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Prescribing trends for sodium valproate in Ireland

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ABSTRACT

Purpose: This study was undertaken to describe prescribing practice for the anti-convulsant drug (AED) Sodium Valproate (VPA) in an Irish population of woman of childbearing age during the period of the emergence of new data showing a high rate of developmental abnormalities in offspring of women who took VPA during pregnancy.

Methods: All prescriptions dispensed from community pharmacies in Ireland between 2008 and 2013 inclusive were examined for women aged 16-44 years from all three drug reimbursement schemes in Ireland. Numbers of prescriptions and women on AEDs were identified, as was the rural/urban distribution of the drug along with co-prescribing of folic acid and the oral contraceptive pill. All data analysis was conducted using SAS v9.3.

Results: The rate of prescribing of VPA in Ireland declined slightly from 3.5/1000 per eligible population in 2008 to 3.14/1000 in 2013. While rates of prescribing fell for epilepsy, there appeared to be a rise in prescription for other indications of VPA. In 2013, co-prescription of folic acid or oral contraceptives was relatively low across all community schemes. Finally, an address distant from academic specialist centers predicted a higher exposure to VPA.

Conclusion: Recently the European Medicine's Agency suggested that alternatives to VPA be considered before prescribing to women of childbearing age. Despite this, the rate of VPA prescribing in Ireland appears to be increasing for indications other than epilepsy. It may be necessary to improve the dissemination of information about the potential negative effects of VPA in this population.

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1. Introduction

Up to one third of people receiving antiepileptic drugs (AEDs) are women of reproductive age [1] and approximately 1 in 250 pregnancies are exposed to AEDs [2]. It is generally accepted that exposure to AED medications during pregnancy increases the risk of major congenital malformations (MCMs) from between 1–2% to between 4–9% [3–9].

VPA was first licensed in 1978 for the management of a particular form of non-convulsive epilepsy called 'absence' epilepsy but anecdotally, it was found to be a useful treatment in a broad spectrum of seizure types and has thus been a commonly prescribed drug treatment for various forms of epilepsy for many years. The particularly high risk of MCMs with foetal exposure to VPA has been known for decades with first reports of Spina Bifida emerging in 1981 [10]. The current risk of all forms of MCMs with VPA is approximately 10% [11]. However, studies since 2009 in preschool children exposed in utero to VPA show that up to 30–40% experience delays in learning, speech, memory, motor and behavioral development [9,12–17]. In 2010, the Liverpool and Manchester Neurodevelopment Group (LMNDG) suggested that VPA demonstrates a dose–dependent relationship with developmental outcome and more recent evidence suggests that the risks are higher when VPA is taken with other AEDs as combination therapy [13,17,18]. Furthermore, the spectrum of developmental problems that children exposed to VPA in utero includes an increased risk of both autistic spectrum disorder and attention deficit/hyperactivity disorder (ADHD) compared with the general population [12,13,19].

Finally, a recent Cochrane review analysed 22 prospective cohort studies and 6 registry studies and supported notion that

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children exposed to valproate in utero were at an increased risk of poorer neurodevelopmental scores compared to the general population [20]. However, it cautioned that VPA is still a very effective drug for some and that strict counselling should be in place to allow women with epilepsy (WWE) to make informed decisions.

In light of this new information about VPA, we aimed to determine how this affected prescribing practice in the Republic of Ireland in terms of the number of women of childbearing age (16-44) taking VPA between 2008–2013, the time period during which the increased risks associated with the drug became clear and to further examine co-prescribing of folic acid 5 mg and contraceptives in order to see if prescribers, who had no option but to use VPA, were taking precautions against the known risks.

2. Monitoring prescribing practice for AEDs in Ireland

Residents in the Republic of Ireland can obtain prescribed medications through three different community drug schemes allowing for reasonably accurate monitoring of prescribing of VPA nationally in Ireland. General Medical Services or Medical Card Scheme (GMS) provides for free medicines on a means tested basis taking into account individual or family finances and age. The second scheme is on private prescription through the Drug Payment Scheme (DPS), whereby, medicines above a certain monthly payment threshold will be reimbursed by the state for out of pocket expenses above this threshold. The final scheme is the Long Term Illness (LTI) scheme which entitles a patient with one of 15 eligible illnesses, including epilepsy, to free medicines.

Because epilepsy is the only condition on the LTI scheme for which VPA is conventionally prescribed in over 16 year olds, and because the LTI scheme is not means tested, it is correct to assume that the LTI scheme provides a precise accounting of the national prescribing of VPA for epilepsy alone. The other schemes are more likely to reflect the mixed prescribing practice for VPA across the disease spectrums of epilepsy, bipolar disease and migraine. Unfortunately, it is not possible to deduce what level of specialisation the prescribers have in each scheme although the LTI prescribers, by virtue of the requirement for a confirmed diagnosis of epilepsy, are more likely to be neurologists.

3. Methods

Pharmacy claims data from the GMS, DPS and the LTI schemes were used. The details made available via the Health Service Executive (HSE)-primary care reimbursement services. The dispensing data contains demographic details on the patients (age, gender and location of residence), information on the medicine dispensed such as the drug name, strength and quantity of tablets/capsules dispensed. No clinical or outcome data is available. All prescription items are coded using the WHO Anatomical Therapeutic Chemical (ATC) classification.

All prescriptions dispensed from community pharmacies from 2008 to 2013 inclusive were examined for women aged 16–44 years from all schemes. Numbers of prescriptions, and patients on drugs associated with epilepsy were identified using the ATC code N03. In particular, VPA was identified by code N03AG01. Percentage use and associated 95% confidence intervals are presented. Numbers of patients who received at least one prescription for VPA in 2013 were examined by urban and rural geographical residence for GMS and LTI schemes separately. Rates of prescribing per 1000 population of VPA by urban or rural geographical area of residence were calculated using the same total eligible female population aged 16–44 years from the 2011 Irish census for both the GMS and LTI eligible, to ensure comparability and for total rates to be calculated. These rates are presented with 95% confidence intervals using the Poisson method. In addition, we examined the co-prescription of folic acid 5 mg (ATC code B03BB) and oral contraceptives (ATC codes G03A)/IUD (G02AB03) in women receiving VPA in 2013. In Ireland, the 5 mg preparation of folic acid must be obtained on prescription so we do not have data on women who may be taking the 0.4 mg dose that is available over the counter.

All data analysis was conducted using SAS v9.3 and significance at $p < 0.05$ is assumed.

4. Results

The number of women who received VPA between the ages of 16–44 years in Ireland from 2008–2013 are shown in Fig. 1. In 2008 3.5 per 1000 women between 16 and 44 were prescribed VPA (95% CI 3.38, 3.61) and VPA accounted for 28% (95% CI 27.65%, 28.35%) of all AEDs prescribed in 2008. By 2013 the rate the rate of prescribing had dropped to 3.14 per 1000 (95% CI 3.04, 3.36) while VPA accounted for 20% (95% CI 19.75%, 20.25%) of all AEDs prescribed in 2013.

The largest decline in VPA prescribing was in the Drug Payment Scheme (DPS) and which fell from a contribution of 9.3% (95%CI 5.0%, 13.5%) to 3.2% (95%CI 0, 7.5%) of all patients on VPA. There was a decline in the proportion of patients on VPA originating from the LTI scheme from 23.2% (95%CI 19.3%, 27.1%) to 20.8% (95%CI 16.9%, 24.7%) whereas there was a rise from 67.5% (95%CI 65.0%, 70.0%) to 76.0% (95%CI 73.9%, 78.2%) in the proportion of patients from the GMS. Fig. 1 presents the monthly trend in numbers on VPA over time comparing the LTI scheme (blue line), which is a precise trend of VPA prescribing in epilepsy only, versus the combined trend for the two other schemes (GMS and DPS–red line) which reflects prescribing across the range of indications for VPA (Epilepsy, Migraine, Bipolar Disease).

The percentage of women co-prescribed folic acid (5 mg) and oral/IUD contraceptives with VPA in 2013 is captured in Fig. 2. The percentage of VPA in the LTI scheme co-prescribed folic acid is considerably higher than in the GMS medical card scheme (30% vs. 10%) which may reflect the varying conditions that the drug is being used for within the GMS scheme. The level of co-prescribed oral and IUD contraceptives is also low for those receiving VPA within the GMS scheme. The co-prescribing of contraceptives with VPA was not captured in the DPS and LTI scheme. Only those eligible for the GMS scheme have all their claims captured by the pharmacy as all medicines are reimbursable. Under the LTI and DPS

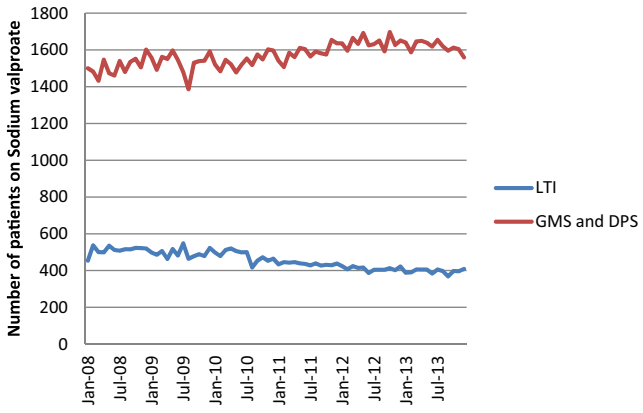

Fig. 1. Numbers of women aged 16–44 years on sodium valproate by community drug scheme from 2008–2013. The LTI scheme (blue) represents a very precise trend for national prescribing of VPA for epilepsy alone. The combined GMS and DPS trend (red) represents prescribing across a range of indications.

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