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

pointing to an increased clearance. ESL demonstrated no significant enzyme-inducing effect on LTG metabolism while there was a 20% and 34% decrease in the C/D-ratio of LTG in combination with OXC and CBZ, respectively.

Conclusion: Possible pharmacokinetic interactions have been studied for ESL as compared to OXC and CBZ. The pharmacokinetics of ESL is not affected by enzyme-inducing AEDs or VPA and does not affect the metabolism of LTG, in contrast to OXC and CBZ. The study demonstrates the value of using TDM-databases to explore the potential for pharmacokinetic interactions of new AEDs.

P564
TWO-DIMENSIONAL METAL NANOPARTICLE ARRAYS TOWARDS QUANTIFYING CARBAMAZEPINE IN HUMAN PLASMA

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Purpose: To make available to the epileptologist a technique to determine in a short time (few minutes) the concentration of carbamazepine in human plasma. This allows to improve checking the compliance of the patients to the treatment.

Method: We deposited thin gold films whose surface nanostructure is optimized via a strict control of the parameters of a laser-generated plasma that expands through an ambient gas and lands on a suitable (glass, (100) Si) support. The gold films constitute substrates to reveal the presence of analytes (e.g., carbamazepine) in a droplet (typical volume 50 μl) of human plasma absorbed at the substrate surface and then dried. Enhanced intensity of a probe laser radiation (785 nm) scattered by the substrate provides a fingerprint of carbamazepine (Surface Enhanced Raman Spectroscopy - SERS). The intensity of selected peaks in the collected SERS spectrum of carbamazepine is related to the drug concentration in the plasma.

Results: Carbamazepine presence was assessed down to 4×10^{-4} M on standard solutions in methanol. We prepared solutions of carbamazepine in human plasma from a healthy volunteer at the concentrations of 500, 300, 100 mg/l. Notwithstanding background contributions arising from molecular species usually present in plasma, we recorded carbamazepine SERS features around 718, 1,220, 1,305, 1,565, 1,600, 1,620 cm^{-1}. Presently carbamazepine features around 1,565 and in the 1,600–1,620 cm^{-1} region are distinguishable in spectra from solutions in serum from a patient treated at the concentration of 11.9 mg/l.

Conclusion: The proposed technique is minimally invasive, fast (minutes), cheap (about 1 Euro per exam). It is suitable to be adopted at the point of care. A robust, portable Raman apparatus is available (through an industrial collaboration) and can be adopted in Developing Countries.

P565
KETOGENIC DIET IN REFRACTORY CHILDHOOD EPILEPSY: INTRODUCTION OF AN ALL LIQUID FORMULATION IN AN OUTPATIENT SETTING

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Purpose: Ketogenic diet (KD) and its variants have been proven to be effective in childhood epilepsy. Because the diet has a considerable impact on daily life, early and rapid assessment of efficacy is highly desirable. The aim of our study was to evaluate whether this was possible by introducing an all liquid KD in an outpatient setting.

Method: In a prospective, observational, open label pilot study children with refractory epilepsy started with classic KD as a ready to use liquid formulation (KetoCal 4:1 LQD) taken orally or by tube. Efficacy was determined at 6 weeks and, in case of KD-continuation, adaptations to the diet were made from an all liquid diet to meals. To increase carbohydrate and protein content, MCT was added. Primary outcome parameter was time to response (>50% seizure reduction). Secondary outcome parameters were time to achieve stable ketosis, efficacy, and retention rate at 26 weeks.

Results: Sixteen children (2–14 years) participated. The median time to response of the 4 responders (25%) was 14 days (range 7–28 days). Mean time to achieve stable ketosis was 6.9 days. Efficacy did not importantly change after 6 weeks. Retention rate at 26 weeks was 43%. 3/16 children had hypoglycaemia and/or high ketosis during the first week that could be easily controlled. Two children switched from oral to tube feeding during the first 6 weeks on all liquid diet.

Conclusion: Introduction of KD in an all liquid formulation is feasible and contributes to fast and stable ketosis. Acceptance of KetoCal 4:1 LQD was positive. Although the response rate in our study was low, median time to response was 2 weeks. The retention rate of 43% shows that, apart from seizure reduction, also other aspects are important like seizure type, increase of alertness, and physical well-being.

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Pharmacology/AEDs 2
Monday 12th September

P566
ANTICTOGENIC AND ANTIEPILEPTOGENIC PROPERTIES OF PERAMPANEL IN MATURE AND IMMATURE RATS

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Purpose: Perampanel (PER) is a non-competitive AMPA antagonist approved as antiepileptic drug for both focal seizure and primary generalized seizure. We explored anti-ictogenic and anti-epileptogenic effects of PER in rats at different stages of development.

Method: Using a rapid kindling model in P14, P21, P28 and P60 rats, we studied two doses of PER: 1 and 2 mg/kg injected intra-peritoneally 30 min before afterdischarge assessment.

Results: PER 2 mg/kg significantly increased the afterdischarge threshold (ADT) at P28, P21 and P14 while PER at 1 mg/kg increased ADT in P21 rats only. PER 2mg/kg also shortens the afterdischarge duration (ADD) at P28 and P14. At P28, P21 and P14, PER increased the number of stimulations required to develop a stage 4–5 seizure in a dose-dependent manner with almost complete elimination of stage 4–5 seizures in all immature animals (P28, P21 and P14). In contrast, at P60 PER had no effect on the number of stage 4–5 seizures.

Conclusion: PER anti-ictogenic and anti-epileptogenic effects differing according to brain maturation. The antiepileptogenic effect of PER was stronger in younger animals.