NINTH EILAT CONFERENCE ON NEW ANTIEPILEPTIC DRUGS (EILAT IX)

Sitges, Spain, June 15 – 19, 2008

PROGRAM

Under the auspices of

The Hebrew University of Jerusalem, Israel

Epilepsy Therapy Project, USA

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ORGANIZING COMMITTEE

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ACKNOWLEDGEMENTS

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GENERAL INFORMATION

VENUE
Melia Sitges
Joan Salvat Papasseit, 38, Sitges - Barcelona, Spain 08870
Tel: +34 93 8110811, Fax: +34 93 8949034

LANGUAGE
The Conference will be conducted in English.

REGISTRATION / HOSPITALITY / INFORMATION
Desks will operate at the Melia Sitges Hotel as follows:

Sunday, June 15	from 15:00 -20:00 hours
Monday, June 16	from 07:00 -14:00 hours
Tuesday, June 17	from 07:30 and during session times
Wednesday, June 18	from 07:30 and during session times
Thursday, June 19	from 08:00 and during session times
Friday, June 20	from 08:30 and during session times

NAME BADGE
Your name badge is included in the material which you received upon registration. Please wear your badge to all conference sessions and events.

PROJECTION
Computer projection is available. Please see the technician before the beginning of your session.

POSTERS
Posters will be on display in the Poster area at the back of the Tramuntana Hall, for the duration of the Conference. Presenters are requested to refer to page xx of the program to find the board number assigned to them. Please use the poster board with the same number.

Posters should be mounted on Monday, June 16, between 07:30 and 08:00 hours and must be removed by Thursday, June 19 at 10:30 hours. Please note, that the organizers cannot be held responsible for posters that are not removed on time.

TRAVEL AND ACCOMMODATION
Target Conferences, the official Conference travel agent, will be happy to assist participants requiring additional hotel accommodation, tours, car rentals, transfers, etc. Please apply to the Hospitality Desk. Payment for any of these services can be made in travelers checks, Eurocheques (in the currency of the issuing country), foreign currency or major credit cards.

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SOCIAL PROGRAM

SUNDAY, JUNE 15, 2008
20:00 GET-TOGETHER BUFFET
In the Melia Sitges Garden

MONDAY, JUNE 16, 2008
16:30 AFTERNOON TOUR OF BARCELONA
Please meet in the lobby of the Melia Sitges at 16:15 hours.
Buses will depart promptly at 16:30

WEDNESDAY, JUNE 18, 2008
20:00 GALA DINNER
Tramuntana Hall 3, Melia Sitges

ACCOMPANYING PERSONS' PROGRAM

Registered accompanying persons are invited to join the Get-Together Reception, half day tour of Barcelona and the Gala Dinner. In addition, shuttles to/from Barcelona will be arranged during sessions.

SCIENTIFIC PROGRAM

SUNDAY, JUNE 15, 2008

16:00 *Coffee*

16:30 - 18:30 **CARISBAMATE SATELLITE SYMPOSIUM** **Tramuntana Hall**
Johnson & Johnson Satellite Symposium

CARISBAMATE: THE NEUROPHARMACOLOGY OF A NOVEL NEUROMODULATOR
H.S. White, University of Utah, USA

CARISBAMATE: PHARMACOKINETIC / PHARMACODYNAMIC EFFECTS
R.H. Levy, University of Washington, USA

CARISBAMATE: CLINICAL DATA
G. L. Holmes, Dartmouth Medical School, USA

MEASURING SUCCESS IN EPILEPSY TREATMENT
S. Shorvon, University College London, UK

PANEL DISCUSSION
G.P. Novak, Johnson & Johnson Pharmaceutical Research & Development, USA

MONDAY, JUNE 16, 2008

08:00 – 08:30 **Opening Session** **Tramuntana Hall**

OPENING REMARKS AND GREETINGS
M. Bialer, Organizing Committee, Israel

GREETINGS
R.H. Levy, Organizing Committee, USA
P. Wolf, President, ILAE, Denmark
W. Lammert, Epilepsy Therapy Project, USA

08:30 – 13:00 **Session I** **Tramuntana Hall**

OLD AND NEW AEDs IN GENERALIZED EPILEPSIES

Chairpersons: **E. Abadie,** France
R. Katz, USA

08:30 GENERALIZED EPILEPSIES: CLASSIFICATION, EPIDEMIOLOGY AND UNMET NEEDS
R. Guerrini, University of Pisa**,** Italy

08:50 Discussion

09:00 PREDICTING EFFICACY OF AEDs IN GENERALIZED EPILEPSIES
H.S. White, University of Utah, USA

09:20 Discussion

MONDAY, JUNE 16, 2008 (cont.)

OLD AND NEW AEDs IN GENERALIZED EPILEPSIES (cont.)

CLINICAL TRIALS OF NEW AEDs IN GENERALIZED EPILEPSIES: TOO LITTLE, TOO LATE? DIFFERENCES IN PERSPECTIVES

09:30 Syndromes with Onset in Early Childhood
O. Dulac, Necker-Enfants Malades Hospital**,** Paris, France

09:50 Discussion

10:00 Syndromes with Onset in Adolescence and Adults
K. Eriksson, Pediatric Research Centre, Tampere, Finland

10:20 Discussion

10:30 *Coffee*

11:00 The Regulator
R. Katz, FDA, USA

11:20 Discussion

11:30 The Pharmaceutical Industry
P. Verdru, UCB S.A., Belgium

11:50 Discussion

12:00 ORPHAN DRUGS FOR RARE SYNDROMES
C. Chiron, Necker-Enfants Malades Hospital**,** Paris, France

12:20 Discussion

12:30 OLD AND NEW AEDs IN THE TREATMENT OF IDIOPATHIC GENERALIZED EPILEPSIES: REVIEW OF THE EVIDENCE AND PLACE IN THE TREATMENT ALGORITHM
P.H. Ryvlin, Hôpital Neurologique, Lyon, France

12:50 Discussion

13:00 *Enriched Coffee Break*

13:30 – 15:15 **Session II** **Tramuntana Hall**

NOVEL FORMULATIONS AND ROUTES OF ADMINISTRATION OF AEDs: INNOVATION

Chairpersons: **S. Johannessen,** Norway
P. Wolf, Denmark

13:30 MODIFIED RELEASE FORMULATIONS OF AEDs: REAL PROGRESS OR MARKETING GIMMICK?
E. Trinka, University Hospital Innsbruck**,** Austria

13:50 Discussion

14:00 **Debate**
SHOULD WE AVOID THE USE OF GENERIC PRODUCTS OF AEDs?
Pro: **C.W. Bazil**, The Neurological Institute, New York, USA
Con: **E. Perucca**, University of Pavia, Italy

14:30 Discussion

14:45 WHAT IS THE BEST FOR EMERGENCY TREATMENT WHEN THE I.V. ROUTE IS NOT AVAILABLE?
J. Cloyd, University of Minnesota, USA

15:05 Discussion

TUESDAY, JUNE 17, 2008

08:00 – 10:15 **Session III – A** **Tramuntana Hall**

DRUGS IN DEVELOPMENT

Chairpersons: **M. Bialer**, Israel
R.H. Levy, USA

08:00 BRIVARACETAM (ucb 34714)
P. von Rosenstiel, *UCB S.A.,* Belgium

08:20 Discussion

08:30 CARISBAMATE (RWJ-333369)
G.P. Novak, *Johnson &Johnson Pharmaceutical Research & Development,* USA

08:50 Discussion

09:00 CSC700-800
F. Gleeson, *Cascade Therapeutics*, Canada

09:10 Discussion

09:15 2-DEOXY-GLUCOSE
Presented by **T.P. Sutula**, University of Wisconsin, USA

09:35 Discussion

09:45 ESLICARBAZEPINE ACETATE (BIA 2-093)
BIAL - Portela & Cª., S.A., Portugal
Presented by **E. Ben Menachem**, University of Gothenburg, Sweden

10:05 Discussion

10:15 *Coffee*

TUESDAY, JUNE 17, 2008

10:45 – 12:45 **Session III – B** **Tramuntana Hall**

DRUGS IN DEVELOPMENT

Chairpersons: **E. Perucca,** Italy
H.S. White, USA

10:45 GANAXOLONE
E. Garofalo, *Marinus Pharmaceuticals,* USA

11:05 Discussion

11:15 HUPERZINE
Presented by **S. Schachter**, Harvard Medical School, USA

11:35 Discussion

11:45 JZP-4
TBA, *Jazz Pharmaceuticals,* USA

12:05 Discussion

12:15 LACOSAMIDE (SPM 927)
E. Ben-Menachem, University of Gothenburg, Sweden

12:35 Discussion

13:00 *Lunch*

14:00 – 16:00 **Session III – C** **Tramuntana Hall**

DRUGS IN DEVELOPMENT

Chairpersons: **S.I. Johannessen,** Norway
H.J. Kupferberg, USA

14:00 NAX 5055
NeuroAdjuvants, USA
Presented by **G. Bulaj**, University of Utah, USA

14:20 Discussion

14:30 PROPYLISOPROPYL ACETAMIDE (PID)
Jazz Pharmaceuticals, USA
Presented by **M. Bialer,** The Hebrew University of Jerusalem, Israel

14:50 Discussion

15:00 RETIGABINE
H. Mansbach, *Valeant Pharmaceuticals*, USA

15:20 Discussion

15:30 T2000 – PRECLINICAL DATA
Presented by **M. Gasior**, presently at *Cephalon, Inc.*, USA

15:50 Discussion

16:00 *Coffee*

16:30– 18:30 **Session III – D** **Tramuntana Hall**

DRUGS IN DEVELOPMENT

Chairpersons: **B. Schmidt,** Germany
T. Tomson, Sweden

16:30 T2000
H. Rutman, *Taro Pharmaceuticals,* USA

16:50 Discussion

17:00 TONABERSAT
P. Blower, *Minster Pharmaceuticals,* UK

17:20 Discussion

17:30 VALROCEMIDE
Presented by **M. Bialer,** The Hebrew University of Jerusalem, Israel

17:50 Discussion

18:00 YKP3089
S.J. Lee, *SK Life Science,* USA

18:20 Discussion

08:00 – 10:30 **Session IV – A** **Tramuntana Hall**

PROGRESS REPORT ON SECOND-GENERATION TREATMENTS

Chairpersons: **I. Leppik**, USA,
P.H. Ryvlin, France

08:00 FELBAMATE
Presented by **I. Leppik**, University of Minnesota, USA

08:20 Discussion

08:30 GABAPENTIN
Presented by **B. Schmidt,** Wittnau, Germany

08:50 Discussion

09:00 LAMOTRIGINE
Presented by **F.M.C. Besag**, Twinwoods Health Resource Centre, London, UK

09:20 Discussion

09:30 LEVETIRACETAM
F. Tonner, *UCB S.A.,* Belgium

09:50 Discussion

10:00 OXCARBAZEPINE
Presented by **C. Elger**, University of Bonn, Germany

10:20 Discussion

10:30 *Coffee*

11:00 – 13:30 **Session IV – B** **Tramuntana Hall**

PROGRESS REPORT ON SECOND-GENERATION TREATMENTS

Chairpersons: **M. Baulac**, France
A. Kanner, USA

11:00 PREGABALIN
Pfizer Inc. USA
Presented by **B. Uthman,** University of Florida and McKnight Brain Insitute, USA

11:20 Discussion

11:30 RUFINAMIDE
A. Yeates, *Eisai,* UK

11:50 Discussion

12:00 STIRIPENTOL- PRECLINCIAL DATA
Biocodex, France
Presented by **J.L. Fisher,** University of South Carolina, USA

12:20 Discussion

12:30 STIRIPENTOL
Biocodex, France
Presented by **C. Chiron,** Necker-Enfants Malades Hospital, Paris, France

12:50 Discussion

13:00 TIAGABINE
Presented by **R. Kälviäinen**, Kuopio University Hospital, Finland

13:20 Discussion

13:30 *Lunch*

Deleted: *Break*

14:30 – 18:00 **Session IV – C** **Tramuntana Hall**

PROGRESS REPORT ON SECOND-GENERATION TREATMENTS

Chairpersons: **C.E. Elger**, Germany
S. Shorvon, UK

14:30 TOPIRAMATE
S. Ness, *Johnson & Johnson Pharmaceutical Research & Development,* USA

14:50 Discussion

15:00 VIGABATRIN
S. Sagar, *Ovation Pharmaceuticals, Inc,* USA

15:20 Discussions

15:30 ZONISAMIDE
R. van Maanen, *Eisai* ,UK

15:50 Discussions

16:00 *Coffee*

16:30 OXCARBAZEPINE MODIFIED-RELEASE (MR) FORMULATION
Desitin Arzneimittel GmbH, Germany
Presented by **B.J. Steinhoff,** Epilepsy Center Kork, Germany

16:50 Discussion

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17:00 VALPROIC ACID (DIVALPROEX SODIUM) EXTENDED-RELEASE (ER) FORMULATION
Abbot Neuroscience, USA
Presented by **D.G.A. Kasteleijn-Nolst Trenite**, La Sapienza University, Rome, Italy

17:20 Discussion

17:30 LAMOTRIGINE EXTENDED RELEASE (ER) FORMULATION
K.E. VanLandingham, *GlaxoSmithKline*, USA

17:50 Discussions

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08:30 – 12:00 **Session V** **Tramuntana Hall**

COMMON TARGETS AND MECHANISMS OF ACTION OF DRUGS FOR THE TREATMENT OF EPILEPSY AND OTHER CNS DISORDERS: IS THERE AN OVERLAP?

Chairpersons: **E. Perucca**, Italy
T. Tomson, Sweden

08:30 EPILEPSY AND NEUROPATHIC PAIN
M. Devor, The Hebrew University of Jerusalem**,** Israel

08:50 Discussion

09:00 EPILEPSY AND BIPOLAR DISORDERS
A. Harwood, Cardiff School of Biosciences, UK

09:20 Discussion

09:30 EPILEPSY AND MIGRAINE
M.A. Rogawski, UC Davis School of Medicine, USA

09:50 Discussion

10:00 *Coffee*

10:30 EPILEPSY AND ADDITIONAL CNS DISORDERS
S. Shorvon, University College London, UK

10:50 Discussion

11:00 THE UTILIZATION OF AEDs IN NON-EPILEPTIC CNS DISORDERS-CLINICAL PERSPECTIVES
A.M. Kanner, Rush University Medical Center, USA

11:20 Discussion

11:30 TOWARDS A BETTER UNDERSTANDING OF AED SITES OF ACTION: IMAGING EVALUATION OF ANTIEPILEPTIC DRUGS
W.H. Theodore, NIH, USA

11:50 Discussion

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12:00 – 14:00 Session VI Tramuntana Hall Deleted: 13:50

OPPORTUNITIES AND PERSPECTIVES IN NEW AED DISCOVERY

Chairpersons: **R. Twyman,** USA
H.S. White, USA

12:00 CREATING OPPORTUNITIES TO FUND NEW THERAPIES FOR EPILEPSY
J. Cramer, Epilepsy Therapy Project, USA

12:10 Discussion

12:20 CURRENT PERSPECTIVES IN NEW AED DISCOVERY: PANEL DISCUSSION
S. Collins, Neurotherapeutics Pharma, USA
R. Kaminski, UCB S.A., Belgium
R. Twyman, Johnson & Johnson Pharmaceutical Research & Development, USA
H.S. White, University of Utah, USA
M. Bialer, The Hebrew University of Jerusalem, Israel

13:50 Closing Remarks
S.I. Johannessen, National Center for Epilepsy, Norway

16:00 – 19:30 **REGULATORY ISSUES ON AED CLINICAL DEVELOPMENT**
A CEA-Sponsored Symposium
Tramuntana Hall

Chairpersons: **M. Baulac**, France
M. Pavlovic, EMEA

16:00 THE CURRENT EMEA GUIDELINE (2000-2007) ON AEDs: A RETROSPECTIVE EVALUATION AND THE RATIONALE FOR A REVISION
M Baulac, Hopital de la Pitie-Salpetriere**,** France

16:25 RETROSPECTIVE OVERVIEW OF THE REGULATORY WORK ON AEDs AT THE FDA
TBA, USA

16:50 THE ADD-ON INDICATION: ANYTHING NEW?
A. Elferink, Medicines Evaluation Board of the Netherlands, The Netherlands

17:15 RATIONALE FOR REQUIRING PLACEBO-CONTROLLED ADJUNCTIVE THERAPY STUDIES IN REFRACTORY PARTIAL EPILEPSY IN CHILDHOOD AND SPECIFICITIES ABOUT THE EPILEPTIC ENCEPHALOPATHIES IN CHILDHOOD
C. Chiron, Necker-Enfants Malades Hospital, Paris, France

17:40 DISCUSSION ON ABOVE TWO TOPICS
Chaired by **E. Ben Menachem,** University of Goteborg, Sweden

18:00 *Coffee*

18:30 STATUS EPILEPTICUS AND IV FORMULATIONS
S. Shorvon, University College London, UK

18:55 DISCUSSION ON ABOVE TOPIC
Chaired by **M. Bialer**, The Hebrew University of Jerusalem, Israel

FRIDAY, JUNE 20, 2008

09:00 – 12:00 **REGULATORY ISSUES ON AED CLINICAL DEVELOPMENT A CEA-Sponsored Symposium** **Tramuntana Hall**

Chairpersons: **J. French,** USA
C. Deguines, France

09:00 MONOTHERAPY TRIALS USING SUBOPTIMAL CONTROLS: PROS AND CONS
J. French, New York University Medical Center, USA

09:25 THE USE OF HISTORICAL CONTROLS IN REFRACTORY POPULATIONS
J. French, New York, University Medical Center, USA

09:45 DISCUSSION ON THE ABOVE TOPICS
Chaired by **E. Perucca,** University of Pavia, Italy

10:05 *Coffee*

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10:25 ACTIVE CONTROL TRIALS FOR THE MONOTHERAPY INDICATION: PROS AND CONS
T. Tomson, Karolinska University Hospital, Stockholm, Sweden

10: 50 IMPROVING THE UTILISATION OF HISTORICAL TRIALS IN NEWLY DIAGNOSED POPULATIONS
T. Marson, World Events, UK

11:10 DISCUSSION ON THE ABOVE TOPICS
Chaired by **M. Baulac**, Hopital de la Pitie-Salpetriere, France

11: 30 CONVERSION TO MONOTHERAPY AND ACTIVE CONTROL TRIALS: INDEPENDENT OR COMPLEMENTARY DATA FOR MONOTHERAPY APPROVAL?
J. French, USA**, M. Pavlovic,** EMEA, France**, T. Tomson**, Sweden, **E. Perucca,** Italy, **M. Baulac**, France

POSTER PRESENTATIONS

Board No.

1. RAPID ONE STEP ACCURATE, CHEAP AND RELIABLE METHOD FOR CYP2C9 GENOTYPING
I. Bejarano-Achache, M. Bialer, M. Shaham, Y. Caraco
Israel

2. DRUG-RESISTANT FOCAL EPILEPSIES: SURGICAL TREATMENT
V. Bersnev, T. Stepanova, V. Kasumov, R. Kasumov, Russia

3. TDM AND PHARMACOKINETIC VARIABILITY OF NEW AEDS IN CHILDREN
C. Johannessen Landmark, E. Rytter, S.I. Johannessen, Norway

4. EVALUATION OF ENANTIOSPECIFIC ANTIALLODYNIC ACTIVITY OF PROPYLISOPOPYLACETAMIDE, AN AMIDE DERIVATIVE OF A CHIRAL CONSTITUTIONAL ISOMER OF VALPROIC ACID
D. Kaufmann, B. Yagen, A. Minert, M. Tal, M. Devor , M. Bialer
Israel

5. THE VALUE OF CORTICOSTEROIDS TREATMENT BY PAINFUL LEGS AND MOVING TOES (PLMT) SYNDROME WITH CEREBRAL SEIZURES
D. Kountouris, A. Bougioukou, Greece

6. LICL/PILOCARPINE-INDUCED STATUS EPILEPTICUS AND ISCHEMIC HIPPOCAMPAL LESION INDUCED BY ENDOTHELIN-1: TWO MODELS OF EPILEPTOGENESIS IN IMMATURE RATS
H. Kubova, Czech Republic

7. POTENTIATION OF INHIBITORY SYSTEMS RESULTS IN DIFFERENT EFFECTS IN DEVELOPING RATS
P. Mares, Prague, Czech Republic

8. α-FLUORO-2,2,3,3-TRAMETHYLCYCLOPROPANECARBOXAMIDE, A NOVEL POTENT ANTICONVULSANT DERIVATIVE OF A CYCLIC ANALOGUE OF VALPROIC ACID
N. Pessah, M. Bialer, B. Wlodarczyk, R.H. Finnell , B. Yagen,
USA

9. EFFICACY OF ZONISAMIDE IN A RARE CASE OF TYPE II SIALIDOSY
M. Puligheddu, M. Mascia, A. Muroni, R. Mammoliti, G. Gioi, F. Marrosu, Italy

10. ADJUNCTIVE ZONISAMIDE THERAPY FOR REFRACTORY SEIZURES
M. Puligheddu, M. Mascia, A. Muroni, R. Mammoliti, G. Gioi, F. Marrosu, Italy

11. PREGNANCY OUTCOMES FOLLOWING LAMOTRIGINE MONOTHERAPY
A. Rysz, Poland

12. ADMISSION OF CHILDREN TO A REFERRAL CENTRE FOR EPILEPSY - DOES IT MAKE A DIFFERENCE**?**
Elisif Rytter, Cecilie Johannessen Landmark, Svein I. Johannessen Norway

13. PREVALENCE OF ACUTE REPETITIVE SEIZURES (ARS) IN THE UNITED KINGDOM
T. Sullivan, C. Martinez, A. Hauser, USA

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ABSTRACTS

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GENERALIZED EPILEPSIES: CLASSIFICATION, EPIDEMIOLOGY AND UNMET NEEDS

R. Guerrini
Children's Hospital A Meyer and University of Florence, Italy

Idiopathic generalized epilepsies (IGEs) have classically been classified into four major subtypes: (i) childhood absence epilepsy (CAE), (ii) juvenile absence epilepsy (JAE), (iii) juvenile myoclonic epilepsy (JME), and (iv) epilepsy with generalized tonic-clonic seizures (grand mal) on awakening (EGMA). Blurring of IGEs phenotypes in adolescence has led to concept category of 'IGE with variable phenotypes', differently combining generalized tonic-clonic, absence and myoclonic seizures. IGEs have a prevalence of about 0.4% in the general population, with CAE and JME being the most common. Additional syndromes have been considered to be part of the IGE spectrum, including benign myoclonic epilepsy in infancy, myoclonic astatic epilepsy and other less easily characterized syndromes. There has been long lasting consensus on the fact that these syndromes imply absence of structural brain lesions, as well as distinctive clinical and EEG features. Normal developmental skills and cognitive abilities, once considered a hallmark of IGEs are, however, not regularly seen as some patients may present with mild cognitive impairment which is difficult to relate to epilepsy and some may exhibit even severe impairment that might be related to uncontrolled seizures. It has been commonplace for many years that IGEs are usually responsive to drugs, with a relatively high degree of specificity. However, about 10% of patients will show drug resistant seizures and their seizure outcome may not follow the expected age related link. Since no clear criteria for early recognition of such cases have been established, response to drugs is somewhat unpredictable. Better definitions of the early clinical and EEG characteristics that may predict resistance to conventional drug choices and alternative strategies for pharmacological treatment are highly needed.

PREDICTING EFFICACY OF AEDS IN GENERALIZED EPILEPSIES

H.S. White
University of Utah, Anticonvulsant Drug Development Program, Department of Pharmacology and Toxicology, Salt Lake City, UT, USA

Since 1937 when Merritt and Putnam used the cat maximal electroshock seizure model to identify phenytoin from a series of investigational drugs, animal seizure and epilepsy models have played a critical role in the early evaluation of anticonvulsant efficacy. Over the last 70 years, animal models have evolved to include a number of different models for both partial and generalized seizures. Many of the currently available models involve evoking seizures in normal rodents using electrical stimulation and/or chemoconvulsants. In addition to evoked seizures, investigational antiepileptic drugs (AEDs) are routinely evaluated in the kindled rat. Unlike the electrical and chemical seizure models, the kindling model displays many histopathlogical and phenotypic features of temporal lobe epilepsy. The use of these models has clearly been important in bringing new therapies to the patient with partial epilepsy.

Of the models available for predicting efficacy in the generalized epilepsies, the Genetic Absence Epileptic Rat of Strasbourg (GAERS), the WAG/Rij rat along with a number of mutant mouse models display many phenotypic and electrographic features consistent with primary generalized epilepsy. In addition, seizures induced by the chemoconvulsant pentylenetetrazol display many pharmacological features consistent with generalized myoclonic seizures. Similarly, the maximal electroshock model displays phenotypic and pharmacological features consistent with human generalized tonic clonic seizures. More recently, there have been several models of infantile spasms described that display many features of human infantile spasms. However, they have not been routinely employed in AED discovery and thus their predictive validity remains unknown. In addition to these and other animal models, the human photosensitivity model has evolved in recent years to be a moderate throughput model for evaluating the efficacy of AEDs against photically evoked generalized photoparoxysmal EEG responses. Results from a number of recent studies suggest that this human model has reasonable predictive validity. This model is ideally suited for early proof-of-concept studies in humans.

SYNDROMES WITH ONSET IN EARLY CHILDHOOD

O. Dulac
Hopital Necker Enfants Malades, Paris, France

The common characteristic of epilepsy syndromes in early childhood is that there is a major lack of appropriate antiepileptic drugs.
The neonatal period comprises both benign (*familial* or *idiopathic seizures*) and very severe *neonatal epileptic* and *myoclonic encephalopathies with suppression bursts*) conditions, malformations and inborn errors of metabolism being the major causes in which recent insight into pathology has been identified. Although the white matter lacks and myeline and the cortical wiring is incomplete, motor and autonomic components of seizure semiology exhibit the same topography than in adulthood.
Migrating partial seizures in infancy, a very severe and still mysterious condition and *neonatal/infantile benign familial seizures* constitute transitions between the neonatal the infantile periods.
In infancy, *non progressive myoclonic encephalopathy* is mainly severe because of the underlying condition whereas epilepsy is usually controlled when diagnosed early enough. The severity of *HH* and *Dravet syndromes* contrasts the benignity of *simple febrile seizures* and *myoclonic epilepsy in infancy*, whereas *West syndrome* ranges from benign to most severe. Lack of myelin and age-related cortical hyperexcitability determine this particular pattern.

CLINICAL TRIALS OF NEW AEDs IN GENERALIZED EPILEPSIES: SYNDROMES WITH ONSET IN ADOLESCENCE AND ADULTS

K. Eriksson
Tampere University Hospital, Tampere, Finland

Well-defined generalized epilepsy syndromes starting at or after adolescence include three idiopathic syndromes (IGE) with variable phenotypes; juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures (GTC) only as well as one of the progressive myoclonus epilepsies as a symptomatic syndrome; Unverricht-Lundborg disease (ULD-EPM1). However, only few clinical trials have assessed the use of new AEDs in these generalized syndromes and most of the studies available have been done according to seizure type/s only and are of low evidence level (class III-IV).

In general, the responder rates are high in many generalized epilepsies/syndromes, especially in IGE, but not all AEDs are equally effective and some (e.g. CBZ, OCX, PHT, GBP, TGB, VGB) may even exacerbate seizure types other than generalized tonic–clonic. For patients with IGE, the drug of first choice is generally regarded to be VPA because its efficacy in absence, myoclonic and tonic-clonic seizures.

So far the newer AEDs have been studied only in few trials with positive results for LTG in GTCs and absence seizures, TPM in GTCs, LEV in GTCs and JME. The use of these newer AEDs including ZNS in IGEs is, however, evolving rapidly. The European Commission has e.g. granted orphan medicinal designation to brivaracetam for progressive myoclonus epilepsies and two placebo-controlled add-on trials for ULD-EPM1 are under way. To date published data on new AEDs in generalized epilepsies is based mainly on case series while comparative randomized clinical trials in defined syndromes would be needed.

CLINICAL TRIALS OF NEW AEDS IN GENERALIZED EPILEPSIES:
TOO LITTLE – TOO LATE? THE INDUSTRY PERSPECTIVE

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To date, the first epilepsy indication of the newer AEDs (defined as AEDs approved in the USA over the last 15 years: Felbamate, Gabapentin, Lamotrigine, Tiagabine, Topiramate, Levetiracetam, Zonisamide, Oxcarbazepine, Pregabalin) has almost always been "partial onset seizures" with generalized seizures or generalized epilepsies being addressed in new labeling only 3 to 7 years later.
Only 4/9 of these AEDs have been granted an extension of the indications with a generalized seizure type/syndrome.
Apart from preclinical or clinical evidence for narrow spectrum efficacy, other reasons will be discussed to explain the perception that there is "too little, too late".
1. The age range of many of the generalized syndromes often includes the pediatric population, requiring juvenile animal toxicology and pediatric pharmacokinetic data prior to the commencement of studies needed to provide evidence for safety and efficacy;
2. The optimal dose range for the primary indication is typically only well understood after completion of the adjunctive partial onset studies;
3. Difficulties in the implementation of the clinical studies, mainly due to recruitment challenges: competition with marketed drug; the long duration of treatment period in the PGTCS studies; the perceived need for including specific generalized epilepsy syndromes, limiting the pool of available patients; the perceived acceptance of monotherapy with older AEDs in the treatment of some IGEs, confounding the problem with issues related to the "monotherapy study" challenge.
In conclusion, whereas "earlier" and "more" are desirable objectives, it is the author's belief that a lot has already been done, resulting in an extensive fragmentation of the epilepsy indication – compared to many other CNS diseases. It is hoped that discussions like these will contribute in order to achieve "more" and "earlier".

ORPHAN DRUGS FOR RARE SYNDROMES

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Rare syndromes (<1/10.000) are also the most severe and the most pharmacoresistant epilepsies. Most of them associate generalized and partial seizures. Orphan drug status opened the way to develop antiepileptic drugs (AEDs) dedicated to such limited indications. Five AEDs were designated as orphan drugs since 2000. Rufinamide had the most rapid story: designated by EMEA in 2004, it was authorized in Europe in 2007 as add-on therapy in Lennox-Gastaut syndrome over 4 years of age. For stiripentol, it took 6 years for the process to be completed in 2007 at EMEA, for the treatment of Severe myoclonic epilepsy in infancy, as adjunctive therapy to valproate and clobazam, but the authorization was conditioned to additional trials. Brivaracetam was designated by EMEA in 2005 and FDA in 2008, for the treatment of adult progressive myoclonic epilepsy and myoclonia respectively, trials are going on. Clobazam, an old compound extensively approved outside US, was also designated as an orphan drug by FDA in 2008 and is currently on trial as add-on therapy in Lennox-Gastaut syndrome in children in US. More difficult is the development of vigabatrin (VGB) in US and Japan due to retinal toxicity and MRI abnormalities possibly VGB-related. By contrast, VGB is approved elsewhere as first line monotherapy for Infantile spasms, based on randomized trials. Limited recruitment, rapid cognitive decline and ethical constraints are major difficulties so that many syndromes still remain therapeutic orphans. Using innovative methodologies of trials should permit to develop AEDs for more and more rare syndromes.

MODIFIED RELEASE FORMULATIONS OF AEDS: REAL PROGRESS OR MARKETING GIMMICK?

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The question raised in title is provocative, but touches two important issues: Firstly, the ultimate treatment goal of seizure freedom without side effects is hardly achieved. Secondly drug companies are enterprises, which follow the rules of the market. They have to be inventive and innovative to comperte successfully on the market, sometimes to the detrimen of real improvement in the treatment of patients.

Some of the adverse effects of certain AEDs with a short plasma half life (less than 4-6 hours) are related to their toxic peak concentrations. Modified release formulations with slow release and uniform absorption over, let us say, 8 hours or longer may improve tolerability, by elimination of peaks in the drug concentration. Another potential advantage is the reduction in frequency of administration of the drug as compared with conventional dosage forms – possibly by improved compliance of the patients. Such preparations are offered in all fields of medical drug treatment. Many modified release preparations fulfill these expectations and are regarded as the preferred formulation in some situations like antidepressant treatment or treatment of bipolar disorders. To what extent this also applies to the drug treatment of patient with epilepsy is a matter of debate. Though, some preparations have shown clear advantage in tolerability (e.g. carbamazepine SR) compared to the standard formulation, others did not (e.g. gabapentine) and their potential advantage has to be demonstrated in prospective clinical trials. Such products may also have some drawbacks. Generally, interpatient variability in terms of the systemic concentration of the drug is greater for the modified release preparations. In addition, not only the time interval between the doses is greater, but also the deleterious effect of a missed dose.

Most often used currently available modified release formulations of AEDs are with carbamazepine, oxcarbazepine, and valproate. Newer AEDs with modified release formulations are e.g. levetiracetam and gabapentin. These preparations are usually more expensive and their specific advantages in the treatment of the patient with epilepsy have to be demonstrated. Currently available modified release formulations of AEDs will be reviewed critically.

SHOULD WE AVOID THE USE OF GENERIC PRODUCTS OF AEDS

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Given the high cost of health care, governments and insurers are under increasing pressure to enact cost-saving measures. Generic agents are associated with lower cost and are reasonable for many conditions, however in epilepsy substitution can result in dangerous consequences. Even one seizure in a previously controlled patient can cause injury, loss of driver's license, or death. For bioequivalence and therefore license of generics, the 90% confidence interval of both area under the drug concentration-time curve (AUC) and peak concentration must fall between 80 and 125% of the reference compound. An American FDA review showed an average difference of 3-4%, with standard deviation 3%. However, in over 5% there was a 10% or greater variance from the mean AUC (Nightingale et al, JAMA 1987;258:1200-4). This is potentially significant for patients with epilepsy. Change between different generic manufacturers (23 for gabapentin) – common practice in the U.S. - compounds potential differences. A survey of neurologists showed that breakthrough seizures and adverse effects are common with changing to generics, resulting in additional telephone consultations, office and emergency room visits, and hospital admissions (Wilner, Epilepsy Behav 2004; 5:995-8). These costs, plus additional blood testing, could more than offset cost savings of generics. A study of compulsory change to generic (Andermann et al, Epilepsia 2007;48:464-9) showed that compared to other classes, AEDs were more likely to be switched back to brand (12.9-20% versus 1.5-2.9%). A review of previous studies (Crawford et al, Seizure 2006; 15:165-176) found several generic carbamazepine generic preparations whose 90% confidence range fell outside of the required 80-125% interval. Additionally, there were reports of variable rates of absorption. While clearly more objective information is needed about clinically significant differences between brand name and generic drugs, physicians should err on the side of caution in patients with epilepsy, and avoid the use of generic agents whenever possible.

SHOULD WE AVOID THE USE OF GENERIC PRODUCTS OF ANTIEPILEPTIC DRUGS? A CASE IN FAVOUR OF GENERICS

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A generic is a pharmaceutical product which is marketed under the non-proprietary name and has the same qualitative and quantitative composition in terms of active substance as the brand, and equivalent bioavailability. Generics bring huge benefits in terms of drug affordability and budget savings, and release resources to address other health care needs. Although theoretically the bioavailability of a generic can be reduced (or increased) by as much as 20% (or 25%) compared with the brand, in practice such a difference is most unlikely to occur because the need to maintain the 90% confidence intervals (not the mean value!) within the acceptable range implies that mean plasma concentrations after administration of a generic differ relatively little from those observed after administration of the brand product. In fact, no adequately controlled study has ever demonstrated that use of generics causes harm in terms of lesser seizure control or greater susceptibility to adverse effects. Individual case reports suggesting altered clinical responses after generic switching are difficult to interpret, because of reporting bias and difficulties in excluding the role of confounders. Overall, differences in drug concentrations related to use of different formulations appear to be relatively small compared with those induced by other sources of kinetic variability. Nevertheless, the possibility exists that in some patients fully controlled on a critical drug concentration, even a modest change in steady-state plasma drug levels could lead to seizure breakthrough or toxicity, particularly when facilities for monitoring drug levels are unavailable. For this reason, given the severe consequence of a seizure relapse in seizure-free individuals, generic switching is not advisable in patients who are seizure-free. Switching from one generic to another is also not recommended, because bioequivalence is guaranteed for each generic versus the brand, but not between different generics.

WHAT IS THE BEST ROUTE FOR EMERGENCY TREATMENT WHEN THE IV ROUTE IS NOT AVAILABLE

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Seizure emergencies including acute repetitive seizures and status epilepticus require prompt treatment with drugs that have a rapid onset of action. Delay in starting therapy can result in refractory seizures, greater morbidity, and costlier care. Intravenous benzodiazepines are generally considered the treatment of choice, but the need for trained personnel and medical facilities can delay starting therapy. Alternate routes permit earlier initiation of therapy by nonmedical caregivers. The choice of route depends upon the patient's condition, the drug and the skills of the caregiver. Alternative methods of drug delivery include intramuscular, buccal, nasal, and rectal routes. All have limited absorptive surface that favors drugs, which are lipid soluble, available as solutions, and highly concentrated. Clonazepam, diazepam, and midazolam possess most of characteristics needed to treat seizure emergencies. Intramuscular administration of midazolam and diazepam given via an autoinjector may have sufficiently rapid onset of action for use in treating seizure emergencies, but have yet to undergo controlled clinical trials. Rectal diazepam is highly effective and safe when administered by caregivers, but many object to the route. Studies on intranasal clonazepam, diazepam, and midazolam have been performed with promising results. If formulations challenges can be overcome, the ease of use, rapid onset of effect, and safety of intranasal drug administration suggest that this route may be the best alternative when the intravenous route is not available.

BRIVARACETAM (UCB 34714): A NOVEL SV2A LIGAND

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Brivaracetam (ucb 34714) is a novel high-affinity synaptic vesicle protein 2A (SV2A) ligand, currently in development for epilepsy. Brivaracetam has 10-fold higher affinity for SV2A than levetiracetam (Keppra®) and also has inhibitory activity at neuronal voltage-dependent sodium channels. Brivaracetam is more potent and efficacious than levetiracetam in various animal models of epilepsy. Brivaracetam is almost completely absorbed, weakly protein-bound, extensively metabolised and eliminated renally. It has linear pharmacokinetics and a plasma half-life of ~8 hours. Brivaracetam (5–150 mg/day) has a highly predictable exposure in individual patients and low potential for clinically relevant pharmacokinetic drug-drug interactions at therapeutic doses. At single doses of 10–80 mg, brivaracetam has shown potent activity in suppression of photoparoxysmal discharges in the photoparoxysmal response model of patients with photosensitive epilepsy. The efficacy, safety and tolerability of brivaracetam as adjunctive therapy in patients (16–65 years) with focal epilepsy with/without secondary generalisation, inadequately controlled with 1–2 AEDs, was evaluated in two double-blind, randomized, placebo-controlled studies. In study N01193, patients received placebo (n=54) or adjunctive brivaracetam 5 (n=50), 20 (n=52) or 50 (n=52) mg/day b.i.d. without titration for 7 weeks. Brivaracetam was efficacious and displayed a strong dose-response relationship in *i)* percent reduction over placebo in partial-onset seizure frequency/week (primary analysis; 22.1%, p=0.004 at 50 mg/day; 14.9%, p=0.062 at 20 mg/day; 9.8%, p=0.240 at 5 mg/day); *ii)* reduction in partial-onset seizure frequency/week from baseline (53.1%, p<0.001 at 50 mg/day; 42.6%, p=0.014 at 20 mg/day; 29.9%, p=0.086 at 5 mg/day vs. 21.7% on placebo); *iii)* ≥50% responder rate (55.8%, p<0.001; 44.2%, p=0.002; 32.0%, p=0.047 for brivaracetam 50, 20 and 5 mg/day vs. 16.7% for placebo). Eight, 7.7 and 7.7% of patients on 5, 20 and 50 mg/day respectively were seizure free over the 7-week treatment period, compared to 1.9% on placebo. In study N01114, patients received placebo (n=52) or brivaracetam 50 (n=53) or 150 (n=52) mg/day b.i.d. over 3-week titration and 7-week stable-dose periods. Statistical significance versus

placebo was not achieved in the primary parametric efficacy analysis (partial-onset seizure frequency reduction over placebo). However, the 50 mg/day dose reached significance for median percent reduction from baseline in weekly seizure frequency (38.2% vs. 18.9% on placebo, p=0.017) which shows a clinical treatment effect. 9.4 and 5.9% of patients on 50 and 150 mg/day respectively were seizure-free over the 10-week treatment period, compared to 1.9% on placebo. Exposure-response modelling revealed that the ED_{50} for seizure frequency reduction was 20 mg/day, with maximum reduction at 50–100 mg/day. Retention of brivaracetam and placebo-treated patients in both studies was high (91%–98%). Seizure freedom was achieved in 6–9% of brivaracetam patients. Treatment-emergent adverse events (TEAEs) were reported by similar proportions of patients in brivaracetam and placebo groups in the pooled analysis of these studies. The incidence of CNS-related TEAEs was very low and comparable between groups. The most frequent TEAEs were headache, somnolence, fatigue, nausea and dizziness. No major differences between the brivaracetam and placebo groups were found for any individual AEs, laboratory parameters or vital signs. Phase 3 clinical development of brivaracetam as adjunctive treatment in patients with uncontrolled partial onset seizures is currently ongoing.

CARISBAMATE

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Carisbamate (RWJ-333369; S-2-O-carbamoyl-1-*o*-chlorophenyl-ethanol) is a novel neuromodulator under development for the treatment of epilepsy. Carisbamate has been demonstrated to possess a potent broad-spectrum anticonvulsant profile in rodent models of generalized and partial epilepsy at doses well below those eliciting toxicity. Analysis of the disposition of carisbamate in humans has indicated that it undergoes complete absorption and extensive metabolism, with greater than 92% excreted in the urine as unchanged drug. The principal route of metabolism is through glucuronidation. Carisbamate has exhibited linear pharmacokinetics in repeated-dosing studies. The half-life of approximately 12 hours enables twice-daily (BID) dosing with an immediate-release oral formulation. In addition, the results of food-effect bioavailability studies indicate that carisbamate can be prescribed to patients irrespective of food intake.

Studies have shown that carisbamate has minimal effect on the activity of the CYP2D6, and CYP3A4 P450 isozymes. CYP2C9 activity was weekly inhibited by BID dosing of carisbamate. Co-administration of carisbamate produces no clinically significant changes in the pharmacokinetics of lamotrigine, valproic acid, carbamazepine, phenytoin, ethinyl estradiol, norethindrone, or warfarin. Plasma concentrations of carisbamate are reduced by 36% with the

co-administration of carbamazepine, by 47% with the co-administration of phenytoin, and by 10% to 20% with the co-administration of an oral contraceptive. When the pharmacokinetics of carisbamate was examined in subjects with moderate and severe renal impairment, only clinically insignificant differences were observed in the mean plasma maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of carisbamate. However, mean plasma AUC after single-dose administration of carisbamate was approximately 16% greater in subjects with mild hepatic impairment and 107% greater in subjects with moderate hepatic impairment compared with subjects with normal hepatic function.

A randomized, double-blind, placebo-controlled, dose-ranging Phase IIb study evaluated daily dosages of 100, 300, 800, and 1600 mg in subjects

with partial onset seizures (n = 537 randomized). Carisbamate was efficacious at doses of 300, 800, and 1600 mg, and the tolerability of 300 mg and 800 mg was very favorable. The most common adverse events in the trial were dose-dependent and were seen principally at the maximal dosage; these included headache, dizziness, somnolence, and nausea. Phase III trials of carisbamate for adjunctive use in partial onset seizures are in progress.

CHARACTERISATION OF CSC 700-008 AS A BROAD SPECTRUM ANTIEPILEPTIC DRUG

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Our objective was to identify novel, broad spectrum AED's with superior tolerability and safety to valproate. Broad spectrum AED property was initially defined as robust efficacy in both the MES and s.c. PTZ seizure tests with subsequent verification using other seizure based assays. In-vivo screening of a novel chemical series lead to the identification of CSC 700-008 which has an oral ED_{50} of 4.6 and 33.6mg/kg in the rat MES and s.c. PTZ assays respectively. At an equivalent dose range, CSC 700-008 also completely suppresses the abnormal spike-wave EEG in the GAERS model of absence-type epilepsy. The mechanism of action of CSC 700-008 is, as yet, unknown.

Detailed in-vivo pharmacokinetic evaluation in the rat reveal CSC 700-008 to have good oral bioavailability (F%=61%), long oral half-life (approx. 16h), and predicted plasma drug levels in the range 5-50µM across multiple models of epilepsy. Drug exposure as measured by C_{max} and AUC is linear to dose.

Safety assessment of CSC 700-008 suggests no interaction with the major CYP isoenzymes, and no functional hERG property, when tested up to 100 µM. Irwin and acute toxicity studies suggest a maximally tolerated oral dose of 400mg/kg in the rat. Taken together, these studies suggest CSC 700-008 to be a broad spectrum member of the AED class, with additional efficacy in animal models of anxiety and neuropathic pain.

NOVEL ANTICONVULSANT AND ANTIEPILEPTIC ACTIONS OF 2-DEOXY-D-GLUCOSE (2DG)

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2-deoxy-D-glucose (2DG), a glucose analogue used for decades as a tracer for measurement of regional glucose utilization in autoradiograpic and PET imaging, has acute anticonvulsant and chronic antiepileptic actions in a variety of preclinical screening models. 2DG differs from glucose only by removal of a single oxygen atom at the 2-position, undergoes activity-dependent uptake into neural circuitry in response to increases in cellular energy demand and seizures, and inhibits glycolysis by preventing isomerization and subsequent steps of glycolysis. Acute anticonvulsant and chronic antiepileptic effects of 2DG have been observed in four *in vivo* models: 1) 6Hz seizures in mice (ED50 = 79.7 mg/kg IP), 2) audiogenic seizures in Fring's mice (ED50 = 206.4 mg/kg IP), 3) pilocarpine-induced seizures (250 mg/kg IP 1 hour before pilocarpine administration), and 4) evoked kindled seizures (250 mg/kg IP 30 min prior to perforant path or olfactory bulb stimulation). Chronic *in vivo* antiepileptic effects against kindled seizures include 2-fold slowing of kindling progression. This "disease-modifying" effect against consequences of seizures including kindling progression has been associated with inhibition of glycolysis, which reduces seizure-induced increases of BDNF and its neurotrophin receptor TrkB required for kindling progression by a novel mechanism of metabolic transcriptional regulation involving the repressor Neuron Restrictive Silencing Factor (NRSF), its NADH redox sensor Carboxy-terminal Binding Protein (CtBP), and chromatin modification at the promoter regions of BDNF and TrkB. The anticonvulsant actions of 2DG appear to be broadly suppressive against a variety of cellular and membrane processes contributing to network synchronization, as 2DG suppresses burst discharges induced in hippocampal slices by distinctive mechanisms including elevated $[K^+]_o$, blockade of K^+ channels by 4AP, antagonism of $GABA_A$ receptors by bicuculline, and the metabotropic

group I agonist DHPG. The rapid onset of 2DG's anticonvulsant action within minutes after bath application *in vitro* suggests that its acute anticonvulsant mechanisms are likely to be operating at the membrane or synaptic levels. Preliminary acute and chronic toxicity studies in rats including assessment of open field activity, spatial memory performance, and chronic systemic toxicity at doses spanning 37.5 mg/kg – 1gm/kg/day have demonstrated that therapeutically effective doses appear to be well-tolerated. With a novel spectrum of effectiveness in screening models, a favorable preclinical toxicity profile, and unique mechanisms of action including activity-dependent metabolic regulation of synaptic properties and seizure-induced gene transcription, 2DG may provide a new therapeutic approach for treatment of epilepsy compared to current drugs.

ESLICARBAZEPINE ACETATE

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Eslicarbazepine acetate (ESL) constitutes a third-generation, single-enantiomer member of the long-established family of first-line dibenz/b,f/azepine anti-epileptic drugs (AEDs) represented by carbamazepine (CBZ, first-generation) and oxcarbazepine (OXC, second-generation). ESL shares with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide substitute but is structurally different at the 10,11-position. This molecular variation results in differences in metabolism and is expected to result in improved tolerability and ease of administration (once daily dosing). Unlike CBZ, ESL is not metabolized to CBZ-10,11-epoxide and is not susceptible to auto-induction of its own metabolism. Unlike OXC, which is metabolised to both eslicarbazepine (also called S-licarbazepine, S-MHD or BIA 2-194) and R-licarbazepine (also called R-MHD or BIA 2-195), ESL is a prodrug of eslicarbazepine, which is the drug entity responsible for the ESL pharmacological effect. Recently completed multicenter, randomised, double-blind, placebo-controlled, add-on Phase III studies in partial epilepsy showed a statistically significant decrease in seizure frequency and number of days with seizures and a significant increase in responder rate in patients treated with ESL 800 mg and 1200 mg once-daily compared to placebo. In a completed 1-year open-label extension, significant improvements in quality of life (QOLIE-31) and depressive symptoms (MADRS) were found. In the pooled population of placebo-controlled studies in adult epileptic patients, 45.3% patients treated with ESL and 24.4% patients treated with placebo reported possibly related treatment-emergent adverse events (TEAEs). The possibly related TEAEs with and incidence >2% were (ESL vs placebo) dizziness (18.8% vs 5.7%), somnolence (11.2% vs 7.4%), nausea (6.5% vs 2.4%), diplopia (6.3% vs 1.2%), headache (5.5% vs 2.1%), vomiting (4.8% vs 1.2%), coordination abnormal (4.4% vs 1.8%), vision blurred (3.5% vs 0.9%), vertigo (2.1% vs 0%) and fatigue (2.1% vs 1.8%). The incidence of adverse events was dose-dependent. Adverse events were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment. After 6 weeks, no relevant differences on the incidence of adverse events were apparent between patients treated with ESL and patients treated with placebo. Incidence of behavioural or psychiatric events was low (<1% of patients for any possibly related TEAE reported in either the ESL or placebo groups).

The favourable efficacy and safety profiles indicate that ESL is a valuable addition to the current armamentarium of epilepsy therapy.

JZP-4

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JZP-4 (3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine) is a novel sodium and calcium channel blocker with structural similarity to lamotrigine. JZP-4 was designed to block the formation of the proposed immunogenic arene oxide metabolite through chlorination at C-5 on the phenyl ring. The substitution of a pyrazole ring for a triazine ring also altered the metabolic route from principally glucuronidation to hydroxylation by CYP1A2 at C-5 on the pyrazine ring and then glucuronidation by UGT2B15.. Since JZP-4 has a shorter half-life compared to lamotrigine and possibly less of a risk for rash, it could potentially be titrated to steady state much faster than lamotrigine. At anticipated therapeutic concentrations, JZP-4 is expected to have very low or no inhibitory effect on CYP isozymes. Its actions on the human Nav1.2A channel consisted of inhibition of voltage and use dependent membrane depolarization and a hyperpolarization shift in the voltage-dependent inactivation of transient currents. The Ki values for inducing this hyperpolarizing shift were 1.7 □M for JZP-4 versus 21 □M for lamotrigine. JZP-4 was also found to inhibit high voltage activated Ca^{2+} channels on rat dorsal root ganglia neurons with an IC_{50} at -60mV of 74 □M, whereas lamotrigine had an IC_{50} of greater than 1 mM. Additional studies with cloned cell lines have been undertaken to determine the types of calcium channels affected. In the mouse and rat maximal electroshock (MES) models, JZP-4 had ED_{50}'s of 5.88 mg/kg i.p and 1.25 mg/kg i.p., respectively. The ED_{50} for JZP-4 in the rat MES model following oral administration was 0.94 mg/kg. In previously reported rat MES studies, the oral ED_{50}'s for carbamazepine, felbamate, phenytoin, valproate and lamotrigine were 5.4, 25.3, 28.1, 485 and 1.3 mg/kg, respectively. The therapeutic ratio between mouse MES activity and ataxia in the rotorod test at following i.p. dosing was 16.4 compared to 3.7 for lamotrigine. In the intravenous pentylenetetrazole model in mice, both JZP-4 and lamotrigine were active in prolonging the time to clonic seizure with ED_{50}'s of 5.6 and 10 mg/kg, respectively. Neither compound blocked the development of seizures. In the mouse 6 Hz model conducted, JZP-4 was effective at 22, 32 and 44 mA with ED_{50}'s of 5.28, 10.59, and 18.29 mg/kg i.p., respectively. Since lamotrigine and other sodium channel blockers have not been active in this model, these data are suggestive that JZP-4 may have additional mechanisms of action other than sodium channel blockade.

LACOSAMIDE (LCM)

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Presented by **P. Verdru,** UCB Pharma, USA

Lacosamide (LCM) is a synthetic derivative of the amino acid D-serine which has been fully developed for the adjunctive treatment of partial-onset seizures (with and without secondary generalization) in adults aged ≥16. LCM is being developed in multiple bioequivalent formulations (tablet, syrup, and intravenous solution). LCM protects against a variety of seizure types and demonstrates potential neuroprotective properties in animal models. LCM demonstrates a novel mechanism of action profile by selectively enhancing the slow inactivation of voltage-gated Na^+ channels as well as modulating the activity of collapsin response mediator protein-2. Preclinical data suggest no special hazards for humans based on conventional studies. Oral LCM is completely absorbed and demonstrates linear pharmacokinetics; T_{max} is 1-2 hours and $t_{1/2}$ is 13 hours, allowing b.i.d. dosing. LCM does not significantly bind to plasma proteins (≤15%), and multiple drug-interaction trials demonstrated no relevant interactions. esults suggesting the efficacy of LCM 200-600mg/d as adjunctive therapy in adults with pharmacoresistant partial-onset seizures (taking 1-3 concomitant AEDs) have been demonstrated in three large, randomized, placebo-controlled trials. In the most recently completed trial (SP754, n=405), LCM demonstrated statistically significant efficacy results for 400mg/d and 600mg/d when compared to placebo based on the 50% responder rate and percent reduction in seizure frequency from baseline to maintenance. An earlier trial (SP755, n=485) demonstrated statistically significant efficacy results for 200mg/d and 400mg/d when compared to placebo for the percent reduction in seizure frequency from baseline to maintenance. The 50% responder rate for 400mg/d was statistically significant when compared to placebo, while that for 200mg/d was notably higher than placebo. In the initial large, randomized, dose-ranging placebo-controlled trial (SP667, n=421), the 50% responder rate and the percent reduction in seizure frequency from baseline to maintenance were statistically significant for 400mg/d and 600mg/d, and both were notably greater than placebo for 200mg/d. As these 3 trials were similarly designed, a pooled efficacy analysis was performed which supports the efficacy of LCM at doses of 200-600mg/d. The use of LCM has been

associated with reports of CNS- and GI-related adverse events (AEs) which are typically mild-moderate in nature; overall, those reported most frequently as compared to PBO can be related to dose and include dizziness, diplopia, nausea, vomiting, abnormal coordination and blurred vision. The use of LCM is typically not associated with clinically meaningful changes in laboratory parameters, vital signs, or body weight. A small, asymptomatic increase in PR-interval has been noted.

NAX-5055: SYSTEMICALLY ACTIVE GALANIN ANALOG FOR THE TREATMENT OF EPILEPSY AND PAIN

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For a substantial number of patients with epilepsy and chronic pain, the currently available therapies are often not effective in controlling their symptoms. The neuropeptide galanin and its associated receptors play an important role in controlling neuronal excitability in the CNS, and direct administration of galanin to the brain has been found to possess anticonvulsant and antinociceptive properties in rodent epilepsy and pain models. As such, the galanergic system represents a novel molecular target for pharmacological manipulation. We designed and synthesized galanin-based analogs that display systemic bioavailability, metabolic stability, and penetrate the blood-brain-barrier. The lead compound, NAX-5055, remained remarkably potent following i.v., i.p. or s.c. administration in the 6 Hz test over an increasing range of intensities (i.e., 22, 32, and 44 mA), and in the corneal kindled mouse model of epileptogenesis. The pronounced antinociceptive effects of NAX-5055 were observed in the formalin test in both male CF1 mice and male Sprague-Dawley rats. NAX-5055 significantly attenuated mechanical allodynia in the rat sciatic nerve partial ligation model of chronic pain. These results demonstrate that galanin plays an important role in regulating hyperexcitability and support further preclinical development of NAX-5055 for the treatment of neurological disorders. Supported by grants from the Epilepsy Therapy Project and The Epilepsy Foundation of America.

PROPYLISOPROPYL ACETAMIDE (PID)

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Propylisopropyl acetamide (PID) is a CNS-active constitutional isomer of valpromide (VPD), the CNS-active corresponding amide of valproic acid (VPA), that is currently being developed by Jazz Pharmaceuticals, CA, USA. In contrast to VPD that serves as a prodrug to VPA in humans, PID is likely to act in humans as a drug on its own. Metabolic stability of PID enantiomers relative to VPA was determined by incubation with various human liver enzyme sources (hepatocytes, S9 fraction, microsomes, and mitochondria) at substrate concentrations of 1 μM to 50 μM. After 120 min incubation with hepatocytes at concentrations of 1-10uM, no degradation/metabolism was detected for (R)-PID. For (S)-PID, 76.9% remained at the end of 120 min. A second hepatocyte study using 50 μM substrate was conducted. Apparently only VPA was metabolized by the hepatocytes (only 2% remaining after 2h). No/minimal degradation/metabolism could be observed in the incubations with (R)- or (S)-PID. A glucuronide metabolite could be detected for VPA. No metabolism was observed in S9 with (R)-PID and VPA, and very little (~6.5%) consumption was observed with (S)-PID. No metabolism of PID enantiomers or VPA could be measured in microsomes or mitochondria.

PID (racemate and/or individual enantiomers) demonstrated anticonvulsant activity in various anticonvulsant animal models that were previously described. In all these anticonvulsant tests, PID (racemate or individual enantiomers) was 3-30 times more potent than VPA. (R)- and (S)-PID showed stereoselectivity in the 6Hz and scMet models with (R)-PID being more potent than its enantiomer The antiallodynic activity of PID was evaluated in the Chung model for neuropathic pain. In rats (R)-PID, (S)-PID and (R,S)-PID produced dose-related reversal of tactile allodynia with ED_{50} values of 46, 48, 42mg/kg, respectively. The individual PID enantiomers were not enantioselective in their antiallodynic activity. No sedative side-effects

were observed at these doses. Following i.p. administration of the individual enantiomers, (S)-PID had lower clearance (CL) and volume of distribution (V) and a shorter half-life ($t_{1/2}$) than (R)-PID. However, following administration of (R,S)-PID, both enantiomers had similar CL and V, but (R)-PID had a longer $t_{1/2}$. Both of PID enantiomers, and the racemate, are more potent antiallodynic agents than VPA and have similar potency to gabapentin and thus have a potential to become new drugs for the treatment of neuropathic pain. Unlike VPA and similar to (R)-PID and (S)-PID, the corresponding acids of the PID enantiomers (R)-PIA and (S)-PIA failed to exert a teratogenic effect in SWV-Fnn mice sensitive to VPA-induced teratogenicity following a single dose at day 8.5 of gestation.. Although VPA is one of the leading AEDs, its clinical use is restricted in women of child-bearing age and in children due to its teratogenicity and hepatotoxicity. The development of individual PID enantiomers and their introduction as new non-teratogenic and non-hepatotoxic new CNS agents that are more potent than VPA, can offer a suitable response to these clinical needs and for the treatment of therapy-resistant patients.

RETIGABINE

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Retigabine (N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester) is the only antiepileptic drug (AED) that directly activates (opens) voltage-gated potassium (KCNQ) channels that conduct M-current – a critical regulator of neuronal excitability. Retigabine demonstrates potent anticonvulsant activity in a broad array of acute and chronic seizure models. It is also active in novel models in which animals are resistant to conventional AEDs, consistent with a unique mechanism/site of action. The clinical profile of retigabine is characterized by linear pharmacokinetics, ~8 hour half-life, metabolism by hydrolysis/acetylation and glucuronidation, primarily renal elimination, and low potential for to affect concentrations of other AEDs. In a double-blind, placebo-controlled Phase 2 dose-ranging study, seizure control was improved by the addition of 600, 900 or 1200 mg/day retigabine vs. placebo, with differences being significant at the higher two dosages. The results of this Phase 2 study have been replicated by one reported Phase 3 double-blind, placebo-controlled study documenting the efficacy of 1200 mg/day retigabine in adults with refractory partial-onset seizures. Open-label studies have demonstrated that effectiveness is maintained during long-term treatment. The most common adverse events associated with retigabine are nonspecific, dose-related CNS effects. As the first direct KCNQ-channel opener, retigabine establishes the therapeutic potential of voltage-gated potassium (KCNQ/M-current) channels as molecular targets in epilepsy and other diseases characterized by neuronal hyperexcitability.

T-2000, A PRODRUG OF 5,5-DIPHENYL-BARBITURIC ACID (DPB)

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5,5-diphenyl-barbituric acid (DPB) was synthesized in the early 1930s but its development came to a standstill due to the lack of hypnotic efficacy and weak anticonvulsant properties revealed in these early studies. Given its structural similarities to the two prototypical antiepileptic drugs, phenobarbital and diphenylhydantoin, the interest in DPB was renewed by A. Raines and his colleagues some 40 years later. Subsequent studies provided strong evidence that DPB produces pharmacological effects that resemble those produced by its structural congeners. In electrophysiological studies, DPB suppressed high frequency repetitive neuronal discharges in cat motor nerve terminals in a manner similar to that of diphenylhydantoin whereas it depressed synaptic discharges in the cat spinal cord in a manner similar to that of phenobarbital. However, how exactly DPB interacts with different binding sites at the $GABA_A$ receptor complex or other receptors and/or channels remains to be evaluated. DPB was found to be effective against pentylenetetrazole (PTZ) and maximal electroshock (MES) seizure tests in mice and rats. When tested in the rotarod test, DPB demonstrated very good therapeutic index (TI) particularly after oral administration in mice and rats (TI ranged from 22 to >337 depending on the seizure test and species). Pharmacokinetic profile of DPB also appeared favorable. Exposure to the drug was dose-dependent and there was a good correlation between brain and plasma concentrations. DPB also significantly potentiated the effects of valproic acid against MES-induced seizures in mice, which would suggest potential beneficial effects of DPB in add-on therapy. DPB demonstrated some anti-epileptogenic properties. Specifically, it decreased the development of kindled seizures induced by PTZ and cocaine. The efficacy in the latter model implies its potential utility in some neuropsychiatric syndromes associated with a dysfunction of the dopaminergic neurotransmitter system. In summary, although DPB represents neither a novel chemical class nor mechanism of action, it shows several favorable properties with potential therapeutic utilities in the treatment of epilepsy and perhaps some other neuropsychiatric disorders. Currently, a pro-drug of DPB, T-2000 (1,3-dimetoxymethyl-5,5-diphenyl-barbituric acid), is under development for the potential treatment of epilepsy and essential tremor by Taro Pharmaceuticals.

PHARMACOLOGY, TOXICOLOGY, METABOLISM AND PHARMACOKINETICS OF T2000, A NOVEL NON-SEDATING BARBITURATE

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T2000 is a member of the barbiturate class of drugs, a class which has been in wide clinical use for over one hundred years. T2000 is a prodrug and is rapidly metabolized to monomethoxymethyl-5,5-diphenylbarbituric acid (MMMDPB) and 5,5-diphenylbarbituric acid (DPB). T2000 and its metabolites exhibit useful pharmacologic properties at dosages not limited by sedation. T2000 is being investigated for treatment of essential tremor, myoclonus dystonia and epilepsy.

T2000 and metabolites suppress neural repetitive firing, without significant effects on GABA, due to effects on potassium or sodium channels. The metabolites are active at the $GABA_{A\alpha 1}$ receptor and dopamine transporter.

T2000 has little potential for QT interval prolongation and produced no physiological or behavioural signs of physical dependence in rats.

T2000 and metabolites are substrates and inhibitors of CYP2C19, CYP2C9 and CYP3A4. They are not transported by P-glycoprotein. The metabolites are potent inducers of CYP3A4.

Chronic 26-week rat (750 mg/kg/day) and 52-week dog (450 reduced to 150 mg/kg/day) studies indicated dose-dependent increase in liver weight, hepatocellular hypertrophy, and enzyme induction, reversible after 4 weeks recovery.

The pharmacokinetics of T2000 and metabolites are linear in man. Half-lives of T2000, MMMDPB and DPB range between 9-29 hours, 8-27 hours and 27-65 hours, respectively. After 1200 mg daily (600 mg bid) oral doses of T2000 for 2 weeks, mean C_{max} of T2000, MMMDPB and DPB were 0.79, 47 and 68 μg/mL, respectively.

TONABERSAT, A NOVEL BENZOYLAMINO BENZOPYRAN COMPOUND WITH POTENT ANTICONVULSANT ACTIVITY

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Tonabersat (SB-220453) is a first-in-class novel benzoylamino benzopyran compound which demonstrates potent anticonvulsant activity. Tonabersat selectively and specifically binds to a distinct stereoselective site in the CNS believed to be at the neuronal gap junction. This binding site is present in the brain of several species, including humans and other primates. Highest levels of binding are in the superficial layers of the cerebral cortex and granular cell layer of the cerebellar cortex. Investigation of over 100 standard pharmacological agents (including sumatriptan, amino acid analogues and modulators of Na+/K+ channels) revealed that none demonstrated any significant affinity for the tonabersat binding site. Furthermore, receptor binding assays have demonstrated that tonabersat shows no affinity for the site of action of established anticonvulsants, highlighting the unique mechanism of action of this class of compounds. ctivity demonstrated in animal seizure models indicates that tonabersat is comparable in potency with current anti-epileptic drugs: the ED_{50} calculated for tonabersat as an anticonvulsant in rats was 3.1 mg/kg. Tonabersat is an effective inhibitor of electrographic seizure activity in rat hippocampal brain slices. In vivo experiments have demonstrated that, at doses of 0.3 to 10 mg/kg, tonabersat increased the seizure threshold for electrically or chemically induced seizures. Animal models have demonstrated potent inhibitory effects of tonabersat on both cortical spreading depression and trigeminal nerve stimulation, key processes in the development of migraine. Pharmacokinetic studies in man have demonstrated that tonabersat is well absorbed following oral administration with a median T_{max} of between 3 and 5 hours. The terminal half-life of between 24 and 40 hours is suitable for a once daily dosing regimen desired for a prophylactic therapy. Tonabersat does not induce CYP4503A enzymes in man and the primary route of clearance is hepatic. Safety studies have demonstrated that tonabersat was well tolerated with an overall benign safety profile; specifically there were no toxicologically significant effects on cardiovascular or renal function. Animal experiments using supratherapeutic doses showed no effects expected to limit dosing

options in man, suggesting a large therapeutic index is likely.linical trials have investigated the potential therapeutic application of tonabersat in migraine prophylaxis. Proof-of-concept studies have demonstrated significant reductions in migraine attacks. 62% of tonabersat treated patients vs. 45% on placebo reported ≥50% reduction in attacks and 90% less use of rescue medication. The pharmacological profile of tonabersat suggests a potential therapeutic role for this compound as a prophylactic anticonvulsant treatment in epilepsy.

VALROCEMIDE

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Valrocemide (VLR, N-valproyl glycinamide) was selected from a series of N-valproyl derivatives of GABA, glyicne and taurine because of its favourable pharmacokinetic and anticonvulsant activity profile in preclinical screening models. VLR pharmacokinetic-based design was aimed to enhance brain penetration as compared to VPA, by converting VPA carboxylic acid to a carboxamide moiety and utilizing the glycinamide-glycine biotransformation as a major metabolic pathway.

VLR has a wide spectrum of anticonvulsant activity in various animal models including the 6 Hz psychomotor seizure mice model and the hippocampal-kindled rat model. VLR is more potent than valproic acid (VPA) in the following anticonvulsant models: a) maximal electroshock (MES) test (mice and rats); b) Frings mice, and c) bicuculine- and picrotoxin-induced-seizures in mice. VLR is also more active than VPA in the spinal ligation model for neuropathic pain and in the amphetamine-induced hyperactivity rat model for mania. In all these animal models VLR acts as a drug on its own and not as a prodrug to VPA, since there is no biotransformation of VLR to VPA in rodents and VLR is mainly metabolized to an inactive metabolite valproyl glycine

In humans VLR has linear pharmacokinetics at a dose range of 250 mg to 400 mg. Following oral administration to humans 57-75% of the VLR dose is excreted in urine as valproyl glycine and 10-20% of the dose is excreted unchanged in urine. Preliminary studies in epileptic patients indicated that the VLR-to-valproyl glycine biotransformation might be moderately induced by enzyme inducing AEDs. VPA is a minor metabolite of VLR and the fraction of VLR biotransformed to VPA has been estimated to be 4-6%. Following repetitive dosing of VLR (2 g bid) to epileptic patients, mean VPA plasma levels were 22 mg/L, and were significantly lower than VPA's therapeutic range (50-100 mg/L). VLR thus might be developed into a product with efficacy comparable to VPA without the dose-related side effects of VPA. A controlled release (CR) formulation of VLR has been developed and its AUC was found to be bioequivalent to that of a VLR immediate release formulation. Following repetitive dosing of VLR

to healthy subjects VLR did not affect the pharmacokinetics of CYP1A2, 2C9, 2C19 or 2D6 probe drugs. VLR reduced midazolam (CYP 3A4 probe) plasma exposure (AUC) by 33% which was mild compared to the 94% reduction of midazolam AUC caused by CBZ and PHT.

In July 2005, Teva Pharmaceuticals returned VLR to Yissum, the Technology Transfer Company of The Hebrew University of Jerusalem. In June 2006 Yissum and Shire LLC entered into a worldwide license whereby Shire LLC would continue the development of VLR. In December, 2007 Shire LLC terminated its agreement with Yissum due to a portfolio decision. Subsequently, on February 2008, valrocemide was in-licensed from Yissum by Desitin (Hamburg, Germany) which received the rights for Europe. Currently, both Desitin and Yissum are looking for a co-development partner for who will be granted the rights for VLR in North America.

YKP3089

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YKP3089 is a novel neurotherapeutic compound under development at SK Life Science. It has potential to be a versatile CNS drug with efficacy in epilepsy, anxiety, neuropathic pain, bipolar disorder, dementia and schizophrenia among others.

YKP3089 show efficacy in a broad spectrum of animal models of epilepsy. YKP3089 shows potent efficacy in both electrical and chemical animal models of epilepsy and more interestingly in refractory epilepsy models. For example, YKP3089 shows ED50s at non-toxic dose levels at all 3 tested frequencies in the mouse 6-herz test. YKP3089 also protects against lithium-pilocarpine-induced intractable seizures.

In addition, positive effects were observed in many animal models of anxiety after IP and PO administration to both mice and rats. YKP3089 is more efficacious in the Bennett and Chung models of neuropathic pain compared to gabapentin. The novel compound shows a high safety margin with low potential for cardiovascular, genotoxicity and teratogenicity.

Phase 1 clinical trials were completed in the United States and data show a favorable PK profile with a half-life suggesting once-per-day dosing. YKP3089 was well-tolerated in single and multiple dose clinical trials with low incidence of adverse effects.

FELBAMATE: 14 YEARS POSTMARKETING UPDATE AND 20+YEARS OF CLINICAL USE

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Felbatol (felbamate) was approved for marketing in the United States in 1993, and at the time was the first antiepileptic agent (AED) approved by the Food and Drug Administration (FDA) since valproic acid in 1978. Felbatol was initially indicated as first-line monotherapy and adjunctive therapy in the treatment of partial seizures with and without generalization in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with the Lennox-Gastaut syndrome in children.

Although, prior to approval, the overall safety profile of Felbatol during double-blind and open-label clinical trials was favorable, during the first year of commercialization serious bone marrow and hepatic toxicity were reported. Approximately 110,000 patients were treated with Felbatol between August 1993 and August 1994. By October 1994, 33 cases of aplastic anemia had been reported in patients treated with Felbatol in the United States. These figures extrapolated to approximately 300 cases of aplastic anemia per 1,000,000 patients exposed to Felbatol. In August 2000 and in September 2007, two add cases of aplastic anemia were reported. The first in a 42 year old female and the later reported in a 14 year old postpubertal female.

Regarding this most recent case of aplastic anemia, thrombocytopenia, but not red cell anemia or leukopenia, occurred during the time of adjunctive therapy with Felbatol and Keppra. Felbatol was replaced by topiramate, and the thrombocytopenia resolved. Approximately 4 months later, the CBC declined dramatically and pancytopenia was diagnosed while the patient was on topiramate and phenobarbital. Aplastic anemia was confirmed by bone marrow biopsy.

To date, 18 cases of liver failure associated with Felbatol have been reported. Sixteen of these occurred by the end of October 1994 and two additional cases occurred within the next 2 years (1995 & 1996). Although Meda Pharmaceuticals have received no additional reports of liver failure, sporadic reports of liver enzyme elevations and drug-induced hepatitis

have been received. During this period the company estimates that close 45,000 patients have been exposed to Felbatol.

We reviewed all subjects treated for more than 2 years with felbamate at MINCEP. Overall, 77 persons met entry criteria; mean treatment time was 7.5 years with the longest 20.3 years; total patient years of treatment was 577. Significant weight loss (mean 5.1 kg; $p < 0.001$) occurred from pre to 1 year of FBM treatment, but weight was regained by the time of the last visit. No clinically significant changes in laboratory parameters occurred. Older age was associated with a significant decrease in felbamate clearance. Significant reduction in generalized tonic-clonic and simple partial seizures ($p=0.03$ and 0.02) was seen both at one year after initiation and at the time of the last visit.

GABAPENTIN - THE STORY GOES ON, AN UPDATE

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Despite off-patent and generically available worldwide, Clinical Trials.gov currently lists 63 formal studies with gabapentin (GBP), just completed, ongoing or about to start in 2008, in a broad variety of potential uses and indications, beyond the approved adjunctive treatment of partial onset seizures and neuropathic pains. Since the last Eilat-XIII conference, another regulatory trial for submission in Japan has been published, results are in line with known data from earlier European and US parallel group studies in adjunctive partial epilepsy, except for lower placebo response in Japan. In addition to SANAD, a number of further trials with a retention endpoint in various epileptic populations and treatment strategies including GBP, confirm the results obtained in the open randomized UK study. With a large body of consistent evidence of GBP´s effectiveness in neuropathic pain conditions, the latest US-, Canadian- and European treatment guidelines place the drug in their respective first choice category. Differences exist as to the wording exactly which neuropathic pain conditions are covered, the labeled ones only, or additionally those with published class I randomized controlled trials (RCTs). There is also growing solid evidence for a place of GBP in perioperative analgesia. From the multitude of other potential indications studied, RCTs in vasomotor hot flushes demonstrated significant benefit over placebo, with a similar effect size as estrogens, in the higher GBP dose range. Trials in areas of unmet medical need, but with difficult trial methodology, such as subjective tinnitus or alcohol, resp. substance abuse gave recently variable results, not supporting general usefulness of GBP in these conditions. In addition to extended release and prodrug formulations, structure-activity work on gabapentinoids, docking at alpha-delta subunits of calcium channels, are ongoing.

LAMOTRIGINE

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Lamotrigine (LTG) is available in over 100 countries and there is an estimated 8.6 million patient-years treatment experience (December 2007). It was originally marketed as an AED and recent trials have confirmed broad-spectrum efficacy in the seizure treatment of children, teenagers, adults and the elderly. Trials and meta-analyses have suggested that it is generally better tolerated than carbamazepine, although probably not more effective in treating partial seizures. It does not appear to be as effective as valproate in treating primary generalised seizures. It may worsen seizures in some syndromes, notably Dravet syndrome (severe myoclonic epilepsy of infants, SMEI). It has been used in a number of non-epilepsy indications. Several trials have shown that it is effective in treating bipolar mood disorders and, in contrast to some other treatments, is not associated with weight gain. Trials in patients with schizophrenia have not revealed convincing efficacy. Similarly, studies on neuropathic pain have generally failed to show benefit. The rate of skin rash is relatively low if slow escalation regimes are used and it has been safely re-introduced after initial rash using very slow escalation. In contrast to some other antiepileptic drugs it does not as appear to be associated with negative effects on cognition, sex hormones or sexual function. A number of case reports of lamotrigine overdose have recorded reduced conscious level and seizures, in at least one case in a person who did not have epilepsy; ataxia, vomiting and status epilepticus have also been reported. LTG concentrations fall in pregnancy and rise, to a lesser extent, with the monthly break in the oral contraceptive. Co-medication with valproate appears to decrease this effect markedly. The overall rate of congenital malformations in offspring born to mothers taking LTG monotherapy in pregnancy is low but there is a suggestion that oral clefts may be increased. There are conflicting reports with regard to the effect of lamotrigine dose on the rate of congenital malformations.

LEVETIRACETAM

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Levetiracetam (LEV, Keppra®) is approved as adjunctive therapy in adults and children with partial-onset seizures (POS), myoclonic seizures associated with JME, and generalized tonic-clonic seizures associated with IGE. LEV is also indicated in Europe as initial monotherapy of POS in adults. A 14-week placebo-controlled trial (LEV n=101; placebo n=97) has shown adjunctive LEV to be effective and well tolerated in children (4-16y) with POS (≥50% responder rate 44.6% LEV, 19.6% placebo, p=0.0002; 6.9% LEV patients experienced freedom from POS over the entire treatment period vs. 1.0% on placebo). A long-term extension trial (>1y) in this population showed LEV sustained efficacy (responder rate 54%) and good tolerability. No negative effect on neurocognitive functioning of adjunctive LEV (n=46) vs. placebo (n=27) was demonstrated (non-inferiority PP analysis) in children (4-16y; IQ ≥65) with POS after 8-12 weeks treatment. Adjunctive LEV (5-day) was also effective and well-tolerated in infants and young children (1m-<4y) with POS. The responder rate in average daily POS frequency (48-hour video-EEG) was 43.1% for LEV (n=58) and 19.6% for placebo (n=51; *p*=0.013). Commonly reported CNS-related adverse events in children included somnolence, headache, hostility, aggression, and nervousness. Clinical trials performed in different Asian populations confirmed the efficacy and good tolerability of adjunctive LEV in adults with POS. A new once-daily LEV extended-release formulation (LEV-XR) has been developed. Once-daily adjunctive LEV-XR (1000mg) in patients (12-70y; LEV XR n=79; placebo n=79) with POS, uncontrolled on 1-3 AEDs, reduced seizure frequency/week over placebo by 14.4% (p=0.038); 43% LEV-XR and 29% placebo patients achieved ≥50% reduction in POS frequency; 10.1% LEV-XR patients experienced freedom from POS over the entire treatment period vs. 1.3% on placebo. In this study, LEV-XR appeared to be better tolerated than in studies with immediate-release LEV.

OXCARBAZEPINE

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Oxcarbazepine is a drug developed out of Carbamazepine avoiding a metabolism pathway which generates epoxide. The latter is thought to be responsible for many side effects. However, the practical use of the drug has shown that many expectancies have been disappointing concerning the side effects, especially in co-medication. From the data available, it is not quite clear what is responsible for the drug. Studies in drugs which may be combined with Oxcarbazepine (i.e. Warfarin) have shown that the reduced enzyme induction has a positive effect compared to Carbamazepine. In combination therapy, as with anti-epileptic drugs however, the side effect profiles did not differ significantly from the one where Carbamazepine was in use. From the data available, it is not quite clear whether Oxcarbazepine itself which is a pre-drug, or its active metabolite 10, 11-dihydro-10-hydroxycarbazepine (monohydroxy derivative, MHD) is causing the side effects. In addition, the half-life of Carbamazepine is within values where extended release formulation could be profitable. Clinical experience shows that a brand of Oxcarbazepine (Trileptal) was changed in its pharmaceutical properties resulting in more side-effects with high dosing in epileptic patients. The studies with the extended release of Oxcarbazepine in comparison to classical Oxcarbazepine showed that in high-dosing, side effect profiles might be better. The analysis of the bio-viability shows that not only the active metabolite is more slowly released, but also Oxcarbazepine itself. Thus, from these data it can be shown that an extended release has a profit, particularly for patient where high-dosed Oxcarbazepine is used compared with classical Oxcarbazepine.

RUFINAMIDE

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Rufinamide is a novel triazole derivative approved in the European Union for use as adjunctive therapy in the treatment of Lennox-Gastaut Syndrome (LGS). A multicentre, double-blind, placebo-controlled trial of rufinamide as adjunctive therapy in 138 patients with LGS showed significant reductions in the frequency of total seizures (32.7% vs 11.7% for placebo), drop attacks (42.5% vs -1.4% for placebo) and seizure severity. Eight randomised controlled trials (RCTs) have been conducted to assess the efficacy and safety of rufinamide in various types of epilepsy in adults and children, with one further study in progress. Rufinamide is generally well tolerated: common treatment-related adverse events include headache, dizziness, fatigue, somnolence, vomiting and nausea. In Europe, the long-term safety of antiepileptic drugs, including rufinamide is being monitored in a novel registry of patients with LGS. Data are collected on seizures which are medically significant, as well as from carer-reported assessments of adaptive behaviour, resource use and quality of life. Additionally, a utility study designed to elicit societal values for health states associated with LGS and for adverse events resulting from pharmacological therapies used to treat this condition, was recently completed.

STIRIPENTOL DIRECTLY INCREASES THE ACTIVITY OF RECOMBINANT $GABA_A$ RECEPTORS

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Stiripentol(STP) has been used as add-on therapy for treatment of epilepsy for many years. Its effects on seizures have generally been considered to be indirect, through inhibition of metabolic enzymes acting upon other anticonvulsant agents. However, a recent report suggested that STP might also act at the neuronal level, increasing inhibitory GABAergic neurotransmission. We examined the effect of STP on the functional properties of recombinant $GABA_A$ receptors (GABARs) and found that it was a positive allosteric modulator of these ion channels. Its activity was influenced by the GABAR subunit composition, with greater potentiation of α3-containing receptors and reduced potentiation when the β1 or ε subunits were present. STP caused a leftward shift in the GABA concentration-response relationship, but did not increase the maximal response. Although the effect of STP shares some characteristics with the neurosteroids, its activity was not inhibited by a neurosteroid antagonist nor by a mutation that reduced positive modulation by neurosteroids. The differential effect of STP on β1- and β2/β3-containing receptors was not altered by mutations that control many other β-selective modulators. These findings suggest that STP acts as a positive allosteric modulator of the GABAR at a site distinct from many commonly used anti-convulsant, sedative and anxiolytic drugs. Its higher activity at α3-containing receptors as well as its activity at δ-containing receptors may provide a unique opportunity to target selected populations of GABARs.

STIRIPENTOL

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Stiripentol (STP) is a new antiepileptic compound made by Biocodex. It is structurally unrelated to all currently marketed anti-epileptic products. It proved to increase the GABAergique transmission through a barbiturate-like effect in the hippocampus of immature rats. Clinical studies were based on the fact that STP also inhibits cytochromes P450 (CYP3A4, CYP1A2, and CYP2C19) in vivo in epileptic patients, leading to increase plasma concentrations of concomitant antiepileptic drugs and to potentiate their antiepileptic efficacy. Whereas the studies in adult patients were disappointing, the adjunction of STP to clobazam and valproate proved to be efficient in Severe Myoclonic Epilepsy in Infancy (Dravet syndrome), a highly refractory epilepsy syndrome, and a limited number of patients was enough in two independent placebo-controlled trials in France and Italy. Designated as orphan drug by EMEA, STP was authorized for this indication in Europe in 2007. Additional studies were requiered, particularely to attempt to differentiate the role of STP per se and this of drug interactions. An european trial is currently designed for this purpose. Based on the large experience in compassionate use (600 patient-years), the most frequent adverse events are loss of appetite, loss of weight, drowsiness, hypotonia and ataxia, that are minimized by optimizing the dose of comedication.

TIAGABINE

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Tiagabine (GABITRIL®, Cephalon, Inc., West Chester, PA) is a highly selective GABA uptake inhibitor. As documented by *in vitro* experiments, the antiseizure activity of tiagabine is believed to be related to its ability to enhance the activity of GABA by inhibiting its uptake into glial cells and presynaptic neurons. Tiagabine appears to interact preferentially with the GAT-1 GABA transporter, and this may limit its activity to regions of the CNS in which GAT-1 plays a significant role (the cortex, cerebellum, and hippocampus).

Tiagabine is indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures. The efficacy of tiagabine as adjunctive therapy has been established in several clinical trials in patients with refractory partial epilepsy. In these trials, tiagabine was generally well tolerated; risk of certain CNS-related adverse effects (especially dizziness) is increased during titration period, but levels off during the fixed dose period. Tiagabine is not associated with increased drowsiness or cognitive adverse effects. Being a GABAergic drug, it has specific sedating mood effects, which on the other hand can lead to increased risk of behavioural adverse effects like depressive mood. Other behavioural adverse effects are nervousness, irritability, confusion and increased anxiety. Tiagabine may exacerbate absence and myoclonic seizures and may induce spike and wave activity/nonconvulsive status epilepticus, so it cannot be used in generalized epilepsies.

Modulation of GABAergic responses may be useful in many other neurological and psychiatric conditions apart from epilepsy. Therefore considerable amount of research has recently been focused for exploring the possibilities to use tiagabine in non-epilepsy indications. So far the studies in other indications like in generalized anxiety disorder have not reached statistical significance on the primary study endpoints. Moreover tiagabine's use has been associated with the occurrence of seizures in patients without epilepsy, which may further limit its use for other indications than partial epilepsy.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED DOSE-RANGING STUDY TO ASSESS THE EFFICACY, SAFETY, AND TOLERABILITY OF TOPIRAMATE ORAL LIQUID AND SPRINKLE FORMULATIONS AS AN ADJUNCT TO CONCURRENT ANTICONVULSANT THERAPY FOR INFANTS (1 TO 24 MONTHS OF AGE, INCLUSIVE) WITH REFRACTORY PARTIAL ONSET SEIZURES

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Objective: To compare the efficacy and safety of topiramate (sprinkle capsules or oral liquid) with placebo as adjunct to other antiepileptic drugs (AEDs) in reducing refractory partial onset seizure (POS) rates in infants.
Methods: This double-blind, international study was conducted from September 2005 - June 2007. Patients (N = 149) with clinical or EEG evidence of refractory POS were randomized (1:1:1:1) to receive topiramate 5, 15, or 25 mg/kg/day or placebo for 20 days with their current AEDs. Topiramate dosing was initiated at 3 mg/kg daily, then uptitrated every 3 days to the assigned dose or maximum tolerated dose. Reduction in seizure rate was assessed as the difference between baseline and endpoint 48-hour video-EEGs. The primary efficacy analysis compared each dose group with placebo, using a step-down procedure.
Results: Mean age of the 130 patients who completed was 12 months, 52% were boys, 61% were white. There was no significant difference ($p = 0.97$) in median percentage reduction from baseline in daily POS rate between topiramate 25 mg/kg (20.4%) and placebo (13.1%). Lower doses were not formally tested, but nominal p-values for these comparisons showed no treatment effect ($p = 0.97$ for the 15-mg/kg/day dose; $p = 0.91$ for the 5-mg/kg/day dose). Treatment-emergent fever, diarrhea, vomiting, anorexia, weight decrease, somnolence, and viral infection, occurred more frequently (≥10% difference) with topiramate.
Conclusion: Efficacy was not demonstrated using topiramate 5, 15, or 25 mg/kg/day as adjunctive treatment for refractory POS in infants 1 to 24 months old. No new safety concerns were noted.

VIGABATRIN AND MRI ABNORMALITIES

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Vigabatrin (VGB) is an AED first approved in Europe in 1989 and recently accepted for review by the US FDA. VGB is currently available in over 50 countries as adjunctive therapy for refractory complex partial seizures (CPS) and as monotherapy for infantile spasms (IS), with an estimated 1.7 million patients exposed. However, regulatory approval in the US has been delayed in part by the finding of histopathologic changes, termed intramyelinic edema (IME), in rodents and dogs exposed to vigabatrin and by reports of MRI abnormalities in a case series of children treated with vigabatrin for IS.

Data collected to investigate these findings include (1) a retrospective analysis of 332 MRI examinations of 205 children treated with vigabatrin for IS, and (2) re-analysis of 2,074 MRI examinations of 668 subjects in clinical trials of vigabatrin for the treatment of CPS. In IS, the estimated prevalence of high T2 MRI signal abnormalities was significantly higher among vigabatrin-treated than vigabatrin-naïve subjects (22% versus 4%; $P < .001$). Of nine subjects with at least one subsequent determinate MRI, resolution of MRI abnormalities occurred in six —vigabatrin had been discontinued in four. In contrast, in CPS 14.2% of vigabatrin-exposed subjects (95% CI, 11.5% to 17.3%) had high T2 MRI signal abnormalites compared with 13.1% of vigabatrin-naïve subjects (95% CI, 8.7% to 18.7%). This difference was not statistically significant.

Vigabatrin is associated with MRI abnormalities in infants treated for IS. These MRI abnormalities generally resolve completely, even in subjects who remain on vigabatrin therapy. In older children and adults with CPS, there is no association of vigabatrin therapy with MRI abnormalities. These data add to the body of information allowing epileptologists to more accurately balance the benefits and risks of vigabatrin treatment.

UPDATE ON ZONISAMIDE

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Zonisamide is licensed (US, Europe) for the adjunctive treatment of partial seizures in adults. A naturalistic open-label flexible-dose study of adjunctive treatment of partial seizures found 44.2% of patients responding and 15.9% of patients being seizure-free in the last trial month (n=208), with a median decrease of 41.1% in seizure frequency. 15.3% of patients dropped out due to adverse events. In an open-label extension study to a randomised placebo-controlled trial in 317 patients with partial seizures, retention rates at 1, 2 and 3 years were 65.3%, 44.5% and 28.8%. 21 patients (6.6%) were seizure-free for any 12 months during the trial. The most common reasons for discontinuation were insufficient therapeutic benefit (n=55, 17.4%) and AEs (n=70, 22.1%). A two-arm non-inferiority study with carbamazepine as active comparator in patients newly diagnosed with partial epilepsy is ongoing. The primary parameter is the proportion of patients seizure-free for at least 6 months. Two placebo-controlled adjunctive treatment studies are ongoing in treatment-resistant primary generalised tonic-clonic seizures and myoclonic seizures respectively. The primary parameter of these 3-month studies is the proportion of patients with ≥50% seizure frequency reduction. To further investigate cognitive function during adjunctive zonisamide treatment of partial seizures, a randomised open-label study with valproate as active comparator is ongoing in patients on carbamazepine monotherapy. After a 10-week flexible dosing period, a fixed-dose period of 2 weeks follows. Outcome parameters are the FePsy computerised neuropsychological test (primary), POMS and ABNAS (secondary).

OXCARBAZEPINE MODIFIED-RELEASE (MR) FORMULATION

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In order to achieve satisfying tolerability, the pharmakokinetic and -dynamic properties of an antiepileptic drug (AED) are particularly important in patients with intractable epilepsies who require high-dose treatment and/or combinations. The immediate-release (IR) formulations of oxcarbazepine (OXC) which were hitherto exclusively available in Germany, lead to a rapid and steep rise of the serum concentration of OXC and its major anticonvulsant metabolite (MHD). Especially in patients on higher dosages neurotoxic symptoms such as vertigo, blurred or double vision or ataxia rather frequently occurred and prevented to reach satisfactory efficacy. In these cases a distribution to a three- or even-four-times application was necessary and still was often not sufficient to allow a dosage increase. A formulation with lower and serum peak concentrations should therefore be helpful to optimize OXC treatment in such patients.
Prior to the labelling of an OXC-modified-release (MR) formulation (Apydan extent®, Desitin Arzneimittel GmbH, Germany) in January 2008, we could show in a small patient series that even the OXC formulation available in Scandinavian countries and offering a less marked serum peak after intake helped to reach better tolerability, when patients were switched from OXC IR in identical dosages.
Therefore it is very satisfying that finally the OXC MR formulation is available for clinical use. First experiences clearly show the amelioration of the OXC therapy options and the unequivocal benefit of the patients requiring high-dosage OXC.

VALPROIC ACID (DIVALPROEX SODIUM) EXTENDED-RELEASE (ER) FORMUALTION

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Divalproex-ER (Depakote®ER, Abbott, [ER]) was developed with the expectation of improved compliance and tolerability. A meta-review of ER studies has shown its' superior tolerability, while compliance data is still being acquired. The "functional" half-life of ER has been determined. Net-zero-order extended absorption for ER has been identified and is clearly distinct from non-sustained-release, conventional enteric-coated, delayed-release [DR] divalproex or enteric-coated particles, VPA syrup or liquid filled VPA capsules. While ER is approved for QD administration, DR is not; a structured simulation shows marked fluctuation in VPA concentrations with QD DR administration compared to QD ER. A subsequent clinical report temporally associates transient clinical toxicity and breakthrough seizures with inadvertent and/or intentional pharmacy substitution of QD DR for QD ER in epilepsy patients. Recently completed studies in the GAERS & kainate rat epilepsy model indicate that total *peak* plasma VPA concentrations are not more efficacious than continuous intravenous VPA infusion. Hence, *peak* seems not to be required for seizure reduction; exposure (area under the plasma-concentration-time curve, AUC) appears to be the relevant kinetic/dynamic metric, giving further impetus for the clinical use of ER over the DR formulation. Minimal variability in lot-to-lot mg potency and tablet dissolution indicates predictability in the performance characetericstics of the ER formulation, which has implications for patient safety and the conduct of AED bioequivalence studies. Abbott recently completed several pediatric trials with DR in epilepsy, bipolar disorder and headache prophylaxis, permitting an additional 6-month period of sales exclusivity before introduction of generics formulations (end of July 2008) in the USA. A prospective, placebo-controlled trial is being conducted concerning the pharmacodynamic EEG effect of small changes in total and free VPA concentration, over a range of 30-100 mg/L via constant infusion of intravenous sodium valproate, within the same patient, with paroxysmal photosensitive response.

Overall, even though DR celebrates 25 years of use in the USA and various sodium valproate/valproic acid formulations 30+ years use elsewhere in the world, clinicians are still learning about the clinical utility of divalproex/VPA and it's unique ER formulation(s).

LAMOTRIGINE EXTENDED RELEASE PHARMACOKINETICS AND EFFICACY IN PATIENTS WITH EPILEPSY

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Objective: To review the pharmacokinetics (PK) and efficacy of lamotrigine extended-release (LTG-XR) in patients with partial and primary generalized tonic-clonic (PGTC) seizures.
Background: Extended release antiepileptic drugs (AEDs) may improve tolerability and effectiveness in comparison to immediate release preparations, by reducing serum concentration fluctuations and improving compliance. The results from trials with once daily LTG-XR will be presented.
Design: Patients 13 years or older were enrolled in an open-label PK trial of conversion to LTG-XR from LTG-IR, and double-blind, placebo-controlled, international add-on trials in partial and PGTC seizures.
Results: 1) Upon conversion from LTG-IR (n=44), steady-state trough concentrations for LTG-XR were equivalent to or higher than those of LTG-IR independent of concomitant AED. A reduction in the LTG Cmax was observed for LTG-XR compared to LTG-IR resulting in a decrease in the peak to trough fluctuation in LTG concentrations. 2) In the partial seizure study (LTG-XR: n=116, PBO: n=120), seizure reductions were 46% (LTG-XR), 24% (PBO), p=0.0004). 3) In the PGTC study (LTG-XR: n=76, PBO: n=77), seizure reductions were 76% (LTG-XR), 30% (PBO), p<0.0001.
Safety outcomes were comparable to previous experience with LTG IR.
Conclusions: 1) Conversion from twice-daily LTG-IR to once-daily LTG-XR can be done on a milligram to milligram basis with maintenance of LTG trough concentrations. 2) LTG-XR is efficacious and well tolerated in patients with partial and PGTC seizures.

EPILEPSY AND NEUROPATHIC PAIN

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Some antiepileptic drugs (AEDs) have been found empirically to provide a measure of pain relief in patients with peripheral neuropathies. Although the analgesic mechanism(s) of AEDs is not well understood, it is widely presumed to be due to the suppression of epileptiform activity in CNS pain pathways. This hypothesis, however, does not account for the fact that some AEDs have analgesic efficacy while others don't. This presentation will consider an alternative possibility. The proposal is based on the accumulating evidence that ectopic discharge originating in the peripheral nervous system (PNS) is the main driver of neuropathic pain. Specifically, ectopia is: 1) the primary nociceptive signal underlying spontaneous neuropathic pain, and 2) a key factor that triggers and dynamically maintains central sensitization, and hence tactile allodynia. At the time of pain onset in rodent models the bulk of the ectopia originates within the dorsal root ganglion (DRG) and is carried centrally in A-beta afferents. The resulting pain and central sensitization may be partially due to upregulation and abnormal release from these neurons of peptides normally associated with C-nociceptors. Such upregulation is one of the consequences of axotomy-induced reorganization of gene expression in DRG neurons. Another consequence is altered expression of ion channels, and the resulting enhancement in affected DRG neurons of depolarizing afterpotentials and high-frequency subthreshold oscillatory potentials. The newly emergent resonance of these neurons enhances their fundamental electrogenesis, and promotes ectopic repetitive firing. A broad range of AEDs that are membrane channel ligands and suppress membrane hyperexcitability have analgesic efficacy. In contrast, AEDs that act synaptically, rather than on membrane excitability, tend to be ineffective as analgesics.

AEDs AND BIPOLAR MOOD DISORDER

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Bipolar mood disorder is a very different illness from epilepsy, yet, with the exception of lithium, all current mood stabilizer drugs are based on anti-epileptics. Understanding why this is the case, is severely hampered by our lack of understanding of the origins of bipolar disorder and the mechanism of drug action. We have developed two model systems to examine mood stabilizer function at the cellular level. The first is a neuronal model based on DRG sensory neurons and enables us to examine effects on primary neuronal cultures, whilst the second, the social amoeba *Dictyostelium* is a genetically tractable system that enables us to probe the underlying mechanism of drug action. Using these systems, we have established that altered inositol phosphate (InsP) signalling is a common target of lithium, valproic acid (VPA) and carbamazepine. In this talk, I will focus on how VPA mediates its effects on cell behaviour and (InsP) signalling, and describe how we have used our cell models to probe the structure-function of VPA isomers and derivatives.

THE CLINICAL USE OF AEDS IN THE TREATMENT OF ACUTE SYMPTOMATIC SEIZURES

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Acute symptomatic seizures are defined as seizures which occur at the time of, and are caused by, an acute systemic or cerebral insult. These seizures although epileptic in nature are not usually considered to constitute epilepsy, although over one third of patients with acute symptomatic seizures subsequently develop epilepsy. The seizures may require antiepileptic drug therapy, but the approach to therapy differs from the approach to epilepsy in a number of ways. The primary goal of therapy is to alleviate or reverse the underlying cause: this takes preference over antiepileptic therapy per se, although both may be needed. In acute structural brain insults
(eg stroke, trauma, infection etc) it is usual to divide seizures into 'early' and 'late' categories with different therapy and prognosis. The role of prophylaxis with antiepileptic drugs after acute symptomatic seizures is controversial, although there is a lack of evidence of clear benefit. If antiepileptic drug prophylaxis is decided upon, how long to administer therapy is also not known. Antiepileptic drug therapy can be complicated by the therapy of the underlying cause, especially if this involves the use of immuno-suppresive drugs or antibiotics, or in such conditions as porphyria or hepatic failure. Many drugs are known to precipitate seizures in susceptible individuals and these may also complicate therapy.

THE USE OF AEDS IN NON-EPILEPTIC DISORDERS OF THE CENTRAL NERVOUS SYSTEM - CLINICAL PERSPECTIVES

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Antiepileptic drugs (AEDs) have been used for a variety of conditions affecting the central nervous system, other than epilepsy. These include psychiatric disorders -mood disorders, anxiety disorders, agitation and intermittent explosive disorders and alcoholism- and pain syndromes including migraine and muscle tension headaches.

Mood disorders: Carbamazepine (CBZ) was the first AED to be prescribed in psychiatric disorders in the 1970's for the treatment of manic episodes in rapid cycling bipolar disorders that had failed to respond to lithium. In randomized double-blind placebo-controlled studies, CBZ was found to display antimanic, anti-depressant and mood stabilizing properties. Valproic acid (VPA) was the next AED to display anti-manic properties and mood stabilizing properties, particularly in patients with rapid cycling bipolar disorders of neurologic or medical cause. On the other hand, VPA did not exhibit antidepressant effects. Of note, while both AEDs were found to show efficacy in rapid cycling bipolar disorders, failure to respond to VPA was a predictor for a good response to CBZ.

Since the establishment of mood stabilizing properties of these two AEDs, the efficacy of most of the new AEDs has been tested in bipolar disorders, but to date, only lamotrigine (LTG) was found to exhibit mood stabilizing properties as well as antidepressant properties in major depressive episodes of bipolar but not unipolar disorders. On the other hand it does not have antimanic effects. Oxcarbazepine is another new AED with antimanic properties, but no proven prophylactic effects in controlled studies.

Anxiety disorders: Benzodiazepines are among the oldest agents used in the treatment of generalized anxiety disorders. Among the first generation AEDs, VPA has been found in several open trials to prevent panic attacks induced by intravenous sodium lactate infusions as well as in patients with spontaneous panic attacks. Gabapentin has been found to be effective in controlled studies of social phobia, while several double-blind controlled studies have established efficacy of pregabalin in the treatment of generalized anxiety disorders.

Various AEDs have been tested for the treatment of post-traumatic stress disorder (PTSD). Small double-blind controlled studies of LTG and open trials of VPA have suggested a beneficial effect.

Aggressive behavior: Double-blind controlled studies have suggested efficacy of CBZ in patients with intermittent dyscontrol disorder as well as in agitated patients with dementia. Open trials with VPA have also suggested a beneficial effect in agitation associated with dementia in geriatric patients.

Alcoholism: Several randomized placebo-controlled studies have established the efficacy of topiramate (TPM) in the treatment of alcoholism. One double-blind-placebo controlled study with GBP also suggested efficacy, while in addition, double-blind placebo controlled studies with VPA demonstrated its efficacy in decreasing alcohol use and stabilizing mood symptoms in acutely ill patients with bipolar disorder and alcoholism. Finally CBZ and OXC have been tested in a variety of double-blind controlled studies and revealed efficacy in minimizing alcohol withdrawal symptoms in patients undergoing detoxifications.

Are AEDs associated with increased suicidality? One cannot examine the use of AEDs in psychiatric disorders without taking into consideration the recent alert issued by the Food and Drug Administration in the USA suggesting that patients randomized to AEDs exhibited twice the prevalence of suicidal ideation and behavior (o.43%) than those randomized to placebo (0.22%) during regulatory studies of 11 AEDs. While suicidal ideation and behavior have been reported with several AEDs including barbiturates, vigabatrin (VGB), TPM, zonisamide (ZNS) and (LEV), this alert yielded unexpected data, as it stated that the increased suicidality was observed in all AEDs including those with mood stabilizing properties. The problem of this alert is that suicidality in epilepsy is a complex problem with multiple inter-related variables. This issue will be discussed in the presentation in great detail.

Headaches: Various AEDs have been found to be effective in the treatment of headaches. Topiramate and VPA are the two AEDs with the best established prophylactic prevention of migraines in double-blind controlled studies, followed by GBP. Gabapentin has been also found to be effective in the treatment of daily tension headaches as well as of high altitude headaches.

TOWARDS A BETTER UNDERSTANDING OF AED SITES OF ACTION: IMAGING EVALUATION OF ANTIEPILEPTIC DRUGS

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Neuroimaging, playing an increasingly important role in the development and evaluation of psychotherapeutic agents, has been used less extensively to study antiepileptic drugs. Magnetic resonance spectroscopy has shown vigabatrin elevates brain GABA levels, at doses up to 3000 mg/day, associated with improved seizure control, until GABA levels reached 2.5 mmol/kg. Increased brain homocarnosine also parallels improved seizure control. Patients who had a good clinical response to vigabatrin had lower pretreatment GABA levels and greater increase on drug than non-responders. Similar results were reported for topiramate and gabapentin.
PET studies investigated AED effects on CMRglc, CBF, and several receptor systems. Barbiturates and benzodiazepines led to much greater reduction than phenytoin, carbamazepine, ethosuximide, valproic acid, or vigabatrin. There was a strong relation between increased CSF GABA and reduced CMRglc. Children treated with VGB had reduced 11C-flumazenil binding, suggesting down-regulation of GABA-benzodiazepine receptors, which might have developmental implications. VGB was associated with decreased basal ganglia SPECT D2 receptor ligand 123I-IBZM binding, a finding possibly related to drug-induced psychosis. 18F-FCWAY100635, a 5HT1A agonist, binding was not affected by CBZ, VPA or lamotrigine, suggesting low serotoninergic effects for these drugs. A small pilot study found no statistically significant difference in 11C-verapamil binding, a marker for multiple drug transporter
(p-glycoprotein) function, ipsilateral and contra-lateral to seizure foci. These studies show the potential, yet to be exploited, for using imaging to study AED mechanisms, effects on brain function, and as surrogate markers for predicting efficacy and toxicity.

CREATING OPPORTUNITIES TO FUND NEW THERAPIES FOR EPILEPSY

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The Epilepsy Therapy Project (ETP) is unique in the CNS translational non-profit sector. Our goal is to advance the development of new therapies for epilepsy. Our mission as a venture philanthropy group is to be the focal point, the resource center and the facilitator for one-stop-shopping for scientists, entrepreneurs, emerging companies, mature pharma companies and investors. ETP provides Translational Research Grants for developing ideas; Commercialization Grants to help entrepreneurs take extra steps that will help in acquiring capital; non-dilutive Loans support young companies; Venture Philanthropy funding to demonstrate confidence in a company. Emerging companies have advice needed to make decisions for their business plans, avenues of development, clinical and regulatory issues. ETP can provide: Scientific Advisory Boards for unbiased review of preclinical data and mechanistic issues; Clinical Advisory Boards to advise on protocol design, investigator training, case report form design, statistical analysis plans, etc.; Business Advisory Boards to advise on product and company development strategy and commercialization, in addition to broader lifecycle opportunities; Clinical Trials Consortium for proof-of-principle clinical trials. ETP *invest* in our mission to advance products and platforms closer to the patients with epilepsy who need them the most. ETP is a focal point for scientists and emerging companies addressing the pipeline gap. Work with us to help us to foster development of new therapies for the millions of people worldwide with uncontrolled seizures.

RAPID ONE STEP ACCURATE, CHEAP AND RELIABLE METHOD FOR CYP2C9 GENOTYPING

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Introduction: The CYP2C9 isoenzyme of the cytochrome P450 system (CYP) is responsible for the oxidation of up to 15% of drugs that undergo phaseI metabolism, including the anticonvulsant agent phenytoin and the anticoagulant agent warfarin. Both drugs have narrow therapeutic window (NTI). Two of CYP2C9 variants (*2 and *3) encode for a protein with decreased enzymatic activity. Rapid genotype analysis of CYP2C9 prior to initiation of these drugs may be of clinical importance.
Objective: To compare the efficiency and accuracy of two genotyping methods of CYP2C9.
Methods: Human genomic DNA was extracted from peripheral leukocytes by DNA purification kit (5prime, USA). DNA samples were sequenced around both variants in order to determine control samples for all existing genotypes: CYP2C9 *1/*1, *1/*2, *2/*2, *1/*3, *3/*3. 37 DNA samples were genotyped for CYP2C9*2 and 28 - for CYP2C9*3, by two methods: (1) High-resolution melting (HRM) using a Rotor-Gene 6000 instrument. Single base variations can be detected based on their melting analysis assay with unlabeled primers. (2) Two steps genotyping consisting of polymerase chain reaction (PCR) followed by digestion with restriction enzyme.
Results: The two genotyping methods disagree in 1out 37 samples for CYP2C9*2 allele and in 2 out of 28 samples for CYP2C9*3. Those samples were genotyped by direct sequencing. The HRM based method was concordant with the sequencing. Further more, the HRM based method produced results on the first run, while only 90% were amplified on the first attempted PCR. Genotyping lasted 3 hours for HRM and 6 hours for PCR followed by restriction enzyme digestion.
Conclusion: HRM analysis provides a simple, rapid and accurate method for CYP2C9 genotyping. Its clear advantages over the traditional method based on PCR and digestion with restriction enzyme are its higher detection rate and the shorter time needed to provide genotype analysis. The unlabeled primers reduced markedly the cost of the genotype analysis in comparison to other Real-time PCR procedures.

DRUG-RESISTANT FOCAL EPILEPSIES: SURGICAL TREATMENT

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In spite of numerous modern anticonvulsants, drug therapy fails in 30-35% of epileptic cases. Surgical treatment of drug-resistant epilepsy gives new opportunities to challenge this grave disease.

The system of clinical-neurophysiologic diagnosis developed at the Institute basing on a complex of modern neurophysiologic (EEG, ECoG, ESCG, SEEG) and neuroimaging (MRI, CT) technologies aimed at obligatory preoperative and intraoperative precision of the epileptic focus site served the basis of strictly differentiated approach in decision-making for strategy, tactics, and extent of adequate surgical treatment with individual peculiarities of epileptogenesis in different forms of epilepsy taken into consideration.

The following strict indications formed the criteria of protocol patients' selection for surgery: obligatory diagnosis verification according to ILAE classification and standards (1997); frequent epileptic seizures (2-3 per month, at least); progredient course of the disease (pharmacoresistance) in spite of purposeful regular antiepileptic therapy using up-to-date basic drugs for a year at least; dynamic EEG monitoring findings indicating a clearly localizable stable epileptic focus with direct clinical and electrophysiologic correlations related to its site.

The results of surgical treatment of 350 drug-resistant temporal epilepsy patients aged 18-52 were analyzed. A conclusion was made that in monotemporal epilepsies an open intervention, i.e. anterior temporal lobectomy is optimal, with positive effect in 78%. Unilateral stereotaxis (amygdalotomy, hippocampotomy) is less effective (51%). Certain minimally invasive methods were developed at the Institute to treat bitemporal epilepsy: these are callosotomy, neurostimulation of extracerebral information areas, bilateral stereotaxic intervention.

TDM AND PHARMACOKINETIC VARIABILITY OF NEW AEDS IN CHILDREN

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Purpose: To study age-dependent pharmacokinetic variations of new antiepileptic drugs (AEDs) in children with epilepsy, based on the dosage, measured serum concentrations and calculated oral clearance in different age groups.
Material and methods: The study includes patients admitted to The National Centre for Epilepsy in Norway in 2007, 285 children (age 0-15 years) and 78 adults (age 16-57 years). Clinical data regarding the use of AEDs, dosage, serum concentrations, age, and body weight were collected from the medical records, and thus, oral clearance was calculated for the various AEDs in age groups 0-1, 2-6, 6-15 years old and adults.
Results: The new drugs used included: levetiracetam and lamotrigine (both used in 25 % of the children), oxcarbazepine (7 %), topiramate (15 %), and zonisamide (3 %). The older AEDs valproate (20 %) and carbamazepine (5 %) were also included, as comedication with these drugs may affect metabolism of the new AEDs. The oral clearance for all AEDs showed age-dependent changes from 150-200 % (except for smaller changes with zonisamide), with the highest values in the youngest children (0-6 years) compared to the older children and adults. Serum concentrations were generally in the lower part of the reference intervals, although higher doses per kg body weight were given in the children compared to the adults. Comedication with valproate and carbamazepine was taken into account and contributed to the greatest variation in clearance of lamotrigine, ↓65 % and ↑35 %, respectively.
Conclusion: TDM is important for an optimal treatment of children with epilepsy. Individualization of the therapy should ideally include a clinical pharmacokinetic evaluation due to the fact that the youngest children have the highest clearance for all the AEDs included, and consequently, achieve lower serum concentrations. Age related change in clearance is an important factor for variability in measured serum concentrations.

EVALUATION OF ENANTIOSPECIFIC ANTIALLODYNIC ACTIVITY OF PROPYLISOPOPYLACETAMIDE, AN AMIDE DERIVATIVE OF A CHIRAL CONSTITUTIONAL ISOMER OF VALPROIC ACID

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Propylisopropylacetamide (PID) is a chiral CNS-active constitutional isomer of valpromide, the amide derivative of the major antiepileptic drug valproic acid (VPA).
Purpose*:*
a) To evaluate the enantiospecific activity of PID on tactile allodynia in the Chung (spinal nerve ligation, SNL) model of neuropathic pain in rats,
b) To evaluate possible sedation at effective antiallodynic doses, using the rotorod ataxia test,
c) To investigate enantioselectivity in the pharmacokinetics of (R)-PID and (S)-PID in comparison to (R,S)-PID following i.p. administration, and
d) To determine electrophysiologically whether PID has the potential to affect tactile allodynia by suppressing ectopic afferent discharge in the peripheral nervous system (PNS).
Method: Racemic PID and its individual enantiomers were administered i.p to 10 rats in a crossover randomized double blind protocol and their antiallodynic activity was assessed. The ED_{50} values were evaluated in the spinal nerve ligation model 60, 120 and 180 min after dosing corresponding to the time to peak antiallodynic effect of (S), (R,S) and (R)-PID respectively.
Plasma concentrations were determined by a gas chromatograph (G.C.) equipped with a chiral column following administration of 60 mg/kg of the racemic mixture and the two stereoisomers i.p. to rats. Electrophysiological recordings were made from the L5 dorsal root (DR) in 6 rats using the teased fiber method, followed by Passive observation of neural activity 60 min after i.p. administration of 80 mg/kg racemic PID.
Results : (R)-, (S)- and (R,S)-PID produced dose-related reversal of tactile allodynia with ED_{50} values of 46, 48, 42mg/kg, respectively. The individual PID enantiomers were not enantioselective in their antiallodynic activity. No sedative side-effects were observed at these doses. Following i.p. administration of the individual enantiomers, (S)-PID had lower clearance (CL) and volume of distribution (V) and a shorter half-life ($t_{1/2}$) than (R)-PID. However following administration of (R,S)-PID, both enantiomers had similar CL and V, but (R)-PID had a longer $t_{1/2}$. Systemic administration of (R,S)-PID at antiallodynic doses did not suppress spontaneous ectopic afferent discharge generated in the injured peripheral nerve, suggesting that its antiallodynic action is exerted in the CNS rather than the PNS. Both of PID's enantiomers, and the racemate, are more potent antiallodynic agents than VPA (ED_{50}=269mg/kg) and have similar potency to gabapentin. Consequently, they have the potential to become new drugs for treating neuropathic pain.

THE VALUE OF CORTICOSTEROIDS TREATMENT BY PAINFUL LEGS AND MOVING TOES (PLMT) SYNDROME WITH CEREBRAL SEIZURES

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Background: PLMT syndrome's clinical image is characteristic and includes, mostly, pain in the feet or legs accompanied by spontaneous involuntary movements of the toes. It usually appears in patients with Hashimoto disease.
Material & methods: We examined three patients with PLMT, two with Hashimoto disease. They all had a complete neurological and neurophysiological control (24-hours electroencephalographical registration-EEG and electromyography -EMG).
We recorded, estimated and compared the results between them before and after the corticosteroids treatment.
Results: The results showed a significant improvement of EEG paroxysmal hyperactivities antimicrosomial for the cases of Hashimoto disease.
Conclusions: Issuing corticosteroids is basic for PLMT treatment in patients with or without Hashimoto disease.

LICL/PILOCARPINE-INDUCED STATUS EPILEPTICUS AND ISCHEMIC HIPPOCAMPAL LESION INDUCED BY ENDOTHELIN-1: TWO MODELS OF EPILEPTOGENESIS IN IMMATURE RATS

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Early brain injury represents frequent cause of epilepsy later in the life. In spite of clinical importance, models of epileptogenesis in the immature brain are limited.
Initial insult (SE or ET-1 injection) was induced to Wistar rats 12 or 25 days old. Development of animals was followed up to adulthood. Spontaneous seizures were detected by video-EEG monitoring. Both acute and chronic morphological changes were detected.
Both insults affected psychomotor development only minimally and some changes occurred only in SE model. In SE model cognitive impairment was less severe but still significant in P12 rats whereas P25 rats were severely impaired. In contrast, injection of ET-1 resulted in cognitive deficit only in P12 group. The video-EEG monitoring indicated spontaneous seizures in a subpopulation of both groups of animals with SE, but epilepsy was more severe in P25. In ET-1 model, epilepsy was more severe in P12 animals. Morphological analysis revealed changes in both models. In SE model severity of damage was higher in P25 group, whereas P12 animals exhibited more extensive lesion in ET-1 model.
SE and hippocampal ischemic lesion induced behavioral changes, cognitive impairment and morphological changes which were model and age-dependent. Both of them can be used to study pathophysiology of early brain injury and to search for new therapeutic strategies.

POTENTIATION OF INHIBITORY SYSTEMS RESULTS IN DIFFERENT EFFECTS IN DEVELOPING RATS

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Potentiation of inhibition is a common mechanism of action of antiepileptic drugs. To study this mechanism in developing animals epileptic afterdischarges were chosen. Rhythmic electrical stimulation of sensorimotor cortical area allows to evaluate different phenomena: movements induced by stimulation (i.e. direct activation of motor system), epileptic afterdischarges (ADs) characterized by spike-and-wave rhythm in the EEG (thalamocortical phenomenon), and accompanying clonic seizures. Drugs influencing GABAergic inhibition phenobarbital, valproate, clonazepam, midazolam and bretazenil, allopregnanolone and pregnanolone were able to suppress ADs and clonic seizures. Benzodiazepines exhibited more powerful action against clonic seizures than against EEG ADs. These effects were observed in all three age groups and they were better expressed in older than in 12-day-old rats. Movements elicited by stimulation were suppressed only by phenobarbital. Drugs influencing both GABA-A and GABA-B receptors (progabide and an inhibitor of GABA reuptake NNC-711) were able to diminish intensity of both motor phenomena and shorten ADs in 18- and 25-day-old rats. GABA-B receptor agonist baclofen exhibited similar action against motor phenomena, but it moderately suppressed electrocorticographic ADs only in 12- and 25-day-old rats. Potentiation of adenosinergic inhibition with 2-chloroadenosine resulted in minimal effects on motor phenomena and a transient suppression of ADs with a rebound augmentation in 18- and 25-day-old rats.

Drugs potentiating action of GABA-A receptors were active at all developmental stages studied, there were only quantitative changes of action. In contrast, drugs influencing both types of receptors and GABA-B receptor agonist baclofen exhibited age-dependent action which differed among these three drugs. Effects of 2-chloroadenosine markedly differ from those of GABAergic drugs.

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α-FLUORO-2,2,3,3-TRAMETHYLCYCLOPROPANECARBOXAMIDE, A NOVEL POTENT ANTICONVULSANT DERIVATIVE OF A CYCLIC ANALOGUE OF VALPROIC ACID

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Valproic acid (VPA) is a one of the major antiepileptic drugs (AEDs) and is also approved for treating bipolar disorders and for migraine prophylaxis. VPA's use, however, is associated with two rare but severe side effects: hepatotoxicity and teratogenicity. In an effort to identify new compounds that are more potent and less toxic than VPA we have synthesized numerous halogenated derivatives of 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMCA) and their amides.
α-fluoro-2,2,3,3-tetramethylcyclopropanecarboxamide (α-F-TMCD) has merged as the most potent compounds of this series.
The anticonvulsant activity of α-F-TMCD was evaluated in the mouse (ip) and rat (po) maximal electroshock (MES), subcutaneous metrazol (scMet) tests, the mouse 6 Hz psychomotor seizure model, the hippocampal kindled rat model and the rat pilocarpine-induced status model. α-F-TMCD exhibited potent anticonvulsant activity in the scMet test (rat-ED_{50}=6 mg/kg, 120 fold more potent than VPA) and a protective index (PI=TD_{50}/ED_{50}) value of 20 and in the mouse (ED_{50}=38mg/kg, 7 fold higher than VPA) and a PI value of 3.2. In the hippocampal kindled rat and in the rat pilocarpine-induced status model
α-F-TMCD had ED_{50} values of 30 mg/kg and 23 mg/kg, respectivly. The ED_{50} values of α-F-TMCD in the 6 Hz psychomotor test were ED_{50}=57 mg/kg and ED_{50}=59 mg/kg at stimulation intensities of 32 mA and 44mA, respectively.
The embryotoxicity and teratogenicity of α-F-TMCD was evaluated in a mouse strain (SWV/Fnn) highly susceptible to VPA-induced teratogenicity. This compound, at doses of 336 mg/kg and 671 mg/kg, was shown to be non teratogenic. Only at dose 13 fold higher than the mouse scMet-ED_{50}, α-F-TMCD was toxic to the pregnant dams and to the embryos.
α-F-TMCD's broad spectrum and potent anticonvulsant activity and its high safety margin compared to VPA, makes this compound a promising candidate to become a new, potent and safe antiepileptic and CNS drug.

EFFICACY OF ZONISAMIDE IN A RARE CASE OF TYPE II SIALIDOSY

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Type II sialidosis is a rare autosomal recessive disease resulting from a deficiency of lysosomal sialidase characterized by dysostosis multiplex, Hurler-like phenotype, mental retardation, hepatosplenomegaly. and seizures. Mutations NEU1, result in progressive lysosomal storage of sialylated glycopeptides and oligosaccharides. Here we describe a case of a young woman aged 24 affected by mild type II Sialidosy. Diagnosis was confirmed by the detection of high urinary sialyloligosaccharides and by the lysosomal enzyme deficiency in fibroblasts cultured. The patient complains of generalised tonic–clonic seizures and daily spontaneous epileptic myoclonus localized in both arm since her infancy (myoclonic progressive epilepsy) treated with VPA, PB, CBZ, TPX and clonazepam. MRI showed a minimal cerebellar atrophy without any visible attaint to white matter. Polygraphyc VideoEEG recordings showed trains of high amplitude fast activity mixed with occasional multiple small spikes. Moreover, long-lasting discharges of myoclonic jerks of both arms were evoked by the attempt to maintain the posture. Myoclonic activity was associated with EEG fast activity on the frontocentral region. Seizure frequency and cognitive performances improved following the introduction of zonisamide at dosage of 50+100 mg\day and discontinuing CBZ, TPX and PB. At present our subject complains rare generalized seizure (less than 1 x month) and mild (and less frequent) mioclonic episodes. Good tolerance of zonisamide was obtained with slow titration.

ADJUNCTIVE ZONISAMIDE THERAPY FOR REFRACTORY SEIZURES

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Zonisamide (ZNS, 1,2 benzisoxazole derivative) has shown activity in various animal models of epilepsy throught several mechanisms mainly revolving on the block of seizure spread. Clinical experience with zonisamide has documented its efficacy in the treatment of epilepsy refractory to treatment with other antiepileptic drugs. We analysed the effects of add-on ZNS (300 mg/day) in patients with severe focal and generalized epilepsies treated with politerapy and/or VNS. Twenty patients (three lesional according MRI) partecipate (mean age 38.3 years); 16 (80%) were affected by partial seizures with or without secondary generalisation (although some of them experienced different seizures), 3 (15%) by Lennox-Gastaut (LG) syndrome and 1 subject suffered from myoclonic progressive epilepsy (MPE). All of them experienced unsatisfactory control despite a stable regimen of 2-3 AEDs (carbamazepine, lamotrigine, valproic acid/sodium valproate or phenytoin) and VNS treatment (8 pt). VideoEEG recordings showed 12 (60%) focal interictal spiking activity (IES) in frontal and fronto-temporal areas; 4 (20%) showed multifocal IES and 4 showed generalized interictal syndromic abnormalities (LG e MPE).
Two (10%) patients require to discontinue the treatment for major side effect (loss of weight and cognitive impairment), 7 (35%) didn't show significative changes, 11 (55%) improved by 50% . Our results suggest the usefulness of zonisamide in refractory epilepsy, while a very slow titration is recommended in order to reduce the initial side effects.

PREGNANCY OUTCOMES FOLLOWING LAMOTRIGINE MONOTHERAPY

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Purpose: To assess clinical significance of data from the North American Antiepileptic Drug Pregnancy Registry (FDA Alert 9/2006) that suggests association between exposure to lamotrigine (LTG) monotherapy during the first trimester of pregnancy and major congenital malformation (MCM).
Method: Eight pregnancies in six women, at delivery age between 25 -34 years with partial-onset seizures were retrospectively reviewed to determine offspring congenital abnormalities. All of the women have been receiving LTG monotherapy before and during pregnancy, between 2003-2007 yr.
Results: The mean pre-pregnancy and pregnancy daily dose of LTG was 240 m (100-450 mg) from 9 to 38 months - respectively: 9,10,11,16,18, 23, 34, 38 months. There were no MCMs in all offspring, but three of them had minor abnormalities. Two of the abnormalities resolved on their own: one was the vesicoureteral reflux (VUR) with mild hydronephrosis and the second was umbilical hernia. Only one anomaly: the polydactyl with the presence of 6 toes on one foot was surgically treated.
Conclusion: The increased major congenital malformations risk were not confirmed in the exposed offspring of observed mothers on long-term LTG monotherapy, however the group is too small to definitive conclusion concerning MCMs.

ADMISSION OF CHILDREN TO A REFERRAL CENTRE FOR EPILEPSY - DOES IT MAKE A DIFFERENCE?

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Purpose: To study the impact of admission to a referral centre for epilepsy on antiepileptic medication, seizure control, adverse effects, and daily life.
Material and methods: The study includes children admitted to The National Centre for Epilepsy in Norway. Data were collected from the medical records of 261 children, and a questionnaire regarding pharmacological treatment, seizure control, and daily life was sent to their parents three months after discharge.
Results: 157 questionnaires (60 %) were completed and returned. Levetiracetam, valproate and lamotrigine were the most frequently used antiepileptic drugs (AEDs) before, during and after the stay at the centre. Levetiracetam was the only drug being more frequently used at discharge/three months after discharge than at admission. Dosage adjustments were made in 83 % of the patients following measurement of serum concentrations and clinical evaluation. The number of adverse effects was reduced by 20 %. Two thirds of the children suffered from one to five comorbid conditions. The number of patients that were seizure free increased by 43 %, and about one third of the patients were seizure free three months after discharge (n=47). According to the parents, 40 % of the children experienced better seizure control, and 47 % of the families experienced a better everyday life after the stay.
Conclusion: Optimalization of the pharmacological treatment of children with epilepsy following a stay at the referral centre has an important impact on their daily life, and the comprehensive care approach is important.

PREVALENCE OF ACUTE REPETITIVE SEIZURES (ARS) IN THE UNITED KINGDOM

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Rationale**:** "Acute repetitive seizures" (ARS) is a term to describe a condition manifested by multiple major seizures occurring over a relatively brief period of time -generally 24 hours- in patients with epilepsy. There is limited information regarding the epidemiology of ARS in the general population.

Methods: We performed a historical cohort study using data from the United Kingdom General Practice Research Database (GPRD) to identify all incident and prevalent cases of active epilepsy in 2005. From among this group, we identified individuals at risk for ARS. This included those with "catastrophic epilepsy syndromes of childhood" and those with a history of cluster seizures in the context of other epilepsy syndromes.

Results: We identified 21,010 people with active epilepsy in the database in 2005. (Prevalence 7.2/1000; age adjusted to the European Standard Population, 6.7; incidence 50/100,000 per year, age-adjusted 48/100,000). We identified 630 people at risk for ARS. The prevalence of "catastrophic epilepsy syndromes of childhood" in the general population was 1.1/10,000 and that of cluster seizures was 1.1/10,000. We estimated the crude prevalence of ARS in the general population to be 2.1/10,000 and 2.4/10,000 (2.2 - 2.6/10,000) age-adjusted to the European Standard Million population. The prevalence of ARS was highest in the 0-9 year age group (5.1/10,000) and fell with advancing age to 0.4 /10,000 in those aged 70 to 89 years old.

Conclusions: This is the first population-based study to provide information on the prevalence of ARS. It affects about 3 % of the population with epilepsy and 0.02% of the general population. More studies are needed to further evaluate this serious epilepsy phenomenon.

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