ABSTRACTS

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Platform Session 1: Antiepileptic Drugs 1
Monday 12th September

0001
PRESCRIBING TRENDS FOR SODIUM VALPROATE IN IRELAND

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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.

Method: 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 patients on AEDs were identified, as were co-prescription with folic acid and the oral contraceptive pill. All data analysis was conducted using SAS v9.3.

Results: In 2008 3.5 per 1,000 women between 16 and 44 were prescribed VPA and VPA accounted for 28% of all AEDs prescribed in 2008. By 2013 the rate the rate of prescribing had dropped to 3.14 per 1,000 while VPA accounted for 20% of all AEDs prescribed.

The largest decline in VPA prescribing was in the Drug Payment Scheme (DPS) and which fell from 14.5% to 4.7%. 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.

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.

0074
MARKED REDUCTION IN SECONDARILY GENERALIZED SEIZURES IN PATIENTS TREATED WITH PERAMPANEL FOR 3 AND 4 YEARS

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Purpose: Perampanel is approved for adjunctive treatment of partial seizures with/without secondarily generalized seizures (SGS) and primary generalized tonic-clonic seizures in patients with epilepsy aged ≥12 years. Here we evaluate seizure outcomes in patients with partial seizures receiving perampanel for 3 and 4 years.

Method: 1,480 subjects enrolled in the prospective, placebo-controlled, double-blind (DB) Phase III studies (Studies 304/305/306) were randomized to placebo or perampanel for 19 weeks (6-week titration+13-week maintenance). On completion, subjects were eligible for open-label extension (OLE, Study 307) study enrollment (16-week blinded conversion+OLE maintenance period). Seizure outcomes included median percent reduction in seizure frequency/28d relative to pre-perampanel baseline and responder rate. Safety outcomes were also evaluated.

Results: Of 1,480 subjects randomized in the DB studies, 1,218 enrolled in the OLE. The last daily dose for most subjects with at least 3 years (N = 436) and at least 4 years (N = 78) of perampanel treatment was 12 mg. Median percent seizure reductions during the last year of perampanel treatment for subjects with at least 3 and 4 years of exposure were 61.98% and 70.63%, respectively. Corresponding responder rates were 59.6% and 67.9%, respectively. The largest median percent decrease during the last year of perampanel treatment occurred in SGS: 87.96% and 100% in subjects with 3 and 4 years, respectively. During the OLE, there were 11 deaths: 10 occurred during perampanel treatment or within 30d after the last perampanel dose; 2 were classified as sudden unexplained death in epilepsy; none resulted from suicidality. Ten of the 11 deaths were investigator assessed as unrelated to perampanel; a death due to convulsions was considered possibly related. No new safety signals were seen during long-term perampanel exposure.

Conclusion: This analysis demonstrated that long-term adjunctive treatment with perampanel for up to 4 years was well tolerated and associated

POSTER TOURS

Basic Science 1
Monday 12th September

P108
THE MYELIN MUTANT *TAIEP* RAT AS A MODEL OF ABSENCE EPILEPSY

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Purpose: The aim to this study was to characterize the spike-wave discharge (SWD) in the myelin mutant *taiep* rat as a model of absence epilepsy.

Method: All subjects (Ss) were maintained under standard animal room conditions. We implanted stainless steel three cortical electrodes, a bipolar hippocampus platinum/iridium electrode, and two additional electrodes in the nuchal musculature and in the left orbit to record EMG and EOG. The Ss were adapated by 5 days to recording conditions and the following day all signals were recorded using the Harmonie system with a sampling rate of 200 Hz and in 5 sec epochs using Sensa module. In offline analysis, we measured the number, duration and main frequencies using fast Fourier transform analysis.

Results: Our results showed that SWD are sexually dimorphic being the males significantly more affected than female *taiep* rats particularly at younger ages (3–6 months, $p < 0.05$); in both sexes the frequency increased in older animals (9–12 months), but the sexual dimorphism persist ($p < 0.05$). In both sexes there were a circadian rhythm in the frequency of SWD being significantly higher in the light phase ($p < 0.05$). All SWD showed a mean frequency around 6 Hz in the hippocampus and in both sexes associated with freezing posture during the crisis, as soon as the SWD ends the subject restore the ongoing activity and the theta rhythm disappear.

Conclusion: The myelin mutant *taiep* rat is an additional model of absence epilepsy to GAERS and WAG/Rij rats and allow us to analyze the neurophysiological mechanisms of cortical hyperexcitability and thalamo-cortical oscillations. Partly founded by CONACYT grants 243247 and 243333 to MCC and JRE, respectively; and also by VIEP-BUAP 2016, PROFOCIE 2016 and CA Neuroendocrinología BUAP-CA-288 through PRODEP-SEP.

P109
EFFECT OF EXTERNAL PERTURBATIONS ON SEIZURE DYNAMICS – IN VITRO RESULTS AND COMPUTATIONAL MODELLING

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Purpose: Understanding of the mechanisms of transition to seizures represents key prerequisite for their successful control. Previously we have demonstrated in vitro that seizures are preceded by detectable changes in neuronal and network dynamics. In the current study we have examined how the excitatory input can modify the transition to seizures.

Method: The experiments were performed in vitro in rat hippocampal slices perfused with artificial CSF containing high potassium (>8 mM). Field potentials from the hippocampal CA1 and CA3 regions were recorded using multiple extracellular electrodes. To study the effect of CA3 activity on CA1, further measurements were taken from isolated CA1 slices.

Results: Spontaneous seizure-like events were generated within the CA1 region with a mean inter-seizure interval of 60.4 ± 4.4 s. Seizures did not occur abruptly, but were preceded by a progressive buildup of high-frequency activity at 200 Hz. The CA3 region generated interictal discharges propagating to CA1 and interfering with the high-frequency activity. Recorded data motivated a minimal mathematical model, with state space defined by mean firing rate and excitability. For intermediate excitability, model contains a bistability of low-firing rate and high-firing rate state. Slow excitability dynamics lead to emergence of cyclic regime shifts between the two states. However, random noise or external perturbation also affect state switching. Simulations demonstrate that during stable part of the interictal period excitatory input reversed transition to seizure, while in low stability states it could induce seizure.

Conclusion: This study demonstrates the dual nature of the effect of excitatory synaptic on input seizure initiation. The impact of the excitatory perturbation depended on the spontaneously slowly changing state of the system. These observation represent plausible explanation for dual, both proconvulsive and anticonvulsive, effect of interictal epileptiform activity.

P110
A NEW RAT MODEL OF INFANTILE SPASMS BASED ON METHYLAZOXYLMETHANOL (MAM)-INDUCED CORTICAL DYSPLASIA

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Purpose: Cortical dysplasia (CD) is a well-established etiology of medically intractable epilepsies and cognitive disabilities in children. We develop a new rat model of infantile spasms using postnatal N-methyl-D-aspartate (NMDA) provocation in rats with prenatal methylazoxymethanol acetate (MAM)-exposed CD and determine the structural and electrophysiological features of this model.

Method: To produce cortical malformations to infant rats, two dosages of MAM (15 mg/kg, IP) were injected to pregnant rats at gestational day 15. The structural changes of the prenatally MAM-exposed rat brain were validated using magnetic resonance imaging. In prenatally MAM-exposed rats and the controls, spasms were triggered by single (15 mg/kg on postnatal day 15 [P15]) or multiple doses (6 mg/kg on P12, 10 mg/kg on P13, and 15 mg/kg on P15) of NMDA and the data of spasms expression were monitored. In prenatally MAM-exposed rats with single NMDA-induced spasms, we obtain the intracranial electroencephalography (EEG) and examine the pre-treatment response to adrenocorticotropic hormone (ACTH) or vigabatrin.

Results: Compared to saline-exposed controls, the prenatally MAM-exposed rats showed thinning of entire cortex and reduced size of both hippocampi. The prenatally MAM-exposed rats showed significantly increased EEG powers (μV^2) of gamma frequency (25–80 Hz) and 80–

P193
PLASMA AND BREAST MILK LEVELS OF LACOSAMIDE BEFORE, DURING AND POST PREGNANCY

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Purpose: Lacosamide (LCM) is an antiepileptic drug approved as adjunctive therapy for partial-onset seizures. In women with epilepsy monotherapy is recommended as safer option in comparison to polytherapy and switch to LCM monotherapy has been already published. The data about LCM plasma levels before and during pregnancy, the rate of umbilical cord/maternal plasma levels and the concentration in the breast milk are of outstanding clinical interest.

Method: We have investigated LCM plasma levels in 27 years old patient with focal epilepsy taking the dose of 200 mg/day before pregnancy and at every trimester. Moreover, we assessed LCM levels in the umbilical cord and at the breast milk before taking the LCM, 2 and 6 h after taking the regular dose. We used a simple HPLC method with UV detection, which was developed and validated for the quantification of lacosamide in human plasma.

Results: Plasma level before pregnancy on 200 mg/day was 19.7 µmol/l (reference range 8–40). During pregnancy the level was 10.11 µmol/l (51.3% of pre-pregnancy value) in the first trimestr, 12.35 µmol/l (62.7%) in the second trimester, 11.45 µmol/l (58.1%) in the third trimester, 9.58 µmol/l (48.6%) 6 weeks before delivery and 15.36 µmol/l (78.0%) at the delivery. As she was seizure free the dose of LCM was not increased. The umbilical cord: maternal ratio was close to 1:1. The concentration in the breast milk 20 days after delivery was 14.27, 21.8, 16.92 µmol/l measured before taking the regular dose of LCM and 2 and 6 h after the administration respectively.

Conclusion: In our patient, LCM plasma levels decreased approximately by 50% during pregnancy without breakthrough seizures. The ratio of umbilical and maternal concentrations suggests full transplacental transfer of LCM. The concentration in the breast milk suggests full transfer of LCM from maternal blood to the breast milk.

Clinical Epilepsy 4
Tuesday 13th September

P194
THE RATE OF CONGENITAL MALFORMATIONS IN EPILEPTIC PREGNANT PATIENTS: A PROSPECTIVE STUDY

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Purpose: The women wiht epileplepsy could have 2–3 times more problem than normal pregnant women. The rate of normal childbear in general popülation is 98% whereas 92–96% in epileptic patients. The aim of this study was to analyse the effects of epilepsy and antiepileptic drug (AED) treatment on pregnancy and the perinatal outcome, prospectively.

Methods: We examined the obstetric and fetal outcomes among women with epilepsy (WWE), who were followed-up at the Department of Neurology and who delivered at the Department of Obstetrics and Gynaecology (n = 43) between 01th January 2013 and 31th December 2015. The mean age of the patients were 28.9 ± 12 (17–40) years.

Results: Eighteen patients (41.8%) have had partial epileps, 25 (58.2%) of them have had primary generalized epilepsy. Of these patients 74% of them were on monotheraphy, 20% of them on polytheraphy medication. There is an increase in seizure frequency in 16% of the patients. The rate of congenital malformations (MCMS) among the newborns of all AEDs exposed mothers was 11.6%. Only one newborn from monotheraphy group, and 2 newborn from politheraphy group have malformation.

Conclusion: In this prospective study, we found that, the pregnancy is not a risk for increase of seizure frequency. The risk for congenital malformations was higher with high dose valproic acid and with politheraphy-exposed pregnancies.

P195
PREGNANCY-RELATED KNOWLEDGE OF WOMEN WITH EPILEPSY – AN INTERNET BASED SURVEY IN GERMAN SPEAKING COUNTRIES

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Purpose: We tried to determine the level of pregnancy-related knowledge of women with epilepsy and their informational needs concerning pregnancy and childbirth issues in German speaking countries.

Methods: A questionnaire was placed on the internet platform of a patient's organisation from 4th August 2015 to 31st to December 2015. The questionnaire consisted of 18 questions addressing the characteristics of the syndromes of epilepsy, the patients experience with pregnancy and the sources of their pregnancy-related knowledge. Another 20 items addressed the level of pregnancy-related knowledge. Each of these items consisted of a 5-point Likert scale. We considered Likert scale answers of 1 and 2 as equivalent to disagreement and of 4 and 5 as agreement with the statement in question.

Results: 192 women (179 patients, 13 relatives) aged 30.5 years on average (SD 10.8) participated. 69 (=35.9%) had a child and another 9 (=4.69%) had been pregnant without live birth. 80.7% agreed that women with epilepsy should visit their neurologist when planning to get pregnant. Apart from this the knowledge concerning pregnancy related issues was fairly low. For instance: Only 17.2% knew that seizure freedom in the last 9 month before pregnancy implies a very low risk to suffer a seizure during pregnancy. Only 22.9% disagreed that women taking antiepileptic drugs generally have an increased risk of complications in pregnancy like premature birth, emergency caesarean birth, dead birth. Only 31.3% disagreed that fetal exposure to valproic acid does no harm to cognitive development of the child.

Conclusion: There are huge information needs concerning pregnancy related issues of women with epilepsy in German speaking countries.

P196
DEVELOPMENT AND VALIDATION OF MODIFIED INCLEN DIAGNOSTIC INSTRUMENT FOR EPILEPSY IN CHILDREN AGED UP TO 18 YEARS

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Purpose: There is shortage of specialists for the diagnosis of children with epilepsy, especially in resource limited settings. Existing INCLEN (International Clinical Epidemiology Network) instruments were validated for children aged 2–9 years. The current study validated modifications of the same including wider symptomatology and age group.