post-implementation periods (ranging from 66.9% to 88.0%). Of note, the migraine indication is not supported by all MAHs. In France, indication of interest was documented for 32.8% and 37.2% of prescriptions. Epilepsy was the main indication for valproate in all countries (ranging from 17.5%

[1] Valproate containing medicines have been authorised for several decades across the European Union (EU) to treat epilepsy and bipolar disorder. In a few countries, marketing authorisation is granted for prevention of migraine attacks.

(France) to 59.5% (PCP panel Germany) with exception of neurologists/psychiatrists panel in Spain. In France, the proportion was low because diagnoses of interest were available only for nearly a third of prescriptions. Bipolar disorder was recorded in less than 20% of all valproate prescription in France, Germany and UK, whereas in Spain (30.3% to 36.7% in the PCP panel, 47% to 55% in the neurologists/psychiatrists panel) and Sweden (about 40%) this diagnosis was more frequent.

In all target countries, concomitant use of medications related to the valproate indications epilepsy, bipolar disorder or migraine headaches was similar in both main study periods. Concomitant use of medications related to the valproate indications epilepsy, bipolar disorder or migraine headaches was recorded in 78.9% and 79.9% of all prescriptions in main pre- and post-implementation periods, respectively, in France. Corresponding figures in Germany were 53.2% and 55.2% (PCP panel) as well as 60.9% and 63.1% (neurologists/psychiatrists panel), in Spain 71.6% and 76.3% (PCP panel) as well as 78.1% and 90.4% (neurologists/psychiatrists panel), in Sweden 77.1% and 80.9%, and in UK 61.3% and 67.5%.

Concomitant use of prescribed hormonal contraceptives or IUD in the age group 13 to 49 years was recorded in 8.6% and 7.2% of incident prescriptions in France in the main pre-and post-implementation periods, respectively. The corresponding figures were 1.9% and 5.9% (PCP panel) and 3.9% and 5.1% (neurologists/psychiatrists panel) in Spain, 9.9% and 9.7% in Sweden and 4.0% and 5.3% in UK. In Germany, no records on concomitant use of hormonal contraceptives or IUD were available in the data provided by PCPs and the neurologists/psychiatrists.

Overall, 923 pregnancies including 451 exposed to valproate (48.9%) from the entire pre-implementation period and 350 including 182 exposed to valproate (52.0%) from the entire post-implementation period were identified in the target countries. In Sweden and UK, the incidence rate of pregnancies exposed to valproate decreased from 0.0095 to 0.0080 per 12 person-months and from 0.0169 to 0.0109 per 12 person-months, respectively.

Discussion

This study provides insights on the prescribing patterns of valproate in five European countries. Findings for the primary objective in Sweden and UK indicate better compliance with prescribing conditions after implementation of RMM. In Germany and Spain, no change in prescription behavior of physicians after the distribution of DHPC and educational materials was observed. Results in first ever valproate users confirm the findings for Sweden and UK and suggest a trend of increased compliance also for Spain and PCPs in Germany. This trend was not found for France. Figures on concomitant use of hormonal contraceptives or IUD have to be interpreted with particular caution, due to the type of contraceptive method being captured in the data sources (only prescribed ones) as well as short time periods used for this analysis to evaluate prescribing behavior at the time of valproate prescriptions. In Sweden and UK, providing the most interpretable pregnancy data in this report, findings show a marked decrease in the incidence of pregnancies exposed to valproate.

In conclusion, this study brought quantitative evidence about the effect of the RMM implemented between end of 2014 and mid of 2015 in France, Germany, Spain, Sweden and UK. Following the new measures to avoid valproate exposure during pregnancy issued by the PRAC in February 2018, new RMM were introduced during the second half of 2018. Therefore, an extension of this DUS is planned to further monitor both the use of valproate in women and the reduction in the number of pregnancies exposed to valproate.