Valproate EU consortium

A drug utilisation study extension (DUS ext.) of valproate and related substances, in Europe, using databases

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ABSTRACT

1. TITLE

A drug utilisation study extension (DUS ext.) of valproate and related substances, in Europe, using databases.

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2. KEYWORDS

Drug utilisation study, Valproate, Risk minimisation measures, pregnancy prevention programme, Europe

3. RATIONALE AND BACKGROUND

Valproate and related substances have been used to treat epilepsy since 1967 and bipolar disorder since 1995 in Europe. In some European countries, they are also used for prophylaxis of migraine attacks.

In 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the safety and efficacy of valproate in women of childbearing potential (WCBP) and pregnant women due to risks of malformations and developmental disorders in infants exposed to valproate in utero. This led to restrictions and risk minimisation measures (RMMs) such as educational materials (EMs) for physicians and patients.

Despite these measures, studies showed that valproate use in WCBP did not significantly change during 2014–2016. In 2017, France requested a reassessment of the RMMs' impact, leading to revised prescribing conditions and a pregnancy prevention programme (PPP) in 2018. The PPP includes pregnancy tests, counselling, effective contraception, and annual treatment reviews. The PRAC also recommended visual warnings on packaging and further studies to monitor valproate use and long-term effects.

Following the endorsement of the PRAC recommendation, marketing authorisation holders must perform a DUS to evaluate the effectiveness of the new RMMs and to better understand valproate-prescribing patterns in various European databases.

4. RESEARCH QUESTION AND OBJECTIVES

This study aimed to address the following research question: "What was the impact of the implementation of the RMMs and PPP on the use of valproate in WCBP in Europe?"

The objectives of the study were the following:

Primary objectives:

- To describe and compare the prescribing practices in WCBP receiving valproate during the pre- and post-implementation periods with respect to elements of PPP separately:
    - Use of contraceptives without interruption during treatment
    - Laboratory plasma pregnancy tests before treatment

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  - Treatment reviews by a specialist at least once per year (using a proxy of consultation by a specialist as a marker for treatment review)
  - Speciality of prescribing physician at initiation
- To describe and compare the proportion of patients for whom all elements of the PPP measurable with this DUS ext. were fulfilled during the pre- and post-implementation periods.
- To describe and compare the incidence of valproate-exposed pregnancies and characteristics of exposed pregnancies during the pre- and post-implementation periods.

Secondary objective:

To describe and compare the following prescribing patterns in WCBP during the pre- and post-implementation periods, overall and in patient subpopulations:

- Demographic characteristics of WCBP prescribed or dispensed valproate in oral form
- Indication for use (epilepsy, bipolar disorder, and other)
- Use of prior medication for valproate indications before valproate initiation.

5. STUDY DESIGN

This DUS ext. was a non-interventional longitudinal retrospective cohort study of WCBP exposed to valproate, conducted with secondary data obtained from electronic medical records or administrative healthcare databases in France, Germany, the Netherlands, Spain, Sweden, and the United Kingdom (UK).

6. SETTING

The selection of databases for the DUS ext. was based on experience acquired during the original DUS to ensure a sufficient number of WCBP valproate users and the provision of information on pregnancy.

The periods were defined as follows:

- **Pre-implementation period (36-month duration):** This period captured 36 months before the end of the distribution of the EM. This pre-implementation period was considered a baseline period and was divided into two sub-periods in relation to the PRAC recommendation (February 2018):
  - **Main period (25–30 month duration):** Starting 36 months before the end date of EM distribution and ending at the date of PRAC recommendations announcement.
  - **Transition period (6–11 month duration):** Starting at the date of PRAC recommendation announcement and ending at the end date of EM distribution.
- **Post-implementation period (36-month duration):** This period captured the 36 months after the end of the distribution of the EM approved by the respective national competent authorities.

The purpose of the transition period was to define the time during which the different countries implemented the RMMs following the PRAC recommendations in February 2018. For the purposes of the study design, the transition period was included in the pre-implementation period to evaluate the impact of the implementation of the RMMs once approved and distributed in each country.

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The index date was defined as the date the first prescription was issued (UK) or dispensed (France, Germany, the Netherlands, Spain, Sweden) for valproate within each of the study periods. The first observed prescription or dispensation for valproate fulfilling the inclusion criteria within the post-implementation period could become the second index date for a patient. Consequently, a patient could have two index dates but only one per study period.

Patients were followed from valproate exposure start to the end of follow-up/censoring date, i.e.:

- Transfer out of the database, e.g. death, emigration, or
- End of the study period of interest (pre-implementation period or post-implementation), whichever occurred first.

7. SUBJECTS AND STUDY SIZE

The study population included WCBP (i.e. 13–49 years old women), receiving at least one valproate prescription or dispensation during the pre-implementation period and post-implementation period.

Based on valproate prescriptions within 12 months before the index date, study participants were categorised as recurrent users (had valproate prescriptions within 12 months before the index date) and incident users (did not have any valproate prescription within 12 months before the index date). Additionally, first-ever users (sub-population of incident users who did not have any record of valproate prescription in the data source prior to the index date) and prevalent users (i.e. overall study population including both recurrent and incident users) were described.

Based on diagnoses and medications used before the index date, study participants were categorised as valproate users with epilepsy, bipolar disorder, other (other psychiatric disorders and migraine), or unknown indication.

Based on the previous DUS with valproate (EU PAS Register Number: EUPAS9678), the incidence of women who became pregnant while on treatment was assumed to be around 0.01 per person-year (i.e. around 10 pregnancies in 1,000 women treated with valproate for 1 year), and the change in incidence between the pre-implementation period and the post-implementation period was assumed to be between 0.001 and 0.01 per person-year. The type I error was assumed to be 5% and the statistical power set at 80%.

To observe a decrease of 0.005 per 1,000 person-years in the incidence rates of pregnancy between the pre- and post-implementation periods, a sample size of 2,584 WCBP would be required to be included over the 3 years of each period (corresponding to 7,750 person-years). To observe a decrease of 0.010 per 1,000 person-years in the incidence rates using the same assumptions, 773 WCBP would be required to be included over 3 years (or 2,319 person-years).

8. VARIABLES AND DATA SOURCES

Exposure was defined as one or more prescriptions or dispensations of valproate during one of the pre-defined study periods. Brand names and generics of all oral forms of valproate salts were considered (sodium valproate, valproic acid, valproate semi-sodium, valpromide, valproate magnesium) and summarised under the term “valproate”.

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Outcomes of interest included demographics and prescribing practices, PPP elements (i.e. annual visits to a specialist, initiation of valproate by a specialist, adequate coverage of concomitant contraception, laboratory plasma pregnancy tests), and pregnancy (e.g. incidence rate of exposed pregnancy, characteristics of exposed pregnancies, pregnancy outcomes):

- Demographics and prescribing practices:
    - Patient's age at index date.
    - Medical history and medications history related to valproate indication (epilepsy, bipolar disorder, and other, i.e. migraine and other psychiatric disorders) before index date.
    - Indication of valproate use at index date algorithmically determined.
    - Speciality of prescribing physicians (neurologist, psychiatrist, paediatrician, general practitioner, other specialities) during valproate treatment.
    - Laboratory plasma pregnancy tests during valproate treatment.
- Compliance with the PPP:
    - Contraception before and during valproate treatment (hormonal patches/vaginal rings, hormonal pills, hormonal implants, any intrauterine devices [IUD], and sterilisation)
    - Adequate coverage of concomitant use of contraception during valproate treatment measured using an adaptation of the proportion of days covered methodology
    - Laboratory plasma pregnancy tests at index date
    - Annual visits to specialists (neurologist, psychiatrist, paediatrician, general practitioner, other specialties) during valproate treatment
    - Initiation of the valproate treatment by a specialist (neurologist, psychiatrist, paediatrician)
    - The number of PPP elements fulfilled (up to two elements for prevalent and recurrent users, up to four elements for incident users)
- Pregnancy
    - Identification and dating of pregnancies were algorithmically determined.
    - The incidence rate of exposed pregnancy was calculated using follow-up time exposed to valproate while not pregnant as time at risk, and number of incident pregnancies while exposed as number of exposed pregnancies.
    - Characteristics of exposed pregnancies (e.g. age at pregnancy, contraception use before pregnancy, exposure during trimesters, initiation and/or discontinuation of valproate during pregnancy, pregnancy outcomes).

The data sources included the French National Healthcare Data System (*Système National des Données de Santé*, [SNDS]) in France, *Betriebskrankenkasse* (BKK), part of the German Statutory Health Insurance (*Gesetzliche Krankenversicherung* [GKV]) in Germany, the Information System for Research in Primary Care (*Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària* [SIDIAP]) in

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Spain, the PHARMO Data Network in the Netherlands, National Health Registers in Sweden, and Clinical Practice Research Datalink (CPRD) GOLD in the UK.

9. RESULTS

The description of the results is based on the potential clinical relevance, and p-values are not reported in the main text in alignment with the guidelines for good pharmacoepidemiology practice of the International Society of Pharmacoepidemiology recommendations. The statistical tests performed assume independence between the groups while there was partial overlap in women included in each of the groups, and these are not adjusted for multiple comparisons, which largely limits their relevance. Hence, trends comparing values between the pre-implementation main period and the post-implementation period are described regardless of the statistical significance. The following terminology for describing trends has been applied to ensure the consistency of the reporting of the results: 0% to 0.9%: “stable/similar”, 1.0% to 2.4%: “varied”, 2.5% to 4.9%: “slightly increased/decreased”, 5.0% and more: “increased/decreased”.

This section presents an overview of the key results of this DUS ext. study, which aimed to understand the impact of the 2018 RMM and PPP implementation on valproate-prescribing practices and the incidence of exposed pregnancies among WCBP in France, Germany, the Netherlands, Spain, Sweden, and the UK.

The results are presented by country separately and organised in three outcome-based subsections of results addressing the study objectives – study population and valproate-prescribing practices, compliance with the elements of the PPP, and incidence and characteristics of exposed pregnancies – within each country.

9.1 France

9.1.1 Study Population and Valproate-prescribing Practices

In France, the population of prevalent valproate users declined by approximately 32% between the pre- (n=82,178) and post-implementation (n=55,675) periods. The proportion of recurrent users decreased from 68.6% to 60.6%, while the proportion of incident users increased from 31.4% to 39.4%.

The mean age at index was stable at around 38 years in both periods for prevalent users. Patients with bipolar disorder were slightly older (mean ~40 years) than those with epilepsy (mean ~36 years) in both periods.

Epilepsy became the most common indication in all users in the post-implementation period, increasing from 50.2% to 55.4% among recurrent users and from 39.6% to 48.1% among incident users. Conversely, the proportion for bipolar disorder indication decreased from 47.7% to 42.2% and from 57.5% to 48.8% in the same groups, respectively.

Prescribing patterns remained broadly consistent in both indications.
Among patients with epilepsy, in recurrent users, general practitioners (GPs) were the main prescribers (~52%), followed by undefined hospital-based specialists (~16%) and neurologists (~13%). In incident users, the main prescribers were GPs (~27%), undefined specialists in hospital (~25%) and psychiatrists (~24%). Notably, neurologists prescribing increased from 8.6% to 14.8% in incident users.

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Among patients with bipolar disorder, in recurrent users, psychiatrists were the main prescribers (~40%), followed by GPs (~30%) and undefined hospital-based specialists (~23%). In incident users, the main prescribers were psychiatrists (~46%), undefined specialists in hospital (~23%) and GPs (~21%).

The proportion of women with epilepsy treated with other antiepileptic drugs prior to valproate initiation increased slightly from 68.0% to 71.9%. The most common drugs remained unchanged: lamotrigine (increasing from 20.6% to 27.3%), clobazam (~14%), levetiracetam (~10%), and pregabalin (~9%).

The proportion of women with bipolar disorder treated with other BD indicated drugs prior to valproate initiation remained stable (~87%). The most frequently used drugs were escitalopram (~19%), paroxetine/venlafaxine (~18%), and aripiprazole/escitalopram (~15%). Lithium use remained low (~5%) in both periods.

9.1.2 Compliance With the PPP

Compliance with the PPP was assessed using four elements: annual visits to a specialist, initiation of valproate by a specialist (incident users only), adequate contraceptive coverage during valproate treatment (PDC ≥80%), and laboratory pregnancy testing before initiation (incident users only).

Among recurrent users, 77.1% and 86.2% were eligible (i.e. ≥455 days of follow-up) for assessment of "*Annual specialist visits*" in the pre- and post-implementation periods, respectively. The proportions were 19.6% and 25.3% among incident users. Among those eligible, the proportion with annual visits remained stable: 53.5% to 52.6% for recurrent users and 70.2% to 69.7% for incident users. By indication, annual visits among incident users were similar across periods for epilepsy (65.6% to 67.1%) and bipolar disorder (73.8% to 73.5%). Among recurrent users, visits declined for epilepsy (48.9% to 45.6%) but increased for bipolar disorder (59.3% to 63.5%).

"*Initiation of valproate by a specialist*" increased from 38.1% to 44.3% overall, with similar trends by indication: from 30.8% to 40.1% for epilepsy and from 43.8% to 49.4% for bipolar disorder. Psychiatrists were the most frequent initiating specialists in both periods, with proportions increasing from 20.3% to 22.9% for epilepsy and from 42.7% to 47.8% for bipolar disorder patients. Initiation by neurologists increased in epilepsy (8.1% to 12.7%), while initiation in hospital settings, by undefined specialty, declined in both indications (epilepsy: from 31.4% to 26.5%; bipolar disorder: from 27.1% to 23.0%). GP-initiated treatment also decreased, from 27.1% to 21.4% for epilepsy and from 20.5% to 18.2% for bipolar disorder.

Sterilized women were considered compliant for the adequate contraceptive coverage and the pregnancy testing PPP elements. The proportion of sterilized women prior to index date increased from 5.7% to 7.5% overall. Similar trends were observed in the epilepsy users, whatever the sub-group. A slightly larger increase was observed among those with bipolar disorder (5.8% to 8.3%).

"Concomitant use of contraception or IUD or sterilization during treatment" increased slightly among recurrent users (52.3% to 55.8%) and remained stable among incident users (51.3% to 52.4%). Adequate coverage (PDC ≥80%) remained stable across periods: 38.3% to 39.5% for recurrent users and 44.0% to 44.7% for incident users. Among those with concomitant use of valproate, adequate coverage was higher but declined slightly for recurrent users (73.2% to 70.8%) and remained stable for incident users (85.7% to 85.3%). Coverage was lower among girls under 18 and women over 45. These trends were consistent across indications.

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The proportion of women with a laboratory pregnancy test before valproate initiation increased from 6.6% to 9.0%. When including women sterilized prior to index date, compliance with this PPP element increased from 12.7% to 16.2% between periods, with similar trends across indications.

Overall, the proportion of patients not fulfilling any PPP elements declined from 36.6% to 33.6% among recurrent users and from 29.2% to 25.5% among incident users. Among recurrent users, the proportion fulfilling one element remained stable (~47%), while those fulfilling two elements (maximum achievable) increased from 16.2% to 18.4%. Among incident users, the proportion fulfilling one element declined slightly (40.6% to 38.0%), while those fulfilling two, three, and four elements increased from 23.4% to 26.0%, 6.0% to 9.1%, and 0.8% to 1.4%, respectively. These patterns were consistent across indications.

9.1.3 Incidence and Characteristics of Exposed Pregnancies

The proportion of pregnant women exposed to valproate remained relatively stable between periods, decreasing slightly from 1.7% to 1.2% among recurrent users and from 2.1% to 1.8% among incident users. Among all pregnancies, the proportion that were valproate-exposed increased slightly for recurrent users (from 47.7% to 49.1%) and remained stable for incident users (36.7% in both periods). By indication, exposure rates were stable for epilepsy (53.0% to 54.4% for recurrent users; 42.1% to 41.2% for incident users) and among incident users with bipolar disorder (33.7% to 33.0%), while a slight decrease was observed for recurrent users with bipolar disorder (41.7% to 39.5%).

The incidence rate of exposed pregnancies (excluding those initiating valproate during pregnancy) decreased from 9.1 to 5.9 per 10,000 person-months overall, and from 8.1 to 4.8 among recurrent users (in whom the proportion of valproate initiation was rare, see below). Considering pregnancies with valproate initiation, the rate of pregnancy exposed to valproate was higher and decreased from 13.0 to 8.1 per 10,000 patients between periods overall and from 36.5 to 25.6 per 10,000 patients among incident users.

The mean age at the start of exposed pregnancy was stable across periods (~31 years), with similar trends across user sub-groups in epilepsy indication. Recurrent users with bipolar disorder were approximately three years older than those with epilepsy, similarly in both periods.

Use of contraception prior to exposed pregnancy increased in recurrent users with bipolar disorder (36.3% to 47.0%), while remaining stable in those with epilepsy (36.0% to 35.8%). Among incident users, overall contraceptive use increased in those with epilepsy (31.0% to 38.3%) and decreased in those with bipolar disorder (42.8% to 38.4%).

Valproate initiation during pregnancy was rare among recurrent users in both periods, but frequent among incident users, remaining stable at ~53%. Valproate initiation during pregnancy was more frequent in incident users with epilepsy (~61%) than in those with bipolar disorder (~43%), with no notable change between periods.

Valproate exposure most frequently occurs in the 30 days before pregnancy or during the first trimester. Among recurrent users, exposure in the 30 days before pregnancy increased from 67.0% to 75.8% in those with epilepsy and remained stable in those with bipolar disorder (69.5% to 68.7%). Among incident users, this proportion decreased slightly in both indications (epilepsy: 30.6% to 29.2%; bipolar disorder: 50.7% to 49.1%).

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Among all exposed pregnancies, exposure remained most common in the first trimester. The proportion of pregnancies not exposed during the first trimester remained stable between periods (11.4% to 12.8%), while it decreased during the second or third trimesters (respectively 50.2% to 46.8% and 42.3% to 40.9%). In exposed pregnancy, recurrent users were primarily treated with doses between 700–1,500 mg/day, while incident users more often received ≥1,500 mg/day, similarly in both periods. These patterns were consistent across indications.

Among exposed pregnancies, discontinuation of valproate occurred more frequently during pregnancy than in the 30 days before. Overall, discontinuation in the 30 days before pregnancy start remained stable in recurrent users (8.6% to 7.8%) and incident users (11.6% to 12.8%). Discontinuation during pregnancy remained stable (~53% for recurrent users; ~70% for incident users).

In epilepsy indication, however, discontinuation varied between periods. Discontinuation in the 30 days before pregnancy decreased (7.9% to 5.5% for recurrent users; 9.7% to 8.8% for incident users). Discontinuation during pregnancy slightly decreased in recurrent (52.0% to 50.2%) but increased in incident users (72.8% to 75%).

In bipolar disorder, variations occurred in the opposite manner. Discontinuation in the 30 days before pregnancy increased (10.0% to 12.7% for recurrent users; 14.0% to 18.2% for incident users). Discontinuation during pregnancy increased for recurrent users (54.6% to 57.5%) but decreased for incident users (65.8% to 61.0%).

Among exposed pregnancies with available outcome data, the proportion of live births remained similar across periods, higher among incident users (56.4% to 56.0%) than recurrent users (48.5% to 48.1%).

The proportion of miscarriage, early termination, or stillbirth was also stable, higher among recurrent users (51.5% to 51.9%) than incident users (43.6% to 44.0%). Assessment of birth defects was limited due to low case counts.

9.2 Germany

9.2.1 Study Population and Valproate-prescribing Practices

In Germany, between the pre- and post-implementation periods, the number of valproate users declined by ~19% (from 2,221 to 1,806). The proportion of recurrent users decreased slightly from 76.8% to 74.6%, while incident users increased from 23.2% to 25.4%.

The mean age of prevalent users remained stable at 35 years, though among incident users, there was a shift from the 25–34 age group to the 35–44 group over time.

Epilepsy was the primary indication for valproate use in both periods, increasing from 75.7% to 79.3%, while bipolar disorder decreased from 22.8% to 19.4%. This trend was consistent across user types, with epilepsy more common among recurrent users (81.3% to 84.9%) than incident users (57.2% to 63.1%). Conversely, bipolar disorder indication declined in both groups (from 17.9% to 14.5% in recurrent users and from 38.8% to 33.8% in incident users).

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Neurologists were the main prescribers in both periods, with stable proportions among recurrent users (41.2% to 41.0%) and an increase among incident users (38.1% to 43.0%). General practitioners were the second most common prescribers, with proportions slightly increasing from 27.6% to 29.1% in recurrent users and from 20.0% to 22.6% in incident users. Among patients with epilepsy, neurologists and GPs remained the primary prescribers, with stable proportions across periods (respectively ~43.1% in recurrent and ~44% in incident users, and ~31% in recurrent ~25% in incident users). The proportion of psychiatrist as prescribers was generally low altogether (~6% in recurrent users) but increased among incident users (from 7.1% to 11.0%). Among patients with bipolar disorder, neurologists and psychiatrists remained the primary prescribers. The proportions of neurologists as prescribers decreased for recurrent users from 32.1% to 26.8% and increased for incident users from 28.5% to 36.7% between periods. The proportion of psychiatrists as prescribers increased in recurrent users from 28.6% to 30.4% and more slightly in incident users from 28.0% to 30.2%.

Among women with epilepsy, prior use of other antiepileptic drugs before initiating valproate increased from 64.1% to 73.0%. The most common drugs were lorazepam (stable at ~21%), levetiracetam (16.9% to 18.7%), lamotrigine (14.6% to 24.2%), and topiramate (11.9% to 18.3%). In women with bipolar disorder, prior use of other BD indicated drugs decreased slightly (from 78.0% to 74.2%). The most frequently used drugs were quetiapine (23.5% to 21.3%), citalopram (21.5% to 19.4%), and venlafaxine (15.0% to 12.3%). Lithium use remaining relatively stable and low (9.0% to 10.3%).

9.2.2 Compliance With the PPP

The proportion of women with at least one annual specialist visit slightly decreased among recurrent users (from 82.6% to 78.6%) but remained stable among incident users (88.9% to 88.7%). Among recurrent users, this decrease was observed in both epilepsy (83.1% to 79.4%) and bipolar disorder (80.2% to 74.5%). Though among incident users, the proportion of women with annual visit to specialist decreased slightly for epilepsy (88.2% to 86.5%) but increased for bipolar disorder (92.0% to 94.4%).

Initiation of valproate by a specialist increased from 84.1% to 87.6%, with higher rates in patients with bipolar disorder (89.0% to 92.9%) than in those with epilepsy (81.7% to 84.8%). Neurologists were the primary initiators for epilepsy, with their share rising from 58.0% to 68.2%, while psychiatrist-initiated prescriptions declined from 15.9% to 13.1%. Among patients with bipolar disorder, psychiatrist-initiated treatment decreased (49.0% to 43.9%), same for initiations by GPs (12.5% to 10.0%), while neurologist-initiated treatment increased (≤39.5% to 49.0%).

Sterilization rates before valproate initiation remained stable among recurrent users (6.2% to 6.0%) and increased among incident users (5.6% to 9.4%). Similar trends were observed across indications, with slightly higher rates among incident users with bipolar disorder (8.0% to 10.3%).

Concomitant use of contraceptive use (including IUD) or sterilization during valproate treatment remained stable among recurrent users (13.2% to 13.7%) and increased among incident users (12.0% to 17.0%). Adequate contraceptive coverage (PDC ≥80%) was stable in recurrent users (9.4% to 8.9%) but increased in incident users (8.7% to 17.0%). Trends were similar by indication, but contraceptive use was more common in recurrent users with epilepsy (14.0% to 14.5%) than in those with bipolar disorder (9.2% to 9.4%).

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Among those using contraception concomitant to valproate treatment, adequate coverage was higher overall, though it declined in recurrent users (71.1% to 64.9%) and increased in incident users (72.6% to 80.8%). The highest adequate coverage was observed in recurrent users aged 45–49 and incident users aged 18–24.

However, adequate coverage varied by indication and user sub-groups: it remained stable in recurrent users with epilepsy (9.5% to 9.4%) but declined in those with bipolar disorder (8.2% to 6.1%). Conversely, among incident users, adequate coverage increased for both indications, more markedly in epilepsy (8.1% to 14.2%) than in bipolar disorder (10.0% to 12.9%).

Laboratory pregnancy testing before valproate initiation remained low (1.9% to 1.3%). When also considering women with prior sterilization, compliance with this PPP element increased from 7.6% to 10.5%. Data by indication were masked due to small sample sizes.

Overall, the proportion of recurrent users fulfilling no PPP elements remained stable (30.1% to 31.4%), while it declined among incident users (12.8% to 10.0%). Among recurrent users, the proportions fulfilling one or two elements (maximum achievable) were stable (63.2% to 62.5% and 6.7% to 6.1%, respectively). Among incident users, the proportion fulfilling one element declined (63.0% to 54.8%), while those fulfilling two or three elements increased (19.6% to 25.5% and 3.3% to 6.8%, respectively). Fulfilment of four elements remained low but increased slightly (1.4% to 2.8%). Trends were consistent across indications.

9.2.3 Incidence and Characteristics of Exposed Pregnancies

The proportion of pregnant women remained stable among recurrent users (2.3% to 2.4%) but declined among incident users (3.3% to 2.4%). The proportion of pregnancies exposed to valproate decreased overall from 62.7% to 53.3%, with a reduction observed in both recurrent users (70.7% to 60.6%) and incident users (44.4% to ≤33.3%; masked due to low counts). The incidence rate of exposed pregnancies declined from 9 to 7 per 10,000 person-months overall, with a decrease among recurrent users (9 to 6 per 10,000 person-months) and a slight increase among incident users (10 to 11 per 10,000 person-months).

Among recurrent users, results were different by indication, the proportion of pregnant women in recurrent users with epilepsy remained stable (2.4% to 2.2%), while it increased in those with bipolar disorder (2.0% to 3.6%). Among incident users, trends were similar across indications, though data for bipolar disorder in the post-implementation period were masked. These patterns translated into a decreased incidence rate of exposed pregnancies in epilepsy (9 to 6 per 10,000 person-months) and an increase in bipolar disorder (5 to 12 per 10,000 person-months), though interpretation is limited by small sample sizes.

The mean age at the start of exposed pregnancies among prevalent users increased slightly from 31.8 to 32.7 years. Overall, the description of most of the pregnancy characteristics was limited due to low counts. Most exposures of pregnancies occurred either in the 30 days prior to pregnancy onset (from 59.5% to 79.2%) or during the first trimester. During the first trimester, most women received daily doses between 700 and 1,500 mg. Data for the second and third trimesters were masked due to low counts.

Among exposed pregnancies with known outcomes, the proportion resulting in live births declined from 52.6% to 42.9%, while the proportion ending in miscarriage, early termination, or stillbirth increased from 47.4% to 57.1%. These findings should be interpreted with caution due to limited sample sizes.

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9.3 The Netherlands

9.3.1 Study Population and Valproate-prescribing Practices

In the Netherlands, the number of women of childbearing potential using valproate declined by approximately 20% between the pre- (n=2,338) and post-implementation (n=1,861) periods. The distribution of recurrent and incident users remained stable across periods, at ~64% and ~36%, respectively.

The mean age at index date was stable at 37 years across all user types. However, patients with epilepsy were generally younger than those with bipolar disorder (35 vs. 39 years), and among patients with bipolar disorder, incident users were slightly younger than recurrent users (38 vs. 41 years).

Epilepsy was the most common indication in both periods; its proportion increased among recurrent users (44.6% to 47.9%) and remained stable among incident users (48.0% to 48.7%). Bipolar disorder showed a modest increase among recurrent users (22.3% to 24.6%) and remained stable among incident users (~26%).

General practitioners were the primary prescribers of valproate in both periods, with their proportion increasing among all users (recurrent users: 77.2% to 80.2%; incident users: 58.6% to 61.8%). In contrast, prescriptions by neurologists decreased overall: from 2.9% to 1.4% among recurrent users, and from 4.8% to 3.1% among incident users. Similar trends were observed for prescriptions by psychiatrists, they decreased from 5.3% to 3.1% and from 9.8% to 2.1% in recurrent and incident users, respectively.

Among patients with epilepsy, GP prescribing increased (from 76.7% to 81.0% for recurrent users and from 58.1% to 65.4% for incident users), while neurologist prescribing declined (from 6.1% to 2.7% and from 8.2% to 5.7%, respectively). For patients with bipolar disorder, GP prescribing increased slightly among recurrent users (66.3% to 69.5%) and remained stable among incident users (54.8% to 53.4%), while psychiatrist prescribing declined (from 11.7% to 7.4% and from 15.0% to 5.2%, respectively).

The proportion of women with prior medication use before initiating valproate increased from 66.9% to 70.1%. Among women with epilepsy, prior use of antiepileptic drugs rose slightly (from 80.9% to 82.7%). The most common prior medications were lorazepam (23.6% to 22.8%), topiramate (20.9% to 19.8%), and levetiracetam (19.1% to 22.5%). Among patients with bipolar disorder, the proportion of women with prior treatment increased from 94.1% to 98.3%, with quetiapine use rising (26.0% to 32.2%), lithium declining (21.0% to 17.5%), and citalopram increasing (13.7% to 19.8%).

9.3.2 Compliance With the PPP

Among recurrent users, the proportion of women with an annual visit to a specialist declined from 23.8% to 13.5%, while among incident users, it remained relatively stable (29.5% to 31.5%). For patients with epilepsy, annual visit to specialists decreased among recurrent users (34.2% to 20.2%) but increased among incident users (40.0% to 46.8%). Among those with bipolar disorder, the proportions decreased for recurrent users (10.9% to 6.0%) and increased for incident users (4.2% to 7.9%).

Initiation of valproate by a specialist decreased overall (38.2% to 33.3%). The proportions were higher among patients with epilepsy (51.5% to 42.9%) than those with bipolar disorder (28.8% to 23.2%). The

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decrease of initiation by a specialist was also more pronounced in the epilepsy indication. Neurologists were the primary initiating specialists for epilepsy, though their proportion declined (43.2% to 39.5%), while GP initiation remained stable (17.1% to 17.3%), and initiation by other physicians increased (30.4% to 39.5%). Among patients with bipolar disorder, psychiatrist-initiated treatment dropped sharply (21.0% to 7.3%), while the proportion neurologist-initiated treatment almost doubled (7.8% to 15.8%). GP initiation declined (24.2% to 18.6%), and initiation by other physicians rose (45.7% to 57.6%).

Sterilization prior to valproate initiation remained rare and stable, among recurrent users (1.5% to 1.1%) and incident users (1.3% to 0.6%). Trends were similar among patients with epilepsy. Among patients with bipolar disorder, it declined from 2.4% to 1.4% in recurrent users, and from 2.7% to 0.0% in incident users.

Concomitant use of contraception, IUD, or sterilization during valproate treatment remained stable between periods (49.6% to 48.3%), as did adequate coverage (PDC ≥80%) (36.0% to 35.0%). Results were similar across user sub-groups. When considering only patients with concomitant use of contraceptive during valproate treatment, the proportion of adequate coverage was higher but unchanged between periods (70.4% to 69.8% for recurrent users; 77.0% to 77.6% for incident users). Coverage was slightly lower in the youngest and oldest age groups.

Among epilepsy patients, the proportions of concomitant use of contraceptive during valproate treatment declined among recurrent users (52.0% to 46.3%) and remained stable among incident users (46.2% to 45.0%). Adequate coverage followed similar trends (35.2% to 33.8% among recurrent; 35.9% to 35.3% among incident users). Among patients with bipolar disorder, concomitant use of contraceptive remained stable across periods (50.0% to 51.2% among recurrent; 43.8% to 44.6% among incident users), while adequate coverage declined among recurrent users (37.2% to 31.3%) and increased slightly among incident users (32.0% to 33.9%).

No laboratory plasma pregnancy tests were recorded before valproate initiation among incident users. Thus, compliance with this PPP element was limited to women who were sterilized at index.

Composite compliance remained low. Among recurrent users, the proportion fulfilling no PPP elements increased (51.2% to 58.4%), while those fulfilling one or two elements declined (from 43.4% to 38.0% and from 5.4% to 3.6%, respectively). Among incident users, the proportion fulfilling no elements rose slightly (39.8% to 41.9%), while those fulfilling one to four elements remained largely unchanged (one element: 42.2% to 41.1%; two elements: 16.4% to 14.9%: three elements: 1.6% to 1.9% and four elements: 0.0% to 0.1%). Patterns were similar across epilepsy and bipolar disorder groups, though among incident bipolar disorder users, the proportion with no fulfilled elements remained stable (48.9% to 48.6%).

9.3.3 Incidence and Characteristics of Exposed Pregnancies

The proportion of pregnancies exposed to valproate declined between the pre- and post-implementation periods, from 87.1% to 68.2% among recurrent users and from 64.7% to 61.5% among incident users. This corresponded to a decrease in the incidence rate of exposed pregnancies from 10 to 7 per 10,000 person-months. Among patients with epilepsy, the proportion of exposed pregnancies remained stable (85.0% to 84.2%), while a marked decline was observed in the bipolar disorder group (83.3% to 33.3%).

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The mean age at the start of an exposed pregnancy was stable across periods and user groups, (averaging ~31 years). Use of contraception prior to exposed pregnancy increased from 21.1% to 34.8%. Initiation of valproate during pregnancy declined among incident users (63.6% to 50.0%).

In exposed pregnancies, valproate exposure most commonly occurred in the 30 days before pregnancy. Exposure in the 30-day pre-pregnancy window increased slightly (52.6% to 56.5%). Across pregnancy trimesters, most pregnancies were exposed to daily doses between 700 and 1,500 mg. Occurrence of valproate discontinuation before pregnancy increased from 10.5% to 26.1%, and discontinuation during pregnancy increased from 26.3% to 43.5%.

Among exposed pregnancies with available outcome data, the proportion resulting in live births declined slightly from 100% to 94.4%. These findings should be interpreted with caution due to the small number of observed pregnancies.

9.4 Spain

9.4.1 Study Population and Valproate-prescribing Practices

In Spain, the number of women of childbearing potential using valproate declined by approximately 18% between the pre- (n=4,020) and post-implementation (n=3,296) periods. The distribution of recurrent and incident users remained stable across periods (64.9% to 63.5% and 35.1% to 36.5%, respectively).

The mean age at index was stable, averaging around 36 years.

In both periods, epilepsy was the predominant indication for valproate use, with stable proportions among recurrent (80.1% to 81.0%) and incident users (59.2% to 61.0%). The proportion of bipolar disorder indication was stable as well: 16.3% to 16.0% of recurrent users and 33.3% to 32.4% of incident users.

Among epilepsy patients, GPs were the main prescribers in both periods. However, their proportion decreased among recurrent users (67.9% to 61.0%) and slightly increased among incident users (42.3% to 44.9%). Neurologist prescribing rose among recurrent users (15.0% to 19.2%) but declined among incident users (28.8% to 23.6%). Psychiatrist prescribing was stable for recurrent users (8.1% to 8.7%) and increased for incident users (23.5% to 27.0%).

For bipolar disorder, GPs remained the primary prescribers among recurrent users, though their proportion declined (57.9% to 47.8%), while psychiatrist prescribing increased (33.8% to 40.4%). Among incident users, psychiatrists were the leading prescribers in both periods, their proportion rising from 46.2% to 55.1%. Prescribing by GPs remained stable (36.8% to 35.8%), while neurologist prescribing declined (14.2% to 7.8%).

The proportion of women with prior medication use before valproate initiation increased slightly (74.2% to 77.7%). Among epilepsy patients, prior use of other antiepileptic drugs rose from 75.5% to 83.3%. The most common were clonazepam (24.8% to 32.1%), lorazepam (stable at ~17%), and topiramate (13.6% to 15.4%). Lamotrigine use also increased (7.5% to 11.6%).

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Among bipolar disorder patients, prior treatment with other BD medications slightly declined (81.9% to 78.2%). The most common drugs were quetiapine (18.3% to 17.2%), citalopram (12.6% to 7.2%), and olanzapine (12.8% to 14.4%). Lithium use remained low (<10%) in both periods.

9.4.2 Compliance With the PPP

Compliance with the PPP remained low across all user groups. Among recurrent users, the proportion with annual visits to a specialist was stable (10.0% to 9.5%), while among incident users, it declined from 19.1% to 14.8%. Similar trends were observed in users with epilepsy, with stable rates in recurrent users (10.0% to 9.3%) and a decrease among incident users (21.9% to 16.5%). For bipolar disorder, the proportion of annual visit to a specialist increased among recurrent users (7.9% to 12.2%) and remained stable among incident users (~13%).

Initiation of valproate by a specialist among incident users remained stable (60.2% to 59.4%). Among women with epilepsy, this proportion declined slightly (59.9% to 57.0%), while it increased among those with bipolar disorder (63.6% to 66.2%).

For patients with epilepsy, neurologist-initiated treatment decreased (31.9% to 25.3%), while psychiatrist and GP initiation increased modestly (from 26.0% to 30.1% and 36.8% to 40.4% respectively). Among patients with bipolar disorder, psychiatrists remained the primary initiators, with their proportion rising from 48.9% to 54.4%.

Sterilization prior to the index date was rare and stable across periods (0.8% for recurrent users; 0.9% to 1.5% for incident users). Among epilepsy patients, rates were stable in recurrent users (0.8% to 0.9%) and increased in incident users (0.7% to 2.2%). Data for bipolar disorder were largely masked due to low counts.

Concomitant use of contraception, IUD, or sterilization during valproate treatment was observed in 13.1% to 14.1% of prevalent users. Adequate contraceptive coverage (PDC ≥80%) increased slightly (6.3% to 7.7%) and was lowest in the youngest and oldest age groups. Among incident users, adequate coverage rose from 7.0% to 9.7%.

Laboratory plasma pregnancy testing before valproate initiation remained low and stable (~1.0%). When including sterilization, compliance with this PPP element increased slightly (1.6% to 2.5%).

Overall, the proportion of prevalent users who did not fulfilled any PPP element remained stable across periods (87.0% to 85.9%), ~13% of prevalent users fulfilled one PPP element, and only 0.3% fulfilled two, which was stable in both periods. Similar patterns were observed in recurrent users. Among incident users, rates were higher: 55.3% to 53.2% fulfilled one element, and 8.0% to 9.3% fulfilled two and 35.9% to 36.0% did not fulfill any element. Fulfilment of all elements was rare. Similar trends were observed across indications and sub-groups.

9.4.3 Incidence and Characteristics of Exposed Pregnancies

The proportion of valproate-exposed pregnancies remained stable among recurrent users (62.3% to 62.9%) and increased among incident users (54.5% to 58.8%). The incidence rate of exposed pregnancies declined in recurrent users from 6.6 to 3.8 per 10,000 person-months, while it remained stable in incident users (6.9 to 6.6 per 10,000 person-months), though estimates in the post-implementation period were limited by small numbers.

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The mean age at the start of exposed pregnancies among prevalent users increased slightly (33.4 to 34.4 years). Prior use of contraceptives among women with an exposed pregnancy and initiation of valproate during pregnancy was limited due to low counts. Valproate exposure most frequently occurred in the 30 days before pregnancy or during the first pregnancy trimester. Exposure to valproate in the 30 days before pregnancy increased from 66.7% to 78.1%. Across pregnancy trimesters, most pregnancies were exposed to daily doses between 700 and 1,500 mg. Discontinuation of valproate before pregnancy rose from 25.8% to 43.8%, while discontinuation during pregnancy remained stable (22.7% to 25.0%).

Among exposed pregnancies with outcome data, the proportion resulting in live births declined from 79.4% to 66.7%. Due to small sample sizes, trends in birth defects could not be assessed.

Overall, exposed pregnancy characteristics were similar across recurrent and incident users, but comparisons between periods were limited by low event counts. No distinct trends were observed by indication (epilepsy or bipolar disorder), with most subgroup data masked.

Sweden

9.4.4 Study Population and Valproate-prescribing Practices

In Sweden, the number of prevalent valproate users declined by approximately 9% between the pre- (n=6,476) and post-implementation (n=5,882) periods. The distribution of recurrent and incident users remained stable, from 64.9% to 63.7% and from 35.1% to 36.3%, respectively.

The mean age at index was 34 years in both periods. Among incident users, there was a modest shift from younger women (aged 18–24) toward older age groups over time.

The proportion of recurrent users with an epilepsy indication remained stable (71.5% to 71.0%), with psychiatrists being the primary prescribers (>38%) in both periods. Among incident users, epilepsy was the indication in approximately 53% of cases, and psychiatrists accounted for over 71% of prescriptions.

Among incident users with epilepsy, prior use of antiepileptic drugs was common and stable (85.5% to 86.7%), with lamotrigine being the most frequently used (53.6% to 53.7%).

For those with bipolar disorder, over 90% had a history of prior BD treatment, with olanzapine use increasing from 25.5% to 30.6%, and lithium use from 20.8% to 26.7%.

9.4.5 Compliance With the PPP

Among recurrent users, the proportion with annual visits to a specialist declined (57.3% to 55.2%), while among incident users, it remained stable (80.9% to 80.0%). Similar patterns were observed in the epilepsy subgroup. In contrast, higher compliance was noted in the bipolar disorder subgroup, though with a modest decline (from 80.2% to 75.9% in recurrent users and from 90.5% to 86.0% in incident users).

Initiation of valproate by a specialist among incident users increased marginally from 92.1% to 93.4%, with psychiatrists being the most common initiators (73.8% to 74.1%), followed by neurologists (15.4% to 16.4%).

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The proportion of prevalent users with prior sterilization remained stable (4.5% to 5.2%), with no notable differences by indication or across subgroups.

Similarly, the proportion with concomitant use of contraception, IUD, or sterilization during valproate treatment increased slightly (45.6% to 48.6%), while adequate contraceptive coverage (PDC ≥80%) remained stable (34.9% to 35.8%). Coverage was lower in the youngest and oldest age groups, with similar trends across subgroups.

No laboratory pregnancy tests were recorded prior to valproate initiation; thus, compliance with this PPP element was limited to women sterilized at index.

Overall, approximately 47% of prevalent users fulfilled one PPP element in both periods, and only 12% fulfilled two, this rate remaining stable over time. Trends were similar in recurrent users.

Among incident users, the proportion fulfilling one element decreased slightly (49.8% to 46.0%), while those fulfilling two or three elements increased (36.5% to 38.8% and 7.7% to 10.3%, respectively). Fulfilment of all four elements remained low (0.6% to 1.0%). No meaningful differences were observed by indication subgroups.

9.4.6 Incidence and Characteristics of Exposed Pregnancies

The proportion of valproate-exposed pregnancies remained stable among recurrent users (47.9% to 48.9%) but decreased among incident users (34.7% to 25.2%). Correspondingly, the incidence rate of exposed pregnancies decreased from 7 to 6 per 10,000 person-months in recurrent users and from 22 to 15 per 10,000 person-months in incident users.

The mean age at the start of exposed pregnancy among prevalent users slightly increased (30.8 to 31.5 years). Prior contraceptive use rose from 26.0% to 42.7% between periods among women with an exposed pregnancy. Valproate exposure most frequently occurred in the 30 days before pregnancy or during the first pregnancy trimester. Exposure to valproate in the 30 days before pregnancy increased from 54.5% to 64.1%. Across pregnancy trimesters, most pregnancies were exposed to daily doses between 700 and 1,500 mg. Among women with an exposed pregnancy, initiation of valproate during pregnancy remained stable (13.8% to 12.6%) and was more common among incident users (38.1% to 36.1%).

Discontinuation of valproate before pregnancy declined slightly (17.1% to 14.6%), while discontinuation during pregnancy increased markedly (43.1% to 61.2%). Median exposure days in the first trimester increased (38.0 to 50.5 days) but declined in the second (40.0 to 20.0 days) and third trimesters (22.0 to 19.5 days).

Among exposed pregnancies with available outcome data, the proportion of live births decreased slightly (61.0% to 57.8%). Assessment of birth defects was limited due to small numbers. Patterns were generally consistent across recurrent and incident users, though subgroup comparisons were constrained by sample size. No notable differences were observed between epilepsy and bipolar disorder subgroups.

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9.5 The UK

9.5.1 Study Population and Valproate-prescribing Practices

Between the pre- and post-implementation periods, the number of valproate users in the UK declined by approximately 42%, from 3,440 to 1,989. The proportion of recurrent users increased from 79.0% to 86.0%, while incident users decreased from 21.0% to 14.0%.

The mean age at index remained stable at approximately 37 years across all user groups, with slightly higher average ages among patients with bipolar disorder (39 years).

Epilepsy was the most common indication in both periods, accounting for 73.7% to 75.6% of recurrent users and increasing among incident users from 52.8% to 57.3%. In contrast, the proportion of recurrent users with bipolar disorder decreased slightly from 18.8% to 16.1%, while it rose among incident users from 29.6% to 33.7%.

Prescriber specialty data were not available.

Among incident users with epilepsy, prior antiepileptic drug use increased from 80.9% to 88.1%. Lamotrigine use rose from 21.7% to 34.4%, levetiracetam from 12.3% to 22.5%, while topiramate declined from 20.2% to 12.5%.

For incident users with bipolar disorder, over 97% had a history of prior use of BD treatment in both periods. The most common drugs were quetiapine (30.4% to 26.6%), sertraline (22.4% to 22.3%), and mirtazapine (21.0% to 19.1%). Lithium use remained low (<10%) in both periods.

9.5.2 Compliance With the PPP

Compliance with the PPP remained low across all user groups. Among recurrent users, the proportion with at least one annual visit to a specialist declined from 23.1% to 19.6%. For incident users, rates were stable overall (43.2% to 44.8%) but diverged by indication: a decrease was observed in those with epilepsy (from 52.8% to 42.6%), while there was an increase in those with bipolar disorder (from 38.3% to 48.6%). Data on initiation by a specialist were not available.

Sterilization prior to valproate initiation remained stable among prevalent users (11.1% and 10.7%) overall. However, patterns were different by indication subgroups. It increased among incident users in both indications (11.0% to 13.8% in epilepsy; 9.3% to 19.1% in bipolar disorder), while it remained stable in recurrent users with epilepsy (10.2% to 9.9%) and decreased in recurrent users with bipolar disorder (14.5% to 8.7%).

Concomitant use of contraception, IUD, or sterilization during valproate treatment was observed in 43.5% to 45.3% of prevalent users and 42.7% to 44.4% of recurrent users. Among incident users, this proportion increased from 46.5% to 50.9%.

Adequate contraceptive coverage (PDC ≥80%) was achieved by 33.5% and 34.4% of prevalent users, with slightly lower rates in younger age groups. Among incident users, coverage increased modestly in those with epilepsy (38.7% to 41.9%) and bipolar disorder (37.4% to 41.5%).

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Laboratory plasma pregnancy testing prior to valproate initiation was rare (<3%) in both periods. However, when considering sterilization data, compliance with this PPP element increased from 10.9% to 17.9%, with similar trends across indications and subgroups.

Overall, approximately 40% of prevalent users fulfilled one PPP element, while only 5% met two, with no change over time. Similar patterns were observed in recurrent users. Among incident users, the proportion fulfilling two elements increased from 13% to 18%, while those meeting all three remained marginal. Similar trends were observed by indication.

9.5.3 Incidence and Characteristics of Exposed Pregnancies

The proportion of exposed pregnancies among all pregnancies slightly decreased for recurrent users (from 78.4% to 76.1%) and remained stable for incident users. The incidence rates of valproate-exposed pregnancies decreased across all user subgroups: from 11 to 6 per 10,000 person-months among recurrent users, and from 23 to 6 per 10,000 person-months among incident users. However, the low number of exposed pregnancies in the post-implementation period (n=5) among incident users limits interpretation.

The mean age at the start of exposed pregnancy increased from 31.1 to 34.6 years among prevalent users. Prior contraceptive use among women with exposed pregnancy rose from 21.2% to 35.0%, while valproate exposure in the 30 days before pregnancy declined from 76.5% to 72.5%. Initiation of valproate during pregnancy remained rare. Discontinuation of valproate before start of pregnancy increased (12.9% to 20.0%), while discontinuation during pregnancy slightly decreased (18.8% to 15.0%).

Exposure duration was lower in the post-implementation period, across all trimesters. Median exposed days dropped from 50.0 to 29.0 in the first trimester, from 63.0 to 32.8 in the second, and from 27.5 to 0.0 in the third.

Among exposed pregnancies with available outcome data, the proportion resulting in live births increased from 61.1% to 73.1%. However, assessment of birth defect trends was limited due to small numbers and incomplete mother-child linkage. Patterns in recurrent users were similar to prevalent users. Low counts limited comparisons with incident users.

No meaningful differences were observed between epilepsy and bipolar disorder subgroups. However, most results were masked due to small sample sizes.

10. DISCUSSION

This DUS ext. study investigated the impact of the implementation of the 2018 RMMs and PPP on the use of valproate among WCBP by assessing real-world data from 2015 to 2021 from six European countries.

10.1 Trends in the Valproate Use

In this study, a slight declining trend in valproate use between the pre-implementation main and the post-implementation periods was found with consistency across countries, aligned with recent evidence suggesting a decline in the use of valproate among WCBP after implementation of the RMMs in 2018.

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The declining trends may be also explained by the impact of the implementation of the 2014 RMMs, which started to be effective during the pre-implementation main period of this study. Following the 2014 RMMs, prescribers may have changed their prescribing practice and may have become more selective when initiating valproate among WCBP. Furthermore, they may have successfully switched the medication of their patients treated with valproate, notably in women who wanted to get pregnant and for whom another effective treatment (i.e. alternative to valproate) was available. On the other hand, patients and caregivers could be unwilling to discontinue valproate or engage in the PPP, despite being aware of new prescribing restrictions.

10.2 Trends in Prescribing Practices

This study also highlights relative changes in prescribing practices of valproate between the pre- and post-implementation of the 2018 RMMs, with a relative increase in prescriptions for epilepsy, and a decline in its use for bipolar disorder across countries. It was also found that the proportion of patients with prior treatment for epilepsy or bipolar disorder before valproate initiation was elevated in both periods, with slight improvement across periods.

10.3 Trends in the Compliance with the PPP

The study found contrasted trends in compliance with the four PPP elements across countries, with a minor increase in France, Sweden, and the UK, no change in Germany and Spain, and a slight decrease in the Netherlands. These results reflect findings from recent web-based surveys among healthcare professionals and patients showing their lack of awareness and poor adherence to the 2018 RMMs.

Compliance with the PPP element "*Annual visit to a specialist*" among prevalent users differed across countries, with no change observed in France (55%) and, Spain (11%), a variation in Sweden (from 60% to 59%), and a slight decrease in Germany (from 83% to 80%), the Netherlands (from 24% to 16%), and the UK (from 25% to 21%). The observed absence of change or decreasing trend in the proportion of patients with an annual visit to a specialist may be due to limited access to speciality care during the COVID-19 pandemic, which overlapped with the post-implementation period and led to an overall decrease in access to and shortage of neurologists and psychiatrists. The considerable differences in the proportions of patients fulfilling this PPP element observed across countries mainly reflect limitations in capturing the information on prescriber's speciality and/or visits to specialists in the selected data sources and to a minor extent, the contrasts in healthcare systems. The consistently higher proportions of patients with an annual visit to a specialist among valproate users with bipolar disorder indication are in line with the EMA recommendation for this indication, which asserts that valproate should be initiated and maintained only by a specialist, and not by a GP.

Compliance with the PPP element "*Initiation by a specialist*" among incident users was contrasting across countries with an increase in France (from 38% to 44%), a slight increase in Germany (from 84% to 88%), no change in Spain (59–60%) and Sweden (92–93%), and a slight decrease in the Netherlands (from 38% to 33%). Differences in trends and magnitude across countries may be explained by data-source-specific limitations in the ability to capture the information, the initial level of adoption of the practice (e.g. it is more difficult to find room for improvement when the practice is already very well established like in Sweden), and contrasting clinical practices suggested by the heterogeneity of proportions of patients initiated by an indication-related speciality (i.e. neurologists for epilepsy and psychiatrists for bipolar

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disorder) and initiated by GPs between the countries. Furthermore, as psychiatric comorbidities are common among patients with epilepsy, valproate may have been initiated due to comorbid bipolar disorder and, in that case, the initiation by a psychiatrist would be relevant even though patients were classified in the epilepsy group by the indication algorithm.

Consistent trends in compliance with the PPP element "*concomitant use of contraceptive during valproate treatment*" were observed across countries among prevalent users, with few to no variation (<3%) between the pre-implementation main period and the post-implementation period. The proportions of prevalent users with overall concomitant use of contraceptives during valproate treatment in the two periods ranged from 44% to 54% in France, the Netherlands, Sweden, and the UK, and around 15% in Germany and Spain. Likewise, the proportion of patients with an adequate coverage of concomitant use of contraceptive during valproate treatment (PDC≥80%) ranged from 35% to 40% in France, the Netherlands, Sweden, and the UK, and from 6% to 10% in Germany and Spain. When considering only prevalent users with concomitant contraception during valproate treatment, compliance rates in the two periods were higher and ranged from 70% to 77% in all countries, except Spain, where they were around 50%. Although variations in trends and magnitudes across user subgroups and indications were observed in each country, overall use of contraceptives and the adequate coverage of concomitant use of contraceptives during valproate treatment among WCBP remained poor to moderate. However, these overall results should be interpreted cautiously since the comprehensive capture of the use of contraceptives across countries was impacted by database limitations (such as partial capture of the contraceptive use in the WCBP population, possible overestimation of the duration of contraceptive use). Although these limitations are likely non-differential with respect to study periods. The absence of a net increase in the concomitant use of contraceptives during the valproate treatment among WCBP found between the periods in the present may reflect, to some extent, the effectiveness of the previous RMMs and recommendations for valproate treatment, which included the use of effective contraceptives. Furthermore, the high rates of compliance among women with concomitant use of contraceptive during valproate treatment suggest that integrating contraception into disease management may be of greater concern for the PPP than achieving adequate coverage once contraception is started. According to the PPP, it is important to first assess the potential of each patient becoming pregnant. These findings suggest that there is room for improvement in the concomitant use of contraceptives during valproate treatment among WCBP. Finally, these findings complement those from similar studies assessing the impact of the 2018 RMMs for valproate among WCBP but used different study designs and/or settings.

A trend indicating minimal to slight increase in the compliance of "*laboratory plasma pregnancy tests before valproate* initiation" was observed among prevalent users across countries. The proportions of patients compliant with this PPP element were stable and low (<5%) in the Netherlands, Spain, and Sweden, slightly increased by 3% in France (from 13% to 16%) and Germany (from 8% to 11%), and increased by 7% in the UK (from 11% to 18%), which doesn't reach expectations. However, half of the patients in France and most of the patients in Germany and the UK were compliant with this PPP element because they were sterilised. Nonetheless, limitations in capturing laboratory plasma pregnancy tests in the selected data sources, also partly explain the observed low compliance rates.

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10.4 Trends in the Incidence and Characteristics of Exposed Pregnancies

A consistent declining trend in exposed pregnancies between the pre-implementation main and the post-implementation periods was observed across the countries, in all user subgroups (with few exceptions) and indications. However, the absolute number of exposed pregnancies remained non-negligible, notably in women with bipolar disorder despite strict contraindications, which is a finding of concern. These findings appear aligned with the recent literature, however, they should be interpreted cautiously considering the database limitations in terms of identifying all pregnancies and accurately determining the use of valproate during pregnancies. Likewise, caution is needed when interpreting the impact of the 2018 RMMs on the observed trends due to the absence of confounder adjustment (e.g. the decline of the fertility rate in the overall population in Europe).

Despite the wide consensus on the teratogenic harms of valproate, exposure to valproate during pregnancy may result from complex clinical decision-making and deliberate reproductive choices from patients. In epilepsy indication, valproate is an effective medication for generalised epilepsy and several specific epilepsy syndromes. For some patients, it is the only medication to allow seizure remission, and treatment withdrawal carries the risk of seizure recurrence. It has been shown that cessation of valproate before pregnancy reduced the risk of foetal malformations; however, seizure control worsened when valproate was withdrawn or reduced. In such cases, the risks of uncontrolled epilepsy need to be weighed against the teratogenic risk of valproate. Moreover, the potential teratogenicity of some alternatives to valproate, such as pregabalin, is yet unknown. In bipolar disorder indication, the efficacy of valproate in the treatment of acute mania, bipolar depression, and as a maintenance therapy is well established, particularly in the prevention of relapses and stabilising mood. However, given the availability of effective alternatives to valproate with low teratogenic risk, such as lamotrigine and atypical antipsychotics, it should not be expected for a woman with bipolar disorder to receive valproate during pregnancy.

In France, the large number of women who initiated valproate during pregnancy corresponded approximately to half of the cases of exposed pregnancies among incident users and high rates of valproate discontinuation during pregnancy in post-implementation periodsuggest the need to consider additional factors for interpretation. Nonetheless, this is also suggesting that valproate may have been prescribed and used while women were unaware of their pregnancy and stopped their treatment when the pregnancy was identified. This hypothesis is supported by the study findings with the scarce use of laboratory plasma pregnancy tests, the low proportion of women exposed to valproate who used contraception before their pregnancy, and the large proportion of women who discontinued valproate during their pregnancy. While caution is needed due to limitations in the assessment of pregnancy testing and contraceptive use as previously described, these results may suggest potentially unintended pregnancies.

All these findings reflect a concerning level of non-compliance to the PPP, which was specifically designed to avoid (i) unplanned pregnancies, and (ii) unnecessary exposure to valproate during pregnancy in epilepsy / any exposure during pregnancy in bipolar disorder.

11. CONCLUSION

This DUS ext. study investigated the impact of the implementation of the 2018 RMMs and PPP on the use of valproate among women with childbearing potential by assessing real-world data from 2015 to 2021,

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from six European data sources: France (SNDS), Germany (BKK), the Netherlands (PHARMO Data Network), Spain (SIDIAP), Sweden (National Registers), and the UK (CPRD GOLD).

The study found an overall decline in the use of valproate among WCBP between pre- and post-implementation of the 2018 RMMs across countries. The assessment of the four PPP elements was impaired to some extent due to limitations in all data sources, which may have partly hindered further assessment of the impact of the 2018 RMMs. Despite this, contrasting trends in compliance with the PPP across the selected countries were observed, with a minor increase in France, Sweden, and the UK, a stable trend in Germany and Spain, and a slight decrease in the Netherlands. Finally, a decline in the incidence rates of overall pregnancies and pregnancies exposed to valproate among WCBP was observed. However, concerns have emerged with pregnancies exposed to valproate among WCBP with bipolar disorder in all countries and the initiation of valproate during pregnancy observed among incident users in France.

In conclusion, although this study did not demonstrate a substantial impact of the implementation of the 2018 RMMs on the individual PPP elements, it supports the growing evidence of the decline of valproate use and the incidence of exposed pregnancy among WCBP in Europe over the past decade. It complements the findings from prior DUS and surveys conducted in the same countries and assesses the impact of these RMMs using different methodological approaches. However, the continuous need to monitor the appropriate prescribing patterns of valproate among WCBP in real-world clinical practice to improve compliance with the PPP persists. The planned qualitative study sponsored by the MAH Consortium of Valproate will help provide insights into the barriers to valproate PPP implementation among healthcare professionals and patients.

12. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma B.V., (Formerly Apotex Europe B.V.); Aristo Pharma GmbH; Arrow Generiques; Betapharm Arzneimittel GmbH; Consilient Health Limited; Crescent Pharma; Desitin Arzneimittel GmbH; Generis Farmacêutica S.A.; G.L. Pharma GmbH; Hexal AG; Lupin Healthcare (UK) Limited; Neuraxpharm Arzneimittel GmbH; Orion Corporation; Sanofi R&D; Stada Arzneimittel Ag; Tecnifar S.A.; Teva Pharmaceuticals Europe B.V.; Viatris Healthcare (Formerly Mylan EMEA SAS); Wockhardt UK Limited.

13. NAMES AND AFFILIATIONS OF PRINCIPAL INVESTIGATORS

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