THIRTEENTH EILAT CONFERENCE ON
NEW ANTIEPILEPTIC DRUGS AND DEVICES
(EILAT XIII)
Madrid, Spain, June 26- 29, 2016

PROGRAM

AND

ABSTRACTS

Under the auspices of
The Hebrew University of Jerusalem, Israel

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CONFERENCE ORGANIZERS
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ACKNOWLEDGEMENTS

The Organizing Committee wishes to acknowledge the following companies and organizations whose generous support has made this Conference possible.

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GENERAL INFORMATION

VENUE
Meliá Castilla Hotel & Convention Center
Capitán Haya, 4328020 Madrid, Spain
Tel. (34) 91 567 50 77
Fax (34) 91 567 50 66

LANGUAGE
The Conference will be conducted in English.

REGISTRATION / HOSPITALITY / INFORMATION
A desk will operate at the Meliá Castilla Hotel as follows:

Sunday, June 26	from 12:00 - 20:00 hours
Monday, June 27	from 07:00 and during session times
Tuesday, June 28	from 07:30 and during session times
Wednesday, June 29	from 07:30 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.

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

POSTERS
Posters will be on display in the lecture hall for the duration of the conference. Presenters are requested to refer to the program book to find the board number assigned to them. Posters should be mounted as of Sunday, June 26 afternoon, and must be removed by the end of the conference. Please note that the organizers cannot be held responsible for posters that are not removed on time.

GET-TOGETHER RECEPTION
SUNDAY, JUNE 26, 2016 - 19:00
An informal get-together to renew acquaintances and meet new colleagues will take place at the Meliá Castilla Hotel.
All registered participants are invited to attend.

CONFERENCE PROGRAM

SUNDAY, JUNE 26, 2016

16:00 – 16:15 **OPENING SESSION**

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

GREETINGS
E. Perucca, Organizing Committee and ILAE President, Italy

16:15 – 17:15 **PLENARY LECTURES**

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

16:15 EPIDEMIOLOGY OF EPILEPSY (COVERING DIFFERENT SEIZURE TYPES AND EPILEPSIES)
E. Beghi, Italy

16:35 Discussion

16:45 UPDATE ON THE EPILEPSY THERAPY SCREENING PROGRAM (ETSP)
J. H. Kehne, USA

17:05 Discussion

SUNDAY, JUNE 26, 2016 (Continued)

17:15 – 17:45 **DEBATE 1**

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

17:15 HAS THE PROBABILITY OF ACHIEVING SEIZURE FREEDOM INCREASED SIGNIFICANTLY IN THE LAST TWO DECADES?
YES: J.A. French, USA **NO: M.J. Brodie,** UK

17:35 Discussion

17:45 - 18:45 PLENARY LECTURES

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

17:45 DIFFICULTIES/CHALLENGES OF ADVANCING NEW EPILEPSY THERAPIES
R. Porter, University of Pennsylvania, USA

18:05 Discussion

18:15 WHAT ARE THE MOST IMPORTANT "ERRORS" (PREDICTION FAILURES) IN PRECLINICAL DEVELOPMENT? WHAT DO THEY TEACH?
H. Klitgaard, Belgium

18:35 Discussion

19:00 *Get-Together Reception*

MONDAY, JUNE 27, 2016

08:00 – 09:40 INNOVATIVE EMERGENCY TREATMENTS

Chairs: **S.I. Johannessen,** Norway
T. Tomson, Sweden

08:00 INTRANASAL MIDAZOLAM (USL261)
W. E. Pullman, *Upsher-Smith Laboratories, Inc.,* USA

08:25 BUCCAL MIDAZOLAM
S. Paillé, *Shire International GmbH*, Switzerland

08:50 IV BRIVARACETAM
UCB Pharma, Belgium
Presented by **E. Trinka,** Paracelsus Medical University, Austria

09:15 PROPOFOL HEMISUCCINATE
Epalex Corporation
Presented by **M.A. Rogawski,** University of California, Davis, USA

MONDAY, JUNE 27, 2016 (Continued)

09:40 – 10:50 **PLENARY SESSION**
HOW TO GET PHARMA INTERESTED IN AED DEVELOPMENT**?**

Chairs: **M. Bialer,** Israel
H.S. White, USA

09:40 **K. W. Sommerville, Vice-President of Clinical Sciences,** GW Pharmaceuticals, UK

09:55 Discussion

10:00 **M. Davis, Head of Seizure Freedom Patient Value Mission,** UCB Pharma, USA

10:15 Discussion

10:20 **W. E. Pullman, Chief Scientific Officer**, Upsher-Smith Laboratories, Inc., USA

10:35 Discussion

10:40 General Discussion

10:50 *Coffee Break*

MONDAY, JUNE 27, 2016 (Continued)

11:10 -12:50 DRUGS IN DEVELOPMENT SESSION 1

Chairs: **M. Bialer,** Israel
S.D. Shorvon, UK

11:10 ACETONE ANALOGS
J. Andrews, *Ketogen Pharma Inc.,* Canada

11:35 ADENOSINE
D. Boison, Legacy Research Institute, USA

12:00 SAGE-547 FOR SUPER-REFRACTORY STATUS EPILEPTICUS
S.J. Kanes, *Sage Therapeutics*, USA

12:25 BMN 190
BioMarin Pharmaceutical Inc., USA
Presented by **N. Specchio,** Bambino Gesù Children's Hospital

12:50 *Lunch*

13:50 – 16:00 DRUGS IN DEVELOPMENT SESSION 2

Chairs: **M. Bialer,** Israel
S.D. Shorvon, UK

13:50 BRIVARACETAM
J. Whitesides, *UCB Pharma*, Belgium

14:15 BUMETANIDE and its DERIVATIVES
Presented by **W. Löscher,**
University of Hannover, Germany

MONDAY, JUNE 27, 2016 (Continued)

13:50 – 16:00 DRUGS IN DEVELOPMENT SESSION 2 (Continued)

14:40 CANNABIDIOL
K.W. Sommerville & K. VanLandingham,
GW Pharmaceuticals, UK

15:05 CANNABIDIVARIN
K.W. Sommerville, *GW Pharmaceuticals*, UK

15:30 EVEROLIMUS
Sponsored by Novartis, Switzerland

P. Curatolo, "Tor Vergata" University Hospital, Rome, Italy

M. Koepp, University College London, UK

16:00 *Coffee Break*

16:30 – 18:10 DRUGS IN DEVELOPMENT SESSION 3

Chairs: **E. Trinka,** Austria
M. Rogawski, USA

16:30 FENFLURAMINE
G.M. Farfel, *Zogenix Pharmaceutical,* USA

16:55 FV-082
M. Slassi, *Fluorinov Pharma Inc.,* Canada

17:20 GANAXOLONE
A. Patroneva, *Marinus Pharmaceuticals Inc,* USA

17:45 OXINYTAMS
M. Poulter, *OB Pharmaceuticals,* Canada

TUESDAY, JUNE 28, 2016

08:00 – 08:30 DEBATE 2

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

08:00 IS KNOWLEDGE OF MECHANISM OF ACTION ESSENTIAL FOR THE DEVELOPMENT OF NEW AEDs?
YES: W. Löscher, Germany **NO: M.A. Rogawski,** USA

08:20 Discussion

08:30 – 09:25 PLENARY LECTURES

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

08:30 REGULATORY ASPECTS FOR APPROVAL OF NEW AEDs IN EUROPE
S. Prilla, European Medicines Agency, UK

08:50 Discussion

09:00 PREDICTORS OF ADVERSE EFFECTS
P. Ryvlin, France

09:15 Discussion

TUESDAY, JUNE 28, 2016 (Continued)

09:25 – 10:25 DRUGS IN DEVELOPMENT SESSION 4

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

09:25 HUPERZINE A (BIS-001)
S.D. Collins, *Biscayne Pharmaceuticals,* USA

09:50 MINOCYCLINE
Presented by **S. Koh,** Northwestern University, USA

10:15 *Coffee Break*

10:45 – 12:50 DRUGS IN DEVELOPMENT SESSION 5

Chairs: **H.S. White,** USA
S.I. Johannessen, Norway

10:45 NAX 810-2
C. Metcalf, *NeuroAdjuvants*, USA

11:10 1OP-2198
C. Crean, *1st Order Pharmaceuticals*, USA

11:35 PITOLISANT (TIPROLISANT)
D. Kasteleijn-Nolst-Trenite,
University of Rome "Sapienza" II, Italy

12:00 PRX 0023 (Nalutozan)
W.H. Theodore, NINDS, NIH, USA

12:25 SAGE-689/217-NEXT GENERATION NEUROACTIVE STEROID GABA-PAMS-DEVELOPMENT PROGRESS UPDATE
A.J. Robichaud, Sage Therapeutics, USA

TUESDAY, JUNE 28, 2016 (Continued)

12:50 *Lunch*

13:50 – 15:05 DRUGS IN DEVELOPMENT SESSION 6

Chairs: **H.S. White,** USA
S.I. Johannessen, Norway

13:50 2-DEOXY-(D)-GLUCOSE
Presented by **T.P. Sutula,** University of Wisconsin, USA

14:15 VALNOCTAMIDE and sec-BUTYLPROPYLACETAMIDE (SPD)
Presented by **M. Bialer**,
The Hebrew University of Jerusalem, Israel

14:40 IMEPITOIN
Boehringer-Ingelheim, Germany
Presented by **W. Löscher,** University of Hannover, Germany

15:05 – 17:40 PROGRESS REPORT ON SECOND-GENERATION TREATMENTS

Chairs: **E. Perucca,** Italy
E. Trinka, Austria

15:05 ESLICARBAZEPINE ACETATE
BIAL, Portugal
Presented by **E. Trinka,** Paracelsus Medical University, Austria

15:30 *Coffee Break*

15:05 – 17:40 PROGRESS REPORT ON SECOND-GENERATION TREATMENTS (Continued)

16:00 LACOSAMIDE
K.J. Werhahn, *UCB Pharma,* Belgium

16:25 PERAMPANEL
A. Laurenza, *Eisai, Inc., USA*

16:50 PREGABALIN
V. Pitman, *Pfizer Inc.,* USA

17:15 STIRIPENTOL
Biocodex, France
Presented by **E. Wirrell,** The Mayo Clinics, USA

WEDNESDAY, JUNE 29, 2016

08:00 – 08:30 PLENARY LECTURE

Chairs: **S. Shorvon,** UK
P. Ryvlin, Switzerland

08:00 WHY DO WE NEED RELIABLE SEIZURE DETECTION SYSTEMS?
P. Ryvlin, France

08:20 Discussion

08:30 – 09:50 NEW MEDICAL DEVICES AND NEUROMODULATION

Chairs: **K. Vonck,** UK
M. Walker, Switzerland

08:30 ALTERNATIVE THERAPIES AND APPROACHES
M. Walker, UK

08:50 EEG-BASED SEIZURE DETECTION SYSTEMS IN EPILEPSY
J. Gotman, Canada

09:10 ECG-BASED SEIZURE DETECTION SYSTEMS IN EPILEPSY
R. Surges, Germany

09:30 CARDIAC-BASED NEW VAGAL NERVE STIMULATION
K. Vonck, Belgium

09:50 *Coffee Break*

WEDNESDAY, JUNE 29, 2016 (Continued)

10:20 – 12:15 NEW MEDICAL DEVICES AND NEUROMODULATION (Continued)

Chairs: **S. Shorvon,** UK
P. Ryvlin, Switzerland

10:20 SEIZURE RESPONSIVE VAGUS NERVE STIMULATION
Cyberonics, Belgium
Presented by **P. Boon,** Ghent University Hospital, Belgium

10:40 TRANSCUTANEOUS VAGUS NERVE STIMULATION (tVNS)
F. Rosenow, University Hospital Frankfurt, Germany

11:05 TRIGEMINAL NERVE STIMULATION
J. Serratosa, Autonomous University of Madrid, Spain

11:20 DEEP BRAIN STIMULATION AND MRI GUIDED LASER ABLATION TECHNOLOGY
J. Giftakis, *Medtronic Neuromodulation*, USA

11:40 RESPONSIVE CORTICAL STIMULATION
M. Morrell, *Neuropace*, USA

12:00 BRAIN SYNCHRONY-CONTINGENT NEUROSTIMULATORS FOR TREATMENT OF DRUG-RESISTANT EPILEPSY
R. Genov, University of Toronto, Canada

12:10 End of Conference and Concluding Remarks

Light snacks will be served

POSTER PRESENTATIONS

Board No.

1. ANTIICTOGENIC AND ANTIEPILEPTOGENIC PROPERTIES OF PERAMPANEL IN MATURE AND IMMATURE RATS
N. Dupuis[1], J. Enderlin[1], P. Dournaud[1], **S. Auvin[2]**
[1]Inserm U1141, Inserm, Paris, France, [2]Pediatric Neurology & Inserm U1141, Robert Debré University Hospital, Paris, France

2. UTILIZATION AND REPORTED ADVERSE EFFECTS OF THE NEWEST ANTIEPILEPTIC DRUGS IN NORWAY
A. Baftiu[1], K. Svendsen[2], S.I. Johannessen[3], P.G. Larsson[4], C. Johannessen Landmark [1,3]
[1]Department of Life Sciences and Health, Oslo and Akershus University College of Applied Sciences, Oslo, Norway, [2]Department of Pharmacy, University of Tromsø, Tromsø, Norway, [3]The National Center for Epilepsy and Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [4]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

3. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS AFTER VARIOUS ROUTES OF ADMINISTRATION OF SEC-BUTYLPROPYLACETAMIDE (SPD), A NEW CNS DRUG POSSESSING A UNIQUE ACTIVITY AGAINST STATUS EPILEPTICUS
D. Bibi[1], H. Mawasi[1], T. Shekh-Ahmad[1], H. Shaul[2], S. Blotnik[2], M. Bialer[3]
[1]Department of Pharmaceutical Sciences, School of Pharmacy, the Hebrew University, Jerusalem, Israel, [2]Clinical Pharmacology Unit, Hadassah University Hospital, Jerusalem, Israel, [3]David R. Bloom Center for Pharmacy, School of Pharmacy, the Hebrew University, Jerusalem, Israel

POSTER PRESENTATIONS (Continued)

Board No.

4. NOVEL ULTRA-LONG TERM SUBCUTANEOUS EEG MONITORING SYSTEM
J. Duun-Henriksen[1], S.W Gangstad[1], L. Blaabjerg[2]
[1]R&D, Hypo Safe A/s, Lynge, Denmark, [2]Medical Trials, Hypo Safe A/s, Lynge, Denmark

5. EARLY-LIFE CLONAZEPAM EXPOSURE LEADS TO PERSISTENT INCREASE OF SEIZURE SUSCEPTIBILITY
K. Hana, F. Petr, M. Pavel
Department of Developmental Epileptology, Institute of Physiology, Academy of Sciences of the Czech Republic, Czech Republic

6. SURVEILLANCE OF ESLICARBAZEPINE ACETATE, OXCARBAZEPINE AND CARBAMAZEPINE IN NORWAY
C. Johannessen Landmark[1,2], A. Baftiu[1], K. Svendsen[3], T. Svendsen[4], S.I. Johannessen[2]
[1]Programme for Pharmacy, Dept of Life Sciences and Health, Oslo and Akershus University College, Oslo, Norway, [2]The National Center for Epilepsy and Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Dept of Pharmacy, University of Tromsø, Tromsø, Norway, [4]The National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

7. PHOTOSENSITIVITY MODEL: STABILITY OF THE PHOTOPAROXYSMAL EEG RESPONSE OVER THE DAY
D. Kasteleijn-Nolst Trenite[1,2], P. Timmings[3], N. Holford[4], **R.C. Reed[5]**
[1]Department of Neuroscience, Sapienza University, Rome, Italy, [2]Medical Genetics, Utrecht Medical Center, Utrecht, Netherlands, [3]Department of Neurology, University of Auckland, Hamilton, New Zealand, [4]Department of Biostatistics, University of Auckland, Hamilton, New Zealand, [5]School of Pharmacy, Husson University, Bangor, Maine, United States

POSTER PRESENTATIONS (Continued)

Board No.

8. EFFECT OF ALISKIREN, A DIRECT RENIN INHIBITOR, ON THE ANTICONVULSANT ACTIVITY OF ANTIEPILEPTIC DRUGS AGAINST MAXIMAL ELECTROSHOCK-INDUCED SEIZURES IN MICE
K. Łukawski[1], G. Raszewski[1], S. Czuczwar[1,2]
[1]Department of Physiopathology, Institute of Rural Health, Lublin, Poland,
[2]Department of Pathophysiology, Medical University, Lublin, Poland

9. AN ANTAGONIST OF AMPA RECEPTORS PERMEABLE FOR CALCIUM AS A POSSIBLE ANTIEPILEPTIC DRUG
P. Mares[1], A. Soukupova[2], E. Szczurowska[2]
[1]Developmental Epileptology, Inst.physiology Czech Academy of Sciences, Prague, Czech Republic, [2]Developmental Epileptology, Institute of Physiology Czech Academy of Sciences, Prague, Czech Republic

10. DIFFERENTIAL EFFECTS OF ANTIEPILEPTIC DRUGS IN A MOUSE MODEL OF MESIAL TEMPORAL LOBE EPILEPSY
C. Roucard[1], B. Pouyatos[1], C. Bouyssières[1], C. Dumont[1], A. Depaulis[2], V. Duveau[1]
[1]Synap Cell Sas, Synap Cell Sas, La Tronche, France,
[2]Grenoble Institute of Neurosciences, U1216 Uga Inserm, La Tronche, France

11. NONCONVULSIVE STATUS EPILEPTICUS: CASE REPORT
J. Saric Sucic, R. Susak, S. Juric, M. Cubra, S.B. Soldo
Department of Neurology, University Hospital Centar Osijek, Osijek, Croatia

POSTER PRESENTATIONS (Continued)

Board No.

12. CLINICAL AND MRI MORPHOMETRY EFFECTS OF ANTIEPILEPTIC DRUGS IN TEMPORAL LOBE EPILEPSY IN UZBEKISTAN
A.T. Umarov, A. Prokhorova, G. Rakhimbaeva, N. Tuychibaeva
Department of Neurology, Tashkent Medical Academy, Tashkent, Uzbekistan

13. DECANOIC ACID, WITHIN THE MCT KETOGENIC DIET, DIRECTLY INHIBITS AMPA RECEPTOR ACTIVITY AS A THERAPEUTIC MECHANISM OF ACTION
P. Chang[1], K. Augustin[1], K. Boddum[2], S. Williams[2], M. Sun[2], J. Terschak[3], J. Hardege[3], P. Chen[1], M. Walker[2], **R.SB. Williams[1]**
[1]Centre for Biomedical Sciences, School of Biological Sciences, Royal Holloway University of London, Egham, Surrey, United Kingdom, [2]Department of Clinical and Experimental Epilspy, Institute of Neurology, University College London, London, United Kingdom, [3]School of Biology, University of Hull, United Kingdom

ABSTRACTS:

ORAL PRESENTATIONS

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EPIDEMIOLOGY OF EPILEPSY (COVERING DIFFERENT SEIZURE TYPES AND EPILEPSIES)

E. Beghi
IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

The epidemiology of epilepsy is the study of the frequency and determinants of the disease in a given population. Differences across countries in the main epidemiological indexes (incidence, prevalence, mortality) must be interpreted in the light of study design and methods. Methodological problems include diagnostic accuracy, case ascertainment, and selection bias. In developed countries the incidence of epilepsy is 40-50/100,000/year. In resource-poor countries, the incidence is likely to be higher, especially in sub-Saharan Africa. Prevalence of active epilepsy is in the range of 5-10/1000 in most geographic areas, although it might be higher in some isolates. The disease peaks in the youngest and oldest age groups and is slightly more prevalent in men than in women. Age-specific incidence rates have changed over time, with a decrease in younger age groups and an increase in the elderly. There is geographic variation in the incidence of putative causes which are most likely associated with genetic and environmental factors, although as yet causality has not been fully elucidated in about one half of cases. The differing distribution of risk factors and determinants has a profound influence on the worldwide frequency of seizure types and epilepsy syndromes. The overall prognosis for seizure control is, however, good as more than 70% of cases will enter remission (about 50% off-drugs). Compared to the general population, people with epilepsy have a 2-3-fold risk of death. Sudden unexpected death (SUDEP) has been increasingly recognized as a major cause of death, mostly in patients with drug-resistant epilepsy. The epidemiology of epilepsy in many resource-poor countries is still ill-defined and further research is needed to elucidate the frequency and causes of the disease in these areas to improve the current management, fill treatment gap, and adopt preventive measures.

UPDATE ON THE EPILEPSY THERAPY SCREENING PROGRAM (ETSP)

J. Kehne, S. Raeissi, B. Klein
Office of Translational Research, National Institutes of Health, NINDS, Rockville, United States

The mission of the NINDS Epilepsy Therapy Screening Program (ETSP) (previously known as the Anticonvulsant Screening Program) is to encourage and facilitate the discovery of new therapeutic agents for the treatment of epilepsy disorders. Researchers from academia and industry in the U.S. and abroad submit compounds for screening in a battery of well-established rodent seizure models. Testing is performed at a contract facility currently based at the University of Utah on a blinded, confidential basis and at no cost to the ETSP participant. The NINDS ETSP staff reports test results to participants and provides advice on next steps for promising compounds. Since its establishment in 1975, the program has contributed to the development of a number of FDA-approved drugs for epilepsy. Based on recent recommendations from working groups of the National Advisory Neurological Disorders and Stroke (NANDS) Council, and ongoing feedback from an External Consultant Board, the program is focusing on refractory epilepsy, epileptogenesis and disease progression, special epilepsy populations, and epilepsy comorbidities. The new name of the program reflects the emphasis on identifying differentiated agents to address the unmet medical needs of epilepsy. Evaluation of a submitted compound for suitability for testing in the ETSP begins with an assessment of the compound's biological and chemical rationale. Accepted compounds with documented identity and purity are then evaluated in assays whose sequence is described in specific flow charts. For example, for the pharmacoresistance flow chart, activity of a test compound in screening assays in an initial Identification stage advances it to a subsequent Differentiation stage comprised of more resource-intensive, disease-relevant models. NINDS has also implemented a web-based research tool called PANAChE (Public Access to Neuroactive & AnticonvulsantChemical Evaluations) which provides open access to nonproprietary chemical structures and biological data for compounds previously screened in the ETSP. This database is populated with known drugs in the public domain and any ETSP compound approved by the participant for inclusion. PANAChE additionally serves as a repository for information on the animal models, assays, and flowcharts used in the ETSP. Finally, given the challenges in identifying potential novel, clinically-differentiated compounds for epilepsy, an important aspect of the ETSP is its flexibility to adapt its screening strategies based on cumulative testing experience and emerging scientific advances in the field.

DIFFICULTIES/CHALLENGES OF ADVANCING NEW EPILEPSY THERAPIES

R. Porter
University of Pennsylvania, USA

The preclinical models available for finding new therapies of anti-seizure drugs are the the most predictable models in all of CNS research. Time and again, for example, the Anticonvulsant Screening Program (ASP) of NINDS, NIH has produced anti-seizure compounds (ASDs) with striking effectiveness in animal models—compounds which have moved successfully to clinical trials and to the marketplace. Yet in spite of these accomplishments, with many new drugs added to our armamentarium in the past few decades, we are left with a two-fold dilemma—A) Many patients continue with uncontrolled seizures and B) Major pharmaceutical companies are disinterested in the CNS--and epilepsy in particular. The reasons for this conundrum are manyfold:

1) Many patients have severe epilepsy which has not responded to any of the old or new drugs, suggesting that either the therapeutic indices of our medications are inadequate (which they surely are for many patients), or that we have not adequately addressed the correct targets for these intractable subjects. The ASP continues to provides new compounds with new mechanisms of the anti-seizure action (Porter et al, 2015), providing new avenues for seizure control.

2) The community is unwilling to accept the concept of incremental gains from each new therapy, stating that the additional expense is not worth the additional outlay. A good example is Germany, where several new ASDs have been repeatedly rejected for reimbursement. This is unfair and is partly politically driven. The treatment of breast cancer is a terrific example of incremental clinical gains without any sudden scientific breakthrough. With tremendous financial and political support, breast cancer patients have, in the UK, for example, benefited from a nearly 50% decrease in relative mortality in the past few decades: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/mortality#heading-Two.

If we were able to properly measure the improvement in seizure control from the myriad of new anti-seizure therapies since 1980, we might see the same overall trend.

3) Programs in CNS disorders are viewed by the pharmaceutical world as both expensive and high risk (Choi et al, 2014). It is hard to argue with the dismal failure rate for CNS disorders such as stroke and dementia. The correct observation that the the success rate for epilepsy compounds is much better has not gotten much traction in the industry; some of this reluctance may be due to the plethora of new anti-seizure drugs that have emerged since 1980.

4) We are good at screening compounds, but not at getting to an IND. The ASP continues to provide excellent candidates for safety and formulation studies, but these compounds often sit on the shelf, losing patent life for lack of an interested financial partner.
5) Human proof of concept for new drugs in Phase IIa and IIb continues to be an expensive challenge. Shortcuts such as the photosensitivity model remain controversial, especially for partial (focal) seizures.
Until we overcome some of these impediments, anti-seizure drug development will continue to struggle and our patients will continue with uncontrolled seizures.

References:

Porter RJ, Kupferberg HJ and Hessie BJ. Mechanisms of action of anti-seizure drugs and the anticonvulsant screening program of the National Institute of Neurological Disorders and Stroke. International Journal of Clinical Pharmacology and Therapeutics 53:9-12, 2015.

Choi DW, Armitage R, Brady LS, Coetzee T, Fisher W, Hyman S, Pande A, Paul S, Potter W, Roin B, and Sherer T. Medicines for the Mind: Policy-Based "Pull" Incentives for Creating Breakthrough CNS Drugs. Neuron 84:554-563 2014.

WHAT ARE THE MOST IMPORTANT "ERRORS" (PREDICTION FAILURES) IN PRECLINICAL DEVELOPMENT? WHAT DO THEY TEACH?

H. Klitgaard
VP, UCB Research Fellow, New Medicines, UCB Pharma, Belgium

Drug discovery and development of new chemical entities (NCE's) are associated with high attrition. At least 10 NCE's has to enter clinical development in order to identify one new drug. In an attempt to reduce this issue, several additional pharmacokinetic (PK), safety pharmacology and early toxicology measures have been introduced to preclinical development during the last two decades. This has improved the ability to detect and eliminate NCE's that lack sufficient drug-like properties for PK and safety reasons, less due to chronic toxicity. However, it has also emphasized that attrition today mainly reflect a lack of ability to translate efficacy from preclinical models to clinical efficacy in phase II and III studies. This issue vary between therapeutic areas, with CNS being associated with relatively high attrition. But within CNS, epilepsy has displayed relatively low attrition. This can mainly be attributed to the early availability of the rodent maximal electroshock seizure (MES) and pentylenetetrazol (PTZ) tests. Both were rapidly validated by phenytoin and trimethadione showing activity in the MES and PTZ tests, respectively, and consequently anticonvulsant activity in epilepsy patients. This led to the suggestion that the MES test may predict efficacy for partial onset and generalized tonic/clonic seizures and the PTZ test efficacy against absence seizures. These two models have led to the identification of more than 30 of the approximately 40 drugs introduced for the treatment of epilepsy. However, the MES test has been associated with false positive observations by prediction of anticonvulsant activity of NMDA antagonists and false negative observations by absence of anticonvulsant activity by levetiracetam, tiagabine and vigabatrin. Inclusion of testing in amygdala kindled rats proved useful to rectify this and to permit high predictability for activity against partial onset seizures and also to predict unwanted psychiatric adverse effects of NMDA antagonists, not identified in normal rodents. The PTZ test has also been associated with false positive observations by prediction of anti-absence activity of tiagabine and vigabatrin and false negative observations by absence of anticonvulsant activity of levetiracetam. Inclusion of testing in genetic absence models (WAG and GAERS rats) proved useful to rectify this and to permit high predictability for absence seizures. This emphasize the importance of including kindling and genetic rodent models to complement the use of the MES and PTZ in order to optimize the ability to predict the clinical potential of NCE's for the symptomatic treatment of partial onset and generalized seizures in epilepsy patients. Future preclinical development in epilepsy will likely focus on identifying NCE's that specifically address drug resistant seizures and

provide antiepileptogenic or disease modifying treatments. This imply a need to focus on new models and paradigms for preclinical efficacy predictions, involving kindling, genetic, syndrome specific and status epilepticus models. These newer approaches seems to hold an unfortunate potential to increase attrition for epilepsy therapy development which should be counteracted by a focus on NCE's that target genetically validated mechanisms. These NCE's should prove an ability, at therapeutic relevant plasma concentrations, to provide a dual, beneficial effect on relevant disease biology and seizure expression in preclinical studies conducted in different models by different investigators. Successful translation would be facilitated by the availability of robust and objective biomarkers. These should determine sufficient target engagement for successful translation of preclinical efficacy observations to clinical activity, impact of the NCE on biological processes downstream to the target pathway in patients and should also enable patient stratification. This continuum of preclinical and clinical research should permit to minimize the risk for failure due to lack of efficacy in late stage clinical development and enable future preclinical development efforts to continue to deliver new epilepsy therapies that can address remaining unmet medical need in the disease.

MIDAZOLAM OROMUCOSAL SOLUTION

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Oromucosal Midazolam has been approved by EMA in 2011 and indicated for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years) . Oral midazolam must only be used by parents/carers where the patient has been diagnosed to have epilepsy. For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available1

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form the hydrochloride salt with acids. These produce a stable solution suitable for oromucosal administration. The pharmacological action of midazolam is characterized by short duration and an anticonvulsant effect[1].

After being released from the nerve terminal, the inhibitory neurotransmitter GABA binds to the GABAA receptor on the post-synaptic membrane of neurons. This opens the chloride ion channel, producing an inhibitory current that counteracts GluR-mediated excitation. Midazolam binds to benzodiazepine receptors in various regions of the brain such as the spinal cord, brain stem, cerebellum, limbic system, and the cerebral cortex[1].
The EU clinical package comprises 5 comparator- controlled studies (1 Buccal Midazolam vs IV Diazepam, 4 Buccal Midazolam vs Rectal Diazepam) [2].
According to the 4 rectal-diazepam-controlled studies, buccal midazolam, administered to 294 children has been shown to be more efficacious than, or at least as efficacious as rectal diazepam in cessation of prolonged seizures [3-6].
Furthermore, buccal midazolam has been reported to be more acceptable and offers benefits over diazepam in terms of ease of use.
Buccal midazolam has also shown to be well tolerated with a comparable safety profile to other BZDs. The most common adverse effects are sedation, somnolence, depressed levels of consciousness and respiratory depression[1].

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INTRAVENOUS BRIVARACETAM

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Brivaracetam (BRV) was recently approved in the EU and USA for adjunctive treatment of focal (partial-onset) seizures, with or without secondary generalization, in adults ≥16 years. Intravenous (IV) administration offers a good alternative when oral dosing is not possible. The safety, tolerability, pharmacokinetics, and bioequivalence of BRV IV formulations have been assessed in three clinical studies (EP0007/NCT01796899, 25 healthy participants; N01256, 48 healthy participants; N01258/NCT01405508, 105 patients with epilepsy).

BRV was well tolerated when administered intravenously or orally, and no deaths or treatment-related serious adverse events were reported. In study N01256, the most common treatment-emergent adverse events (TEAEs) following single-dose BRV (10 mg: oral tablet, 15-minute IV infusion, or 12-second IV bolus) were headache (5 participants, 20.8%), fatigue (4, 16.7%), and somnolence (3, 12.5%), and following dose escalation (BRV 25–150 mg: 15-minute IV infusion or IV bolus [50 mg/min]) were somnolence (21, 87.5%), fatigue (13, 54.2%), dizziness (8, 33.3%), feeling drunk and dysgeusia (each 6, 25.0%); all TEAEs resolved before the end of the study. In the Phase III study N01258, the incidence of TEAEs for patients receiving 200 mg IV BRV (15-minute infusion or 2-minute bolus) were similar for those who initially received oral placebo (36, 70.6%) or BRV (35, 66.0%); TEAEs were reported by 37 patients (71.2%) receiving bolus and 34 (65.4%) receiving infusion.

IV BRV has similar pharmacokinetic parameters whether given as infusion or bolus. In study N01256, pharmacokinetic parameters were similar for 15-minute IV infusion and 12-second IV bolus. The area under the plasma concentration time curve (AUC) was dose proportional, whereas clearance and plasma half-life were dose independent. Overall, IV BRV (infusion and bolus) demonstrated bioequivalence with oral tablets. In study EP0007, 100 mg IV bolus was bioequivalent with 50 and 100 mg oral tablets for AUC0–inf and AUC0–t (maximum plasma concentration was partly outside of the bioequivalence limits for both dose comparisons).

Notably, a positron emission tomography imaging study in rhesus monkeys estimated that BRV enters the brain within 3 minutes following IV administration. Physiologically-based pharmacokinetic modeling predicted that this fast brain entry may also occur in humans; the clinical significance of these findings is yet to be determined.

Oral BRV demonstrated statistically significant efficacy over placebo in Phase III studies; similar efficacy is anticipated with IV administration given the bioequivalence of IV and oral BRV.

In summary, IV BRV appears generally well tolerated and is bioequivalent to oral BRV.

ACETONE ANALOGUES, KETONE GENERATING BODIES AND THE KETOGENIC DIET

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The exact mechanism of action of the ketogenic diet is unknown. Nevertheless ketones do appear to play a role in the anticonvulsant activity of the diet in man and animal models. The body produces several different ketones and studies have shown that some, but not necessarily all, possess anticonvulsant activity.

Acetone is one ketone shown to have anticonvulsant activity, its usefulness as a therapeutic agent however is negligible due to its exceedingly short half-life. Several approaches have attempted to develop acetone analogues and ketone generating bodies to overcome this issue. These approaches have included both direct analogues, prodrugs and carriers all with the intent of increasing the passage of drug into the brain and increasing the effective half-life.

Recent studies have suggested that combining a carrier agent with a ketone generating group is an effective approach for generating novel anticonvulsant drugs which may mimic some aspects of the ketogenic diet. A range of studies will be reviewed on the interactions of ketone groups with anticonvulsant treatments and the development and use of novel carrier systems to improve anticonvulsant efficacy will be presented.

ADENOSINE

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The purine ribonucleoside adenosine is an endogenous anticonvulsant and seizure terminator of the brain. In addition, adenosine affects epigenetic mechanisms thought to be instrumental in epileptogenesis. Therefore, therapeutic adenosine augmentation represents a rational therapeutic approach not only to prevent seizures but also the progression of epilepsy. In the adult brain the availability of adenosine is largely under the control of metabolic clearance through adenosine kinase (ADK), a ribokinase predominantly expressed in astrocytes. We and others have shown that increased ADK is a pathological hallmark of the epileptic brain and intricately linked to epileptogenesis and disease progression. High levels of ADK (as occur in epileptogenic brain foci) result in reduced adenosine. Reduced adenosine in turn lowers seizure thresholds and drives increased DNA methylation. Changes in the DNA methylome are thought to contribute to epileptogenesis and disease progression. We provided robust evidence in different experimental settings that the transient therapeutic augmentation of adenosine (e.g. locally via adenosine releasing silk as discussed at EilatXII) prevents epileptogenesis in etiologically relevant rodent models of temporal lobe epilepsy (TLE). The proven antiepileptogenic effects of adenosine are based on an epigenetic mechanism whereby a transient dose of adenosine triggers lasting changes in the DNA methylome. Since ADK inhibitors had already been considered for clinical translation earlier in this century for the treatment of seizures, chronic pain, and chronic inflammatory conditions, we tested the antiepileptogenic efficacy of the ADK inhibitor 5-iodotubercidin (5-ITU) in the mouse intrahippocampal kainic acid (KA) model of TLE. As evidence for target engagement we found a dose dependent inhibition of DNA methyltransferase (DNMT) activity in the hippocampus of 5-ITU treated animals, which was comparable to those of standard inhibitors. Three days after intrahippocampal KA-induced status epilepticus in mice, 5-ITU was injected i.p. at a dose of 1.6 mg/kg bid for a restricted time span of only five days. Six and nine weeks after the SE, seizures were quantified by intrahippocampal EEGs. While epileptic control animals, which received vehicle instead of 5-ITU, had developed a typical seizure rate of >20 seizures per hour, in the animals transiently exposed to an ADK inhibitor both the seizure incidence as well as the total time spent in seizures were almost completely abolished.
Our data show that the transient systemic use of a small molecule ADK inhibitor can prevent epileptogenesis and provides a rationale for developing small molecule ADK inhibitors for antiepileptogenic therapies.

SAGE-547 FOR SUPER-REFRACTORY STATUS EPILEPTICUS

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SAGE-547 Injection is a proprietary aqueous formulation of allopregnanolone in Captisol® (betadex sulfobutyl ether cyclodextrin sodium). Allopregnanolone is an endogenous, inhibitory neuroactive steroid (NAS) formed in the corpus luteum of the ovary, adrenal cortex, and CNS. Allopregnanolone is a principal metabolite of progesterone, and has been shown in animal studies to regulate neuronal excitability through potent positive allosteric modulation of the GABAA receptor (GABAAR). Allopregnanolone binds to the α1 and α4 subunits of synaptic and extrasynaptic GABAARs, respectively, enhancing GABAAR function and leading to reduced neuronal excitability. This mechanism is being studied for its potential to produce potent anticonvulsant, anxiolytic, and sedative effects.

Considerable evidence supports the study of the role for allopregnanolone in the treatment of seizures and status epilepticus (SE). Allopregnanolone displays anticonvulsant properties in a variety of acute seizure animal models, including the pentylenetetrazol, 6Hz, metrazol, bicuculline, and picrotoxin models. Animal studies also support the hypothesis that enhancement of extrasynaptic GABAA receptor function by allopregnanolone may provide anticonvulsant efficacy when prolonged seizure activity has become pharmaco-resistant to benzodiazepine treatment.

SAGE-547 has been studied in a Phase 1/2 trial (547-SSE-201) as an acute, interventional treatment when third-line standard-of-care therapies have failed to halt SE, a situation in which patients are diagnosed with super-refractory status epilepticus (SRSE). SRSE is a severe form of SE that continues for >24 hours despite multiple therapeutic interventions and failure to be weaned from third-line agents. SAGE-547 demonstrated robust activity in the Phase 1/2 trial, with 77% of 22 evaluable patients meeting the key efficacy endpoint of being successfully weaned off anesthetic agents during SAGE-547 administration. Furthermore, 77% of total evaluable patients were successfully weaned off SAGE-547 without recurrence of SRSE within 24 hours following completion of treatment.

Overall, 64% of patients experienced ≥1 serious adverse event, though none were determined by the Safety Review Committee to be drug-related. Independent of treatment response, six patient deaths occurred, all driven by underlying medical conditions.

SAGE-547 is being investigated in a randomized, double-blind, placebo-controlled Phase 3 trial (547-SSE-301). The study objective is to investigate the safety and efficacy of SAGE-547 in patients with SRSE. Patients are randomized 1:1 (SAGE-547:placebo) and treated for 6 days with a standard SAGE-547 dose, with follow-up

after 21 days. The primary outcome measure is the number of patients able to be weaned off all third-line agents prior to the end of SAGE-547/placebo infusion and remain off all third-line agents for ≥24 hours following the end of SAGE-547/placebo infusion. Non-responders are eligible for open-label, high-dose SAGE-547 treatment. Top-line results are expected in the second half of 2016.

INTRACEREBROVENTRICULAR CERLIPONASE ALFA (BMN 190) IN CHILDREN WITH CLN2 DISEASE: RESULTS FROM A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION STUDY

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Background: CLN2 disease, a rare, inherited, pediatric-onset, neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency, is characterized by seizures, ataxia, rapid loss of language and motor functions, blindness and early death. Cerliponase alfa (BMN 190) is a recombinant human TPP1 enzyme. This phase 1/2, multi-center, open-label, dose-escalation study evaluated the safety, tolerability and efficacy of every other week intracerebroventricular (ICV) infusions of cerliponase alfa in children with CLN2 aged 3 - 16 years.

Design: The first ten subjects were assigned to one of three cohorts in a dose escalation period (30 mg, 100 mg, 300 mg). All subjects were subsequently administered a stable dose of cerliponase alfa (300 mg every other week) for at least 48 weeks. Efficacy was evaluated by monitoring changes in motor and language functions using a CLN2 clinical rating scale.

Results: 24 subjects (9 male, 15 female, mean age 4.3 years [median: 4 years; range: 3-8 years]) enrolled in the study. Almost all subjects (96%) had adverse events (AEs) assessed as study drug-related, the majority of which were Grade 1-2 and included pyrexia (46%), hypersensitivity (33%), seizure(33%),and epilepsy (17%). Serious adverse events (SAEs) assessed as study drug-related were reported in seven(29%) subjects. There were no anaphylaxis/anaphylactoid reactions, study drug discontinuations or deaths due to AEs. The mean (SD)/median rate of decline in CLN2 score of 21 evaluable subjectswas 0.43 (0.84)/0.0 units/48 weeks, in contrast to the 2.09 (0.97)/1.87 units/48 weeksrate of decline observed in 41 natural historypatients.

Conclusions: Enzyme replacement therapy with ICV-administered cerliponase alfa is well-tolerated and slows the progression of functional decline in children with CLN2.

BRIVARACETAM

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Brivaracetam (BRV) is a selective synaptic vesicle protein 2A (SV2A) ligand with higher affinity, and a differential interaction with SV2A, compared with levetiracetam (LEV). This gives BRV a superior ability to inhibit synaptic transmission and vesicle release, resulting in potent and complete seizure suppression in rodent models of focal, generalized, and drug-resistant seizures. BRV has higher lipophilicity and blood–brain barrier permeability than LEV, resulting in faster brain entry, higher SV2A occupancy, and faster onset of action after acute dosing in animal models. Physiologically-based pharmacokinetic modeling predicts that this rapid brain entry extends to humans.

In humans, BRV has a linear and predictable pharmacokinetic profile. BRV is rapidly and completely absorbed throughout the gastrointestinal system, and extensively metabolized, primarily by hydrolysis followed by CYPC19-mediated oxidation.

Adjunctive BRV administered without titration was effective in patients with focal seizures uncontrolled by 1–2 concomitant antiepileptic drugs in three fixed-dose, Phase III studies (N01252/NCT00490035, N01253/NCT00464269, N01358/NCT01261325). In the most recent study, N01358, ≥50% responder rates (odds ratio vs. placebo; 95% CI) were 21.6% for placebo, 38.9% for BRV 100 mg/day (2.39; 1.6, 3.6; $p<0.001$), and 37.8% for 200 mg/day (2.19; 1.5, 3.3; $p<0.001$). Seizure freedom rates (all seizures) were 5.2% ($p=0.003$) for BRV 100 mg/day and 4.0% ($p=0.019$) for 200 mg/day, vs. 0.8% for placebo. Pooled Phase III data (excluding patients receiving concomitant LEV) demonstrated higher ≥50% responder rates for BRV (34.2%, 39.5%, and 37.8% for 50, 100, and 200 mg/day, respectively) than placebo (20.3%). Among LEV-naïve patients, ≥50% responder rates were higher on BRV (37.2%, 48.3%, and 45.2% for 50, 100, and 200 mg/day, respectively) than placebo (22.5%). In those with prior LEV use, ≥50% responder rates were 27.1%, 29.7%, and 31.3% for BRV 50, 100, and 200 mg/day, respectively, versus 17.8% for placebo, suggesting benefit in patients who previously failed LEV. In patients with Type IC seizures at baseline, median percent reduction in seizure frequency per 28 days was greater with BRV 50 mg/day (66.6%; n=62), 100 mg/day (61.2%; n=100), and 200 mg/day (82.1%; n=75) than with placebo (33.3%; n=115).

Exposure to BRV in clinical trials to date is approximately 6000 patient-years, with some patients followed for >8 years. The most common treatment-emergent adverse events (TEAEs) were somnolence, dizziness, headache, and fatigue. Rates of discontinuation due to TEAEs were low.

In conclusion, adjunctive BRV (50–200 mg/day) is effective in patients with focal seizures, with a favorable safety and tolerability profile.

BUMETANIDE AND ITS DERIVATIVES

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There is considerable interest in using bumetanide, an antagonist of the chloride importer NKCC, for treatment of neurological diseases, such as neonatal seizures, epilepsy, autism or ischemic and traumatic brain injury, which may involve deranged cellular chloride homeostasis. Cation-chloride co-transporters such as NKCC1 play an important role in the formation of abnormal excitatory GABAergic neurons and provide a potential target for anti-seizure and anti-epileptogenic treatments. However, use of bumetanide for preventing or treating epilepsy is hampered by its poor brain penetration, which is assigned to its high plasma protein binding (~97-98%) and extensive ionization (>99%) at physiological pH. Thereby the ability of this organic anion to enter the brain by passive diffusion is limited. Brain concentration of bumetanide is further reduced by organic anion transporters actively effectuating brain efflux of the compound upon entrance. Thus, bumetanide concentrations found in the brain are only approximately 1-2 % of concentrations found in plasma, meaning that tolerable systemic doses of bumetanide yield brain concentrations below that required to affect neuronal NKCC1. This is a likely explanation for the disappointing results of the first clinical phase I/II trial with bumetanide in newborn infants with seizures, in which bumetanide was not effective and increased the risk of hearing loss. Over the last ~10 years, we explored several strategies to improve the use of bumetanide or its derivatives for treatment of brain disorders such as epilepsy. These strategies included (1) development of lipophilic, non-charged bumetanide prodrugs that enter the brain before cleavage to bumetanide, (2) inhibition of the brain efflux of bumetanide with probenecid, (3) coadministration of piperonyl butoxide, a compound that inhibits the rapid metabolism of bumetanide, and (4) testing of various bumetanide derivatives that were selected from ~5000 3-amino-5-sulfamoylbenzoic acid derivatives which were synthesized in the 1960s and 1970s at Leo Pharma (Copenhagen, Denmark) during screening for compounds with high diuretic efficacy, finally resulting in the discovery of bumetanide. The aim of the 4th strategy was to find NKCC1-selective drugs with low diuretic and ototoxic potencies.

The first three strategies increased bumetanide levels in rodent brains and the prodrug strategy, in addition, resulted in reduced diuretic activity compared to that of bumetanide. The 4th strategy did not yet result in NKCC1-selective drugs, so that the interdisciplinary group performing these studies started to synthesize various novel bumetanide derivatives, which are currently evaluated. We expect that we will resolve the major disadvantages of bumetanide soon.

CANNABIDIOL (CBD, EPIDIOLEX®) FOR TREATMENT-RESISTANT EPILEPSY 2016 UPDATE

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Cannabidiol (CBD, Epidiolex®) is derived from the Cannabis sativa plant. CBD is reported to be non-psychoactive (1).

The mechanism of action of CBD is not definitively known. CBD binds to the CB1 and CB2 receptors with very little affinity and its primary anticonvulsant activity is not likely from blockade of voltage gated sodium channels (2). CBD modulates intra-cellular calcium flux (3). CBD is an agonist at the TRPV1, 2 and TRPA1 channels, the 5-hydroxytryptamine 1A receptor, and glycine receptors, possibly related to antagonism at voltage-gated Ca++ channels and the G-protein coupled receptor GPR55 (4). CBD also shows anti-inflammatory effects likely to be mediated by its inhibition of adenosine re-uptake. Anti-convulsive activity has been found in acute models of pentylenetetrazol, pilocarpine, penicillin, maximal electroshock, and audiogenic seizures (5). CBD was better tolerated than valproate, ethosuximide, and phenobarbital on the static beam test in animal models (6).

CBD is highly lipophilic and protein bound (5). It is metabolized in the liver by the CYP3A4 and 2C19 isoforms. It is also a potential inhibitor of CYP2B6, 2C8, 2C9, 3A4 and 2C19 isoforms. The latter may be leading to an interaction with the active N-desmethyl metabolite of clobazam (7).

A large open-label compassionate use study across a number of epileptic encephalopathies in children and young adults is ongoing (8). The study to date includes 313 patients with any exposure for safety and 261 (with at least 12 weeks exposure) for efficacy. The average age was 11.8 years old, in patients taking an average of 3 antiepileptic drugs.

Total convulsive seizure counts were reduced by a median of 48.8 % for all patients and 52.3% for Dravet patients between weeks 8 and 12, respectively. There was a median reduction of 71.1% in atonic seizures among patients with Lennox-Gastaut Syndrome over the same period. While a better response was noted in all patients taking clobazam, this was not found in the subsets of patients with a diagnosis of Dravet or Lennox-Gastaut Syndrome.

There were 14 patients (4%) who discontinued for adverse events and 36 (12%) who discontinued for lack of efficacy. Adverse events ≥10% included somnolence and diarrhea (each 23%), fatigue, convulsions and decreased appetite (each 17%), and vomiting (10%).

CBD appears to reduce multiple seizure types with a good safety profile that may be an important treatment for encephalopathic epilepsies of childhood. CBD is now in double-blind placebo controlled trials for the treatment of Dravet and Lennox-Gastaut Syndrome.

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EPILEPSY

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Cannabidivarin (CBDV) is a cannabinoid derived from cannabis sativa and an analogue of cannabidiol (CBD). The only structural difference is the propyl side chain. CBDV was first isolated in 1969 (1) and is far less abundant in cannabis compared to CBD. It is presently in Phase 2 trials for focal epilepsy in adults.

CBDV has shown multiple anti-convulsive effects. In hippocampal slices on a multi-electrode array, it significantly reduced the epileptiform effects of 4-aminopyridine and Mg+2 local field potentials (2). It has shown efficacy in multiple acute animal models of seizures including maximal electroshock, audiogenic, PTZ-induced, and penicillin-induced models and at the highest dose tested in acute pilocarpine-induced seizures (2). The positive effects of CBDV on seizure severity and seizure related mortality were retained when given with ethosuximide, valproate, or phenobarbital (3). CBDV also showed anti-convulsive effects on a lithium pilocarpine model of temporal lobe epilepsy (TLE) (3).

The mechanism of action of CBDV is not precisely known. It is not through interaction with the CB1 receptor (4). Other interactions with the TRP receptors are also not thought to be likely. The mechanism needs further research, especially in comparison to cannabidiol (CBD).

The potential effects on motor function of CBDV were compared to ethosuximide, valproate, and phenobarbital with the static beam test (2). CBDV had no significant effects, unlike the other antiepileptic drugs (AEDs). Cognition and motor performance actually improved with CBDV in animals with TLE. This is very encouraging for the further development of CBDV. Toxicology studies have so far shown no single organ toxicity, even at high doses (5).

The clinical program has included a Phase 1 single ascending dose and multiple dose pharmacokinetic study in healthy human volunteers (6). There was also a single dose intravenous arm. CBDV showed good tolerability. No serious or severe adverse events or discontinuations for adverse events were reported. The details of this study are not yet published. An additional Phase 2 pharmacokinetic and safety study has completed in adult patients with focal seizures that assessed whether CBDV pharmacokinetics could be affected by enzyme inducing or inhibiting AEDs. A Safety Monitoring Board recommended that the second part of the study could safety proceed without adjustments to the dosage of CBDV (6).

The further development of CBDV will require additional pharmacokinetic study to determine the bioavailability and whether there may be active metabolites. It will

be studied in focal epilepsy. Other epilepsies and CNS conditions are being considered.

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EVEROLIMUS

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Everolimus is a selective inhibitor of the mTOR (mechanistic/mammalian target of rapamycin) complex, specifically targeting mTORC1. Everolimus was initially developed as an antitumoral agent, but it later became evident that it could serve as a targeted drug for tuberous sclerosis complex (TSC)-related manifestations.
Preclinical research using animal models, either due to genetic modification or treatment with seizure-inducing agents, has demonstrated that everolimus could exert both an anticonvulsant action and an antiepileptogenic effect in models of genetic and acquired epilepsy.
Everolimus is a substrate of CYP3A4 and PgP. Therefore, its absorption and elimination can be influenced by compounds that affect CYP3A4 and/or PgP, and these compounds should be preferably avoided in patients treated with everolimus. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, adjustments of everolimus dose may be required. Antiepileptic drugs which are inducers of CYP3A4 or PgP, such as carbamazepine, phenytoin and phenobarbital, may decrease everolimus blood concentrations by increasing everolimus metabolism.
There are still limited clinical data on the effect of everolimus in epilepsy. A prospective trial designed to evaluate the safety and efficacy of everolimus on subependymal giant cell tumors followed-up 28 patients for 6 months, and 16 of them underwent 24-h video-EEG monitoring. In this study, seizure frequency during everolimus treatment decreased in 9, did not change in 6, and increased in one. The same group performed a Phase I/II trial to evaluate the efficacy of everolimus in medically refractory TSC-related epilepsy, and reported a >50% seizure frequency reduction in 12/20 patients. Recently, two case series of patients with refractory TSC-related epilepsy treated with everolimus in Germany and Australia have been published, with an overall good response and more than 50% of patients being apparent responders.
A phase III study (EXIST-3) is currently ongoing, aiming to assess the efficacy/safety of everolimus 3-7 or 9-15 ng/mL targeted trough concentration ranges vs. placebo as adjunctive therapy in patients with refractory partial-onset seizures associated with tuberous sclerosis complex. Up to October 2015, 366 patients have been enrolled, and preliminary data are expected in 2016.

ZX008 (LOW-DOSE FENFLURAMINE HCL) FOR UNCONTROLLED SEIZURES IN DRAVET SYNDROME

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Zogenix is developing ZX008, an oral solution of fenfluramine hydrochloride, as an adjunctive therapy for children and adolescents with uncontrolled seizures in Dravet syndrome (DS). DS, also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a severe form of childhood epilepsy described by Charlotte Dravet in 1978 and has been linked to mutations of the SCN1A gene. The condition appears in infancy as frequent febrile seizures and progresses with the development of additional seizures types, comorbid neurological dysfunction, and cognitive impairment. Only one treatment, stiripentol (Diacomit®), is approved in the EU, Canada and Japan for use with clobazam and valproate to treat seizures in DS. Many patients with DS do not achieve adequate long-term seizure control despite polypharmacy and other interventions. Thus, there remains a need for additional treatment options. Based on early preclinical reports of serotonin agonists exerting antiepileptic effect, several neurologists administered fenfluramine (when it was available commercially until 1997) to children with refractory self-induced photosensitive seizures with good outcomes (Aicardi, Gaustat 1995). This then led to a trial of fenfluramine to children with generalized tonic clonic seizures by Boel and Casaer (1996). Building on this work, Ceulemans and Lagae have been investigating fenfluramine for the treatment of DS at 2 academic medical centers in Belgium in 19 subjects ranging over a 27 year period. Results from this ongoing open-label study indicate that fenfluramine administered as adjunctive therapy for uncontrolled seizures to children and adolescents with DS at doses ranging from 0.1 to 0.9 mg/kg/day is associated with clinically meaningful reductions in seizure activity that have been maintained over long periods of time, in most cases from months to years. Further, treatment with fenfluramine was generally well tolerated without any signs or symptoms of cardiotoxicity, the cause of fenfluramine's withdrawal in 1997. It is believed, based on the proof-of-concept study in Belgium, that fenfluramine may be efficacious as adjunctive treatment for patients with uncontrolled seizures in DS and have an acceptable benefit to risk ratio in this population. Zogenix is developing low-dose ZX008 (fenfluramine HCl) oral solution as adjunctive treatment for uncontrolled seizures in children and young adults with DS with ongoing Phase 3 trials running in North America, western EU and Australia. Data from the open-label study, and aspects of the Phase 3 program will be presented.

FV-082: A SAFER ORALLY ACTIVE BROAD SPECTRUM: ANTI-EPILEPTIC DRUG CANDIDATE

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Broad spectrum Anti-Epileptic Drugs (AED) are valued for their potential to treat refractory epilepsy and as general 'neurostabilizers' and have been employed for a variety of neurological diseases. However, the benefits of historical AEDs have been constrained by unintended CNS side effects. Combining proprietary breakthrough chemistry with Fluorinov Pharma and NIH's *in vivo* phenotypic screening strategy identified three completely novel candidate drugs, including **FV-082** with superior safety and efficacy profiles. **FV-082** was elected by ASP screening program as one of the most successful compounds that received a comprehensive profile report (known as a "Red Book) detailing all generated biological and comparative data.

Pharmacology

FV-082 was screened across available *in vitro* and rodent seizure models at ASP, and was found to display an excellent spectrum of anti-seizure activity and safety profiles superior to that produced by Depakote, Neurontin and Keppra. **FV-082** prevented seizures induced by sound in the Audiogenic Seizure (AGS)-susceptible Frings mouse model (i.p) with an ED_{50} value of 13.0 ± 2.0 mg/kg. In addition, **FV-082** displayed significant efficacy in the electrically induced corneally kindled mouse, kindled rat amygdala and hippocampal seizures models. Importantly, **FV-082** was also found to limit seizure spread and elevate seizure threshold in the Mesial Temporal Lobe Epilepsy (MTLE) acute models. Also, the anticonvulsant pharmacology suggests applicability for treating multiple forms of epilepsy, at dose levels that confer a favorable safety margin (therapeutic index ≥ 34). Furthermore, in models of neuropathic pain (spinal nerve injury [SNI] and formalin inflammatory pain, administration of a single dose showed robust efficacy without any signs of sedation.

Safety and Toxicology

Safety assessment of **FV-082** suggests no interaction with the major CYP isoenzymes when tested up to 500 µM and no functional *h*ERG activity when tested up to 20 µM. Further, acute toxicity studies revealed that **FV-082** exhibited a maximally tolerated dose greater than 600 mg/kg in mice (i.p) and rats (p.o). Also, there was a pronounced safety margin between behavioral efficacy and MES neurotoxicity for a protective index >34-fold, with an MTD greater than 1000 mg/kg (p.o) in mice and rats and greater than 120 mg/kg (p.o) in the dog. Further, 14 day Irwin and acute toxicity studies at oral doses of 200 and 400 mg/Kg in rat suggest that **FV-082** is very well tolerated. Furthermore, a telemetry cardiopulmonary

safety indicated no evidence of adverse effects following a single oral dose, up to 120 mg/kg. Moreover, **FV-082** does not have the narrow CNS therapeutic index in animals that is characteristic of many AEDs. Hence, **FV-082** displays a considerably broader CNS therapeutic index superior to historical AEDs. **FV-082** has excellent oral bioavailability and good oral half-life, and excellent plasma drug levels. Profiling across 100 known GPCR, ion channel, transporter and enzyme targets studies suggest that several mechanisms contribute to the observed pharmacological profile of **FV-082** but that no single mechanism is likely to be a major contributor. Based on these promising preclinical data, **FV-082** warrants clinical investigation.

GANAXOLONE

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Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a CNS- selective, positive allosteric modulator of the GABAA receptor. It is a 3β-methylated synthetic analog of the endogenous progesterone metabolite, allopregnanolone, but designed not to activate nuclear (classical) progesterone receptors. Ganaxolone differs from other GABA agents by interacting with both synaptic and extrasynaptic GABAA receptors and at binding sites distinct from benzodiazepines. Seizure protection has been demonstrated with ganaxolone in a broad range of animal seizure models, and unlike other GABAA receptor modulators, ganaxolone does not show tolerance to anticonvulsant activity.

Ganaxolone is being developed as adjunctive therapy for the treatment of focal-onset seizures (FOS) in adults, as well as in two orphan pediatric programs (genetic epilepsies and anxiety and attention in Fragile X Syndrome). In adult epilepsy, we have completed a Phase 2 clinical trial in 147 patients with focal onset seizures who added ganaxolone to their medication regimen and experienced a statistically significant reduction in seizures as compared to patients who added placebo. We are currently conducting a double-blind, randomized Phase 3 clinical trial using a twice daily capsule formulation of ganaxolone at doses up to 1800 mg/day in patients with drug-resistant focal onset seizures. Safety and tolerability from our ongoing studies is consistent with adverse events previously reported in our clinical program of over 1300 subjects. The majority of the adverse events in the ongoing studies (FXS, pediatric genetic epilepsies, and focal onset seizures) are consistent with GABA-ergic mechanism of action or the disease. No clinically important, systematic changes in vital signs, safety laboratory results or ECGs have been noted thus far further supporting that ganaxolone is generally safe and well tolerated.

Marinus recently developed an intravenous (IV) formulation of ganaxolone. This formulation has been tested in Good Clinical Practice (GLP) pre-clinical toxicology studies and found to be safe and well-tolerated. In preclinical models of diazepam-resistant status epilepticus, intravenous administration of ganaxolone produced a sustained reversal (> 5h) of epileptic activity and promoted survival in comparison to animals who received vehicle. Marinus is planning to commence Phase I development of intravenous ganaxolone for treatment of status epilepticus in 2016.

OXINYTAMS

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Oxinytams are new chemical family of compounds that have been developed by Owen Barry Pharmaceuticals. They are small molecules that have a molecular weight of less than 300g. They are easily synthesized in a few steps from readily available precursors. In the past 2 years we have screened over 75 different compounds. Our screen for activity uses voltage sensitive dye imaging (VSDI) which permits us to assay neuronal activity in vitro using rat piriform cortex (PCtx) brains slices. We stimulate the major input to this brain region, the lateral olfactory tract, at differing frequencies for 1 second. This stimulation activates the PCtx circuitry. Each compound was tested at high and low concentrations for their ability to decrease the activation of the pyramidal cell layer. Our screen also assayed for differences in efficacy to block high versus low frequencies stimulus trains. To date we have identified four compounds which at in low nM concentrations block about 50 % of the activation due to a 60 Hz pulse while having little activity on a 20 Hz train. Single cell patch clamp recordings show that these compounds slow sodium channel activation but have little or no tonic block of sodium channel activity. Dose response relationships constructed on two of these compounds (TD 532 and TD 561) showed the 50% block of the sodium channel activity 16 ms after a control voltage step was 10 nM and 10 pM respectively. In the rat amygdala kindling model, TD 532 (100 mg/kg) completely stopped seizures and doubled thresholds to induce a stage 5 seizure. TD 561 (5 and 20 mg/kg) also completely abolished any seizure activity and also doubled threshold to induce a seizure. Histopathology analyses showed that TD532 has no organ toxicity after 25 days of dosing. Acute dosage LD50 for TD 532 was about 600 mg/kg while at doses up to 600 mg/kg TD 561 had no mortality. Neither compound has any significant effect on CYP3A4 activity. An in vitro cardiomyocyte assay showed no effect at the IC80 for both compounds. Finally, motor behaviour assayed in mice was not impaired at doses that block seizure activity. Our preclinical data indicates that we have produced a novel family of compounds that block seizures while having little or no behavioural or toxicological outcomes.

DEBATE:
IS KNOWLEDGE OF MECHANISM OF ACTION ESSENTIAL FOR THE DEVELOPMENT OF NEW AEDS? YES

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Modern drug discovery is one of the most complex scientific areas and involves many different scientific disciplines. The first 100 years of modern drug discovery, starting at the end of the nineteenth century, were largely target and mechanism-agnostic and primarily driven by chemocentric approaches, i.e., approaches based on a specific compound or compound class which served as starting point for further optimization. Serendipity was also an important success factor in many instances. With the advent of modern molecular biology methods and based on knowledge of the human genome, drug discovery has now largely changed into a hypothesis-driven target-based approach. Almost all drug discovery now begins with activity of molecules on a molecular target, and it is hard to imagine how the primary target of such molecules would be unknown. The initial research, often occurring in academia, generates data to develop a hypothesis that the inhibition or activation of a protein or pathway will result in a therapeutic effect in a disease state. The outcome of this activity is the selection of a target which may require further validation prior to progression into the lead discovery phase in order to justify a drug discovery effort. During lead discovery, an intensive search ensues to find a drug-like small molecule or biological therapeutic, typically termed a development candidate, that will progress into preclinical, and if successful, into clinical development and ultimately be a marketed medicine. In addition to target-based drug discovery approaches, phenotypic drug discovery (by simultaneously interrogating multiple, biologically relevant molecular targets and pathways to discover compounds that modulate relevant biological processes in a target/mechanism agnostic fashion) is still useful to identify novel functions for well-studied proteins and thus discover new pathways of therapeutic value. However, phenotypic approaches require significant investment in target deconvolution, although target identity may not be necessary for drug registration. While serendipity and phenotypic screening will remain important, mechanism of action has become a central feature of drug discovery. As in many other areas of drug discovery, discovery of novel compounds for epilepsy therapy is largely changing into a hypothesis-driven target-based approach. Target-based drug discovery enables a great expansion of chemotypes and pharmacophores. Furthermore, it allows causal mechanism-specific interventions rather than purely symptomatic treatment. Thus, target-identification and mechanism-of-action studies will have important roles in discovery of novel epilepsy therapies, including antiepileptogenic treatments.

PREDICTORS OF ADVERSE EFFECTS

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Adverse effects (AEs) of antiepileptic drugs (AEDs) have dramatically high prevalence and impact on quality of life, and are at times life-threatening or fatal. Yet, thanks to many identified risk factors, one can predict the individual risk of AEDs' side effects and minimize it by selecting the most appropriate treatment and dosage. Prediction of AEs starts with a comprehensive knowlegde of each AEDs' tolerability profile. Age, gender, past-history and comorbidities have a major influence on the risk of AEs. Children are at higher risk of idiosyncratic reactions, in particular valproate (VPA) induced hepatotoxicity before 2 year of age and lamotrigine (LTG) induced severe rash, as well as behavioral problems trigerred by barbiturates or benzodiazepines (BZD). Elderly patients are at increased risk of virtually all AEs, including idiosyncratic reactions, often in relation to altered AEDs' pharmacokinetic or pharmacodynamic and more frequent drug-drug interaction. Women carry the specific burden of teratogenicity and interaction with oral contraceptives, while male are at greater risk of vigabatrin-induced visual field defect. Past-history and comorbidities are associated with higher risk of AEs affecting the same system/organ such as idiosyncratic reactions in patients with past-history of similar reaction to other drugs, autoimmune disease, or organ dyfunction, and psychiatric side effects in patients with familial or personal mental health disorders. Specific cautions are needed in patients with learning disabilities who often suffer many comorbidities and lowered capacities to report AEs. Finally, HLA-B*1502 genotype strongly predicts the risk of carbamazepine (CBZ) (and possibly other sodium channel blockers) induced rash in asian populations. A weaker association is observed with HLA-A*3101 genotype in various populations.

BIS-001 FOR REFRACTORY CPS AND DRAVET

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Biscayne Pharmaceuticals is focused on developing and utilizing compounds for the treatment of neurological diseases and cancers. Our lead compound is a synthetic form of the potent acetylcholinesterase inhibitor huperzine A (BIS-001). Huperzine has been used in China for hundreds of years for the treatment of cognition-related disorders, and has displayed potent analgesic effects in animal models of neuropathic, central, and inflammatory pain. Having a novel mechanism of action for the prevention of seizure activity, BIS-001 has displayed potent anti-seizure capabilities in predictive animal seizure models (e.g. 57x more potent than Keppra in the 6 Hz model of refractory CPS; 100% elimination of seizures in knock-in and knock-out models of Dravet/.GEFS+).

In a completed Phase I clinical trial, we demonstrated that the current rapid release form of huperzine resulted in high peak serum levels and thus maximal plasma concentration and time related, class associated side effects. Given the data demonstrating the effectiveness of huperzine in several seizure models, Biscayne is currently developing a novel extended release formulation of BIS-001 to eliminate the rapid pharmacokinetics of the current formulation.

Preliminary and ongoing studies have produced a formulation that has significantly extended in vitro dissolution supporting a twice-a-day dosing target. The benefit/risk profile of BIS-001 is quite differentiated from current therapies, not only because it has potential to reduce seizure activity dramatically, but also because it has cognition-enhancing properties while having a longstanding use experience which helps substantially minimize risk of new tolerability issues.

Accordingly, we hope BIS-001 will be a safe, effective therapy for people afflicted with refractory seizure disorders and plan on entering Phase 2 studies later in 2016.

MINOCYCLINE

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Minocycline is a second generation semi-synthetic, broad-spectrum bacteriostatic tetracycline analogue that has anti-inflammatory, immunomodulatory and anti-apoptotic properties. It is the most lipid-soluble of the tetracycline-class antibiotics, giving it the greatest penetration into the brain.
Anti-inflammatory action of minocycline is mediated by inhibition of excitoxin-induced proliferation and activation of microglia as well as inhibition of the activity of matrix metalloproteinases, inducible nitric oxide synthase (iNOS) and cyclooxygenases-2 (COX-2). Mechanisms of minocycline-mediated neuroprotection include direct action of minocycline on the mitochondria to inhibit cytochrome-c release, blockade of death receptor pathways and inhibition of activated microglia. Thus, minocycline has shown efficacy in focal and global ischemia, traumatic brain injury, SIV-macaque model of HIV CNS disease, experimental autoimmune encephalomyelitis, as well as in animal models of neurodegenerative diseases including Huntington, Parkinson, Alzheimer's, and amyotrophic lateral sclerosis. Role of activated microglia in enhancing neuronal excitability has increasingly gained acceptance as important contributors in pathogenesis of acquired epilepsies. Anticonvulsant action of minocycline was, therefore, tested in vivo by using the maximal electric shock (MES), 6-Hz test and subcutaneous Metrazol (scMET) models of seizures. Minocycline showed dose-dependent anticonvulsant effects in abolishing partial seizure in the mouse 6-Hz seizure test with ED50 of 170mg/kg. Minocycline had no effects on the MES and scMET tests. Minocycline blocked the long-term epileptogenic effect of early life seizures and attenuated spontaneous recurrent seizures following status epilepticus. Likewise, minocycline retarded kindling epileptogenesis, decreased stage 5 seizure duration, reduced after discharge duration and made animals more resistant to seizure generation in amygdala kindled rats. Minocycline has shown to exert acute inhibitory effects on cortical excitability in humans. Minocycline significantly increased the duration of mean cortical silent period, a measure of intracortical inhibition, in a randomized, double-blind, placebo-controlled crossover study of transcranial magnetic stimulation. An open-label trial of minocycline in children with Angelman syndrome established minocycline to be well tolerated and to improve the adaptive behaviors. Similarly, short term treatment with minocycline improved communication, attention and anxiety in children with Fragile X syndrome. These studies raise a possibility of future use of minocycline as a potential disease-modifying agent not only to block epileptogenesis, but to ameliorate neuropsychiatric co-morbidities in pediatric epilepsy. Minocycline has merit to be considered as a novel therapy for epilepsy because of its ability to penetrate the BBB, proven human safety record, low cost and promising preliminary data. Minocycline may work synergistically with compounds targeting other pathological mechanisms of disease progression in epilepsy.

NAX 810-2

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Galanin has demonstrated anticonvulsant effects in animal models of seizures and epilepsy, but the development of this neuropeptide as a therapeutic is hindered by poor metabolic stability and lack of blood-brain barrier penetration. The GalR2-preferring galanin analog, NAX 810-2, has demonstrated efficacy in animal seizure models, namely the mouse 6Hz model and the mouse corneal kindling model, following intravenous and intraperitoneal administration. Furthermore, NAX 810-2 avoids GalR1-mediated reduction in insulin secretion and concomitant hyperglycemia. This analog has been further evaluated in safety and pharmacokinetic studies where the compound was observed to be well-tolerated when administered by i.v. injection to mice at therapeutically active doses. NAX 810-2 has a half-life of approximately 1.2h in mice following i.v. administration and approximately 2h in rats following intraperitoneal administration. In infusion studies, peak plasma levels occurred approximately 1h after infusion onset. Further studies, including safety pharmacology and chronic administration studies, will be conducted in anticipation of an investigational new drug application.

1OP-2198, A 2nd GENERATION KV7.2/7.3 OPENER WITH IMPROVED POTENCY, SELECTIVITY AND KINETIC PROPERTIES

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1OP-2198 is a highly selective, 2nd generation, opener of neuronal Kv7 (KCNQ) potassium channels; the molecular component of the slow activating/deactivating voltage-gated M-current.

In vivo, 1OP-2198 protects against maximal electroshock (MES), sc PTZ, sc Picrotoxin, sc Bicuculline and 6 Hz seizures. In tests conducted by the sponsor, ED50s in MES were 1.1 mg/kg and 2.2 mg/kg in rat and mouse, respectively. ED50s in the other tests were generally ≤5 mg/kg. In CHO cells expressing Kv7.2 and in PC-12 cells EC50 values were 11 and 15nM, respectively. Selectivity of >100-fold against other ion channels and receptors is present when defined as no effect >5% and there is no GABA activity.

In monkey, after IV administration, the mean half-life is 7.8 hours and plasma clearance is 25.7% of hepatic blood flow. After a single oral dose of 1 mg/kg, the mean half-life increases to 11.5 hours; with Tmax occurring at 2.2 hours and peak concentrations of 127nM. There is apparent increasing dose proportionality in monkey; at 10 mg/kg the Tmax is 2 hours and Cmax is 295nM. Upon micronization of drug substance the same 10 mg/kg dose exhibits a 2-fold increase in Cmax and a sustained Tmax from 2-4 hr post dose. 1OP-2198 at concentrations up to 3 μM (highest concentration tested) did not inhibit recombinant expressed CYP enzymes in a nonGLP assay. An in vitro permeability assay based on the MDR1-MDCK cell line demonstrated that 1OP-2198 has high A-B and B-A permeability and an efflux ratio less than 1, which suggests high brain penetration.

The nonclinical IND enabling toxicology package of studies, including 28-day oral toxicity in rats and cynomolgus monkey, based on International Conference on Harmonization (ICH) guidelines in support of oral administration is completed and has demonstrate adequate safety to start clinical trials. Adverse events in the 28-day monkey study were expected CNS AEs mild/moderate in severity within the high-dose group. There was no observable effect on cardiovascular safety at the highest dose evaluated in the monkey and there are no signs of genotoxicity. The First-in-Human (FIH) trial is planned for 2016.

PITOLISANT (TRIPOLISANT)

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Pitolisant (also known as BF 2.649 and tripolisant) is the very first Histamine 3 receptor (H3R) antagonist investigated in patients with epilepsy. Pitolisant, 1-[3-[3-(4-chlorophenyl) propoxy] propyl]-piperidine monohydrochloride, was effective in different seizure models in rats and mice, predictive for generalized and partial type of epilepsies. The anti-epileptic properties of the drug were confirmed in humans, in the "Photosensitivity Model", a Proof of Concept study.
This non-imidazol inverse H3R agonist/antagonist developed by Bioproject (Paris, France), has previously been presented at the EILAT XII conference (Bialer et al., 2015). Since then the interest in H3R antagonists for epilepsy has been growing substantially. An update will be given.

SAGE-217 and SAGE-689: NEXT GENERATION NEUROACTIVE STEROID GABA-PAMS DEVELOPMENT PROGRESS UPDATE

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Neuroactive steroids (NASs), such as allopregnanolone, have been shown in animal studies to be potent positive modulators of ionotropic GABAA receptors (GABAARs). Several of these compounds are being studied for their potential in the treatment of a variety of CNS conditions, including status epilepticus (SE), certain neurological conditions characterized by a high seizure burden, and essential tremor. Next-generation GABAAR-potentiating NASs exhibit substantially reduced off-target liabilities in animal models compared to the known first-generation analogs of similar structure, and furthermore, can be optimized for different routes of delivery (e.g. oral, fast on/off intravenous (i.v.)). SAGE-217 and SAGE-689 are novel next-generation NASs that act as positive allosteric modulators (PAMs) of GABAARs. Similar to SAGE-547, a proprietary formulation of allopregnanolone, these next-generation NASs potentiate the activity of both synaptic and extrasynaptic GABAARs.

SAGE-217 is a next-generation NAS with highly potent and selective activity at GABAARs that, in contrast to endogenous NASs, has an optimized pharmacokinetic (PK) profile intended to support once daily, low dose oral administration. In multiple animal models, SAGE-217 has demonstrated anti-seizure and anxiolytic activity, including potent activity in chronic (mesial temporal lobe epilepsy) and genetic (Fragile-X syndrome) pre-clinical epilepsy models. SAGE-217 is being developed as a treatment for epilepsies characterized by a high seizure burden and other GABAA dysfunction-related disorders, such as essential tremor. A Phase 1 clinical program of SAGE-217 is ongoing, which includes a single ascending, double blind, placebo-controlled trial to evaluate the safety, tolerability, PK, and pharmacodynamic effects of SAGE-217 administered orally in approximately 80 healthy adult volunteers.

SAGE-689 is a next-generation NAS with high selectivity for synaptic and extrasynaptic GABAARs that is being developed as an acute, adjunctive IV therapy for the treatment of patients with SE whose seizures have not resolved following treatment with traditional first-line therapy (benzodiazepines). It has improved aqueous solubility in comparison to SAGE-547, supporting formulation optimized for rapid i.v. delivery. Additional investigational new drug (IND)-enabling safety pharmacology testing of SAGE-689 is ongoing.

SAGE-689 alone, as well as in combination with sub-active doses of diazepam, has been shown to rapidly abort seizures in a pharmaco-resistant SE animal model (lithium-pilocarpine rat model), and has shown a clean drug-drug interaction profile and a wide therapeutic window to date in animal testing. Furthermore, SAGE-689's short half-life allows the potential for response-based dose titration.

REVERSIBLE DOSE-DEPENDENT, SPECIES-SPECIFIC, AUTOPHAGIC CARDIAC MYOCYTE VACUOLATION ASSOCIATED THE NOVEL ANTICONVULSANT, DISEASE-MODIFYING ANTIEPILEPTIC, AND NEUROPROTECTIVE EFFECTS OF 2DG: IMPLICATIONS AND APPROACHES FOR THERAPEUTIC DEVELOPMENT

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2DG (2-deoxy-D-glucose) is a glucose analogue and reversible inhibitor of glucose metabolism with novel acute anticonvulsant, chronic disease-modifying antiepileptic actions, and neuroprotective actions in experimental models of epilepsy and TBI. As glycolysis is a prominent bioenergetic metabolic pathway in both the brain and the heart, it is not surprising that the favorable therapeutic actions of glycolytic inhibition by 2DG on energy dependent CNS pathophysiology underlying epilepsy and TBI might potentially also affect cardiac function. Dietary administration of 2DG in rats was initially reported to induce dose-dependent clinical and pathological cardiac alterations including cardiac myocyte vacuolation with features of autophagy, as might be anticipated in response to metabolic stress from glycolytic inhibition (Minor et al. Toxicology and Applied Pharmacology 243:332–339,2010). Preclinical toxicological studies of 2DG have confirmed dose-dependent, reversible cardiac myocyte vacuolation with features of autophagy in rats, which were not observed in dogs and appear to be species-specific. The alterations were observed at doses of 120-250 mg/kg/day which correspond to body surface area adjusted human doses of ~ 20-40 mg/kg, had onset after 14 days of administration, and were completely reversible with a 14-day recovery as would be expected for autophagy. The development and resolution of myocyte vacuolation was reliably tracked by significant (~2-fold) elevation of the cardiac biomarker NT-proBNP. These preclinical observations, and human oncology studies demonstrating safety and tolerability of 40 mg/kg/day doses for 14 days and longer, support potential therapeutic use of 2DG for acute administration in status epilepticus, seizure clusters, in combination with device therapy, as a neuroprotectant after TBI, and may also support chronic antiepileptic therapy at lower dose ranges.

VALNOCTAMIDE AND SEC-BUTYLPROPYLACETAMIDE (SPD): SECOND GENERATION DRUGS TO VALPROIC ACID

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All SPD anticonvulsant data presented in EILAT XII (2014) have been obtained after i.p. administration. However, i.p. administration to rats cannot be extrapolated to humans but in contrast to i.p., intramuscular (i.m.) dosing in rats can be extrapolated to humans as it is a common extravascular route of administration to humans. In addition, i.m. administration is considered as a "mass-causality friendly" route of administration for medical counter measures to be used in the initial treatment of exposures to chemical threats. Consequently, recently a comparative pharmacokinetic (PK)-pharmacodynamic (PD) analysis of SPD was conducted following i.p., i.m. and i.v. administrations to rats including estimating SPD's absolute bioavailability following these two extravascular administrations.
SPD absolute bioavailability following i.p. and i.m. administration was 76% and 96%, respectively, and its clearance and half-life were 1.8-2.5 L/h/kg and 1.5-1.7h, respectively. SPD brain-to-plasma-(AUC)-ratio (BPR) after the various routes of administration was 1.86 (i.v.), 0.77 (i.m.) and 2.31 (i.p.). In spite of the partial i.p. bioavailability (F=76%) and a reduced BPR after i.m. dosing , the ED_{50} values of SPD and its individual stereoisomers when given at 30 min after seizure (SE) onset were almost identical following i.p. and i.m. administration to rats.SPD lower BPR after i.m. administration may be due to the slower SPD absorption rate compared to the i.p. route. The BPR of VPA, VCD and VPD in rats is 0.16, 1.0 and 1.0, respectively. Thus, SPD's BPR is 12 times better than that of VPA and twice higher than that of VCD and VPD. SPD better brain permeability may be one of the reasons for its better anticonvulsant potency compared to VPA and to VCD in the pilocarpine-SE model. Although SPD's Protective Index ($PI=TD_{50}/ED_{50}$) in the pilocarpine-SE model is less than 1, for a serious life-threatening condition such as refractory status epilepticus (SE), it is extremely important that the convulsive seizures be controlled as quickly as feasible as “time is brain". The finding that SPD is effective against BZD-resistant SE in the pilocarpine and the soman models is extremely important as it suggests that SPD could be an important alternative to the currently available "standards of care". As previously shown in previous work, SPD does indeed preserve long-term cognitive function and reduces neuronal damage as measured by FluorJade B staining. In a recent study SPD’s antinociceptive potential was evaluated in neuropathic and acute inflammatory pain models. SPD was evaluated (in comparison to VPA) in the formalin, carrageenan and writhing tests where SPD showed either higher or equal potency

to VPA. The ability of SPD to modify compound action potentials (CAPs) was evaluated in a rat peripheral sciatic nerve preparation using a modified sucrose-gap recording, where it showed no effects on CAPs properties.

SPD's anti-migraine potential was evaluated in the cortical spreading depression (CSD) and nitroglycerin (NTG) models of migraine. In the CSD model, the SPD-treated group showed a significantly lower median number of CSDs compared to controls. In the NTG-induced mechanical allodynia model, SPD dose-dependently reduced mechanical sensitivity compared to controls. These results show SPD's potential as a promising novel anti-migraine compound, and suggest a GABAergic mechanism of action (Kaufmann et al., 2016).

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IMEPITOIN: A NEW ANTIEPILEPTIC DRUG FOR CANINE EPILEPSY

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Although benzodiazepines (BZDs) offer a wide spectrum of antiepileptic activity against diverse types of epileptic seizures, their use in the treatment of epilepsy is limited because of adverse effects, loss of efficacy (tolerance), and development of physical and psychological dependence. BZDs act as positive allosteric modulators of the inhibitory neurotransmitter GABA by binding to the BZD recognition site ("BZD receptor") of the $GABA_A$ receptor. Traditional BZDs such as diazepam or clonazepam act as full agonists at this site, so that one strategy to resolve the disadvantages of these compounds would be development of partial agonists with lower intrinsic efficacy at the BZD site of the $GABA_A$ receptor. Several partial or $GABA_A$ receptor subtype selective compounds, including bretazenil, abecarnil or alpidem, have been developed as anxioselective anxiolytic drugs, but epilepsy was not a target indication for such compounds. More recently, the imidazolone derivatives imepitoin (ELB138) and ELB139 were shown to act as low-affinity partial agonists at the BZD site of the $GABA_A$ receptor, and imepitoin was developed for treatment of epilepsy. Imepitoin displayed a broad spectrum of anti-seizure effects in diverse seizure and epilepsy models at tolerable doses, and, as expected from its mechanism of action, lacked tolerance and abuse liability in rodent and primate models. In addition to anti-seizure activity, imepitoin and ELB139 exerted anxiolytic effects in various rodent models. The more favorable pharmacokinetic profile of imepitoin in dogs vs. humans led to the decision to develop imepitoin for treatment of canine epilepsy. Based on several randomized controlled trials that demonstrated antiepileptic efficacy and high tolerability and safety in epileptic dogs, the drug was approved for this indication by the European Medicines Agency (*EMA*) and is marketed by Boehringer-Ingelheim under the trade name Pexion®. Preliminary findings in epileptic dogs indicate that, in addition to suppressing seizures, imepitoin also suppresses some of the behavioral abnormalities, including anxiety, associated with epilepsy in dogs. Evaluation of the anti-seizure efficacy of imepitoin in other species such as cats or horses is planned. Hopefully, the favourable profile of imepitoin for treatment of epilepsy in dogs will reactivate the interest in partial BZD site agonists as novel treatments for human epilepsy, too. Indeed, in a recently published proof-of-concept clinical study, abecarnil was demonstrated to exert anti-seizure efficacy in patients with photosensitive epilepsy.

LACOSAMIDE CLINICAL DEVELOPMENT UPDATE

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Lacosamide (LCM, Vimpat®) is approved as adjunctive therapy for adults with focal epilepsy in the US and Europe, and as monotherapy in the US. The ongoing development programme involves extending its geographical reach and new indications.

In the European registration trial SP0993 (NCT01243177), 888 patients were randomized to LCM or carbamazepine controlled-release (CBZ-CR) monotherapy; 886 were included in the full analysis set (FAS) and 805 in the per-protocol set (PPS). Based on Kaplan-Meier estimates, 89.8% of LCM- and 91.1% of CBZ-CR-treated patients (FAS) remained seizure-free for 6 months. Treatment difference was –1.3% (95% CI –5.5, 2.8), demonstrating non-inferiority of LCM to CBZ-CR (lower 95% CI limit > –12%). Results were similar for PPS (91.5% vs 92.8%; –1.3%, 95% CI –5.3, 2.7). Discontinuation due to adverse events (AEs) was lower with LCM (10.8%) than with CBZ-CR (15.6%). Results are under review by regulatory authorities.

In Asia-Pacific, an open-label Phase III trial (EP0057; NCT02124564) is in progress to evaluate the safety of conversion to LCM monotherapy (up to 600 mg/day) in Japanese patients with focal epilepsy. Results are available for trial EP0008 (NCT01710657), where 547 Chinese and Japanese patients with focal epilepsy were randomised and 88.7% completed the trial. Percentage reduction in seizure frequency over placebo was statistically significant with adjunctive LCM 200 and 400 mg/day (29.4% and 39.6% respectively, both $p<0.001$). The safety profile was consistent with previous trials. One-year interim analysis of the open-label extension (EP0009; NCT01832038) has shown that long-term, adjunctive LCM is associated with favourable tolerability and maintained seizure control.

The full paediatric programme is ongoing (SP0848; SP0966; SP0969; EP0034). In SP0847 (NCT00938431), 47 patients aged 1 month–17 years with focal epilepsy received adjunctive LCM, initiated at 2 mg/kg/day (bid) and titrated at 2 mg/kg/day weekly increments to the maximum age cohort-defined dose. Eight patients (5–11 years) received up to 8 mg/kg/day LCM, which determined the dosing (up to 12 mg/kg/day; not exceeding 600 mg/day) for the remaining cohorts (12–17 years; 5–11 years; 2–4 years; 1 month–<2 years). Overall, 24 patients (51.1%) completed the trial, all on target dose, 20 (42.6%) discontinued due to AEs – most frequently vomiting (8.5%), gait disturbance, dizziness and somnolence (all 6.4%). Most patients (n=40, 85.1%) planned to continue LCM in the open-label extension

(SP0848; NCT00938912). The AE profile was generally consistent with that of adults – no new safety concerns were identified. Data from paediatric trials applied to pharmacokinetic models suggest that the exposure-response relationship in children is similar to that established in adults, that adult intravenous infusion duration can be used for children, and that children's weight can be used to guide dosing. Data from SP0969 will provide further clinical evidence.

SP0982 (NCT02408523) is a Phase III, double-blind, randomised, placebo-controlled trial pioneering the use of 'time to second primary generalized tonic-clonic seizure (PGTCS)' as the primary endpoint to evaluate LCM efficacy in adults/children with idiopathic generalised epilepsy. This facilitates entry of patients with a range of seizure frequencies and enables early exit of those experiencing PGTCS, minimising their exposure to suboptimal treatment.

UCB Pharma-sponsored

PERAMPANEL UPDATE

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Perampanel (Fycompa®, Eisai) is a selective, non-competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. It was initially approved in 2012 in the USA and Europe for the adjunctive treatment of partial seizures, with or without secondarily generalized (SG) seizures, in patients aged ≥12 years with epilepsy. Approval was based on the efficacy and safety of perampanel 2–12 mg demonstrated in 1480 patients with partial seizures across three Phase III registration studies: studies 304 (ClinicalTrials.gov identifier: NCT00699972; French JA et al. Neurology 2012;79:589-596), 305 (NCT00699582; French JA et al. Epilepsia 2013;54:117-125), and 306 (NCT00700310; Krauss GL et al. Neurology 2012;78:1408-1415). Subsequent demonstration of efficacy and safety in a Phase III study of 163 patients with idiopathic generalized epilepsy (IGE) and uncontrolled primary generalized tonic-clonic (PGTC) seizures (study 332; NCT01393743; French JA et al. Neurology 2015;85:950-957) led in 2015 to the expansion of the perampanel label in the USA and Europe to include adjunctive use for the treatment of PGTC seizures in patients aged ≥12 years with epilepsy (USA) or IGE (Europe). Additional analyses have demonstrated consistent results in a large (N=707) Asia-Pacific population of patients aged ≥12 years with partial seizures (study 335; NCT01618695); sustained outcomes (up to 5 years) in study 307 (NCT00735397), the open-label extension of studies 304, 305, and 306 for patients aged ≥12 years with partial seizures; and sustained safety and efficacy against PGTC seizures in the open-label extension phase of study 332. Perampanel is also being investigated specifically in pediatric patient groups, including short- and long-term cognition, behavior, growth, and development outcomes in adolescents (aged 12 to <18 years) with partial seizures (study 235; NCT01161524; Meador KJ et al. Epilepsia 2016;57:243-251) and pharmacokinetics of an oral suspension in children (aged 2 to <12 years) with epilepsy (study 232; NCT01527006). Recently, a pooled analysis of patients aged ≥12 years with generalized tonic-clonic (GTC) seizures (SG seizures in studies 304, 305, and 306; PGTC seizures in study 332) showed that perampanel significantly extended the time to the pre-randomization monthly GTC seizure count plus 1 (time to Nth seizure +1), compared with placebo. Further, pharmacokinetic/pharmacodynamic modeling of this pooled data set predicted greater seizure frequency reduction for GTC (either SG or PGTC) seizures than for partial seizures. Future analyses will continue to explore patient groups and seizure subtypes that might particularly benefit from treatment with perampanel.

LYRICA PEDIATRIC EPILEPSY PROGRAM

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Introduction: Lyrica (pregabalin) is an alpha-2-delta (A2D) ligand, approved in more than 130 countries including indications for adjunctive therapy for partial onset seizures (POS), neuropathic pain, and fibromyalgia.

The dose range for pregabalin as adjunctive therapy for POS in adults is 150 to 600 mg/day two or three times daily. Greater than 30,000 subjects have been exposed to pregabalin in clinical trials, approximately 15% from epilepsy studies. Since initial approval, the estimated cumulative post-marketing exposure to pregabalin exceeds 34 million patient-years.

A clinical program in pediatric epilepsy involving a total of 6 multicenter studies continues investigation of epilepsy in this population.

Completed Studies: One pharmacokinetic (PK), safety/tolerability study and one 1-year safety study are completed. Data from these studies was used to determine the dose range for Phase 3 trials in pediatric patients.

Ongoing Efficacy and Safety Studies: Three studies evaluating efficacy and safety in pediatric patients with epilepsy are ongoing. Two studies to evaluate the efficacy and safety of pregabalin for the adjunctive treatment of POS: one 12-week study in children 4 to 16 years of age has completed enrollment and one 2-week study in children age 1 month to 3 years is continuing to enroll patients. One 12-week study in children and adults age 5 to 65 years is ongoing and investigating the efficacy and safety of pregabalin for the adjunctive treatment of primary generalized tonic-clonic seizures. Studies in subjects 4 years of age and older utilize patient-based seizure diary collection and studies in children less than 4 year of age utilize video-EEG (vEEG) seizure recording and collection. A 1-year, open label safety study for those patients who participated in the efficacy and safety trials is also ongoing.

Challenges in Conducting Epilepsy Trials in Pediatric Patients: Pediatric epilepsy trials are scientifically and operationally challenging. Challenges include: inherent difficulties encountered when conducting trials in a vulnerable pediatric population with serious disease, inclusion and duration of exposure to a placebo control particularly in a post-marketing environment, scientifically required inclusion/exclusion criteria to ensure enrollment of appropriate patients, requirement for statistical power for multiple doses included in the studies, full exploration of the pediatric dose range, and technical challenges, e.g. vEEG. Operational challenges include the necessity for a large number of countries and investigators for enrollment and prolonged timelines required to secure approvals of the Clinical Trial Applications and ethics committees. Enrollment by site is

anticipated to be relatively low enrollment requiring diligent investigator engagement over a protracted time period.
Conclusions: An extensive global pregabalin development program in pediatric epilepsy in children 1 month and older is well underway. Completion of the program within required timeframes is challenging and requires diligent application of clinical, statistical and operational risk mitigations.

STIRIPENTOL

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Stiripentol is a positive allosteric modulator of the GABA(A) receptor, and acts at both the gamma-containing (BZD-sensitive) and the delta-containing (BZD-insensitive) receptors. Stiripentol has been found to have neuroprotective effects in the Li-Pi seizure model, as well as when administered either pre or post-exposure to glutamate, and pre-exposure to oxygen-glucose deprivation on astrocyte-neuron cultures. This neuroprotective effect is likely due to the ability of stiripentol to block Ca++-permeable NMDA-sensitive glutamate receptors and voltage-sensitive Na+ and Ca++ channels.

Recent work has also shown that stiripentol may have a novel antiepileptic effect, similar to what is seen with the ketogenic diet. A metabolic switch from glucose to ketone bodies has been shown to result in neuronal hyperpolarization, which is mediated by the astrocyte-neuron lactate shuttle. Stiripentol inhibits LDH, resulting in neuronal hyperpolarization as follows. Within the astrocytes, glucose enters the glycolytic pathway, resulting in production of pyruvate. LDH converts pyruvate to lactate, which is then transported to the neurons by the astrocyte-neuron lactate shuttle. Once in the neuron, LDH converts lactate back to pyruvate, which then enters the mitochondria and is fed into the TCA cycle, generating ATP. High levels of ATP inhibit ATP-sensitive K+ channels on the neuronal membrane, thus limiting efflux of K+ and its resultant neuronal hyperpolarization. Inhibition of LDH leads to reduced levels of ATP, enhanced K+ efflux with greater neuronal hyperpolarization, and thus reduced excitability of the neuron.

Clinically, the most significant use of stiripentol has been in Dravet syndrome, an early-onset, refractory epileptic encephalopathy, as documented in the two pivotal randomized, placebo-controlled, add on STICLO studies. A large, open-label, add-on study in Japan has confirmed its efficacy in this syndrome, with 3 and 12 month responder rates of 67% and 54%, and 3 and 12 month seizure-free rates of 17% and 8.4%. Stiripentol may also have a role in super-refractory status epilepticus, as demonstrated in a small open label study in 5 adults. Stiripentol when added on after a median of 39 days of super-refractory status epilepticus resulted in resolution of status in 3/5 cases, within 2-4 days of treatment onset.

WHY DO WE NEED RELIABLE SEIZURE DETECTION SYSTEMS

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The explosive development of wellness-driven wearable connected devices and mobile health applications have already hit the field of seizure detection and epilepsy management, while in parallel, two FDA approved close-loop medical devices (responsive neurostimulator and EKG-based closed-loop vagus nerve stimulation) are currently providing seizure-triggered antiepileptic treatments. If not yet optimal in terms of sensitivity and specificity, all these technologies shall rapidly evolve to the point where invasive and non-invasive seizure detection systems will prove reliable. Thus, the question is not so much to delineate a rationale for developing such systems, but to appreciate their potential to improve the management of people with epilepsy. In fact, seizure detection offers a large panel of clinical benefit : 1) providing the physician with a reliable assessment of seizure frequency and possibly severity, in order to best adapt and test antiepileptic treatment, 2) enabling seizure-triggered alarm and interventions that might help minimize seizure duration, severity or harmful consequences, 3) collecting information that might help specifying the individual risk of SUDEP and its evolution over time, 4) identifying environmental seizure-triggers that could lead to their prevention or anticipation.

ALTERNATIVE THERAPIES AND APPROACHES

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There have been considerable recent advances in the development of viral vectors that self-inactivate and are not immunogenic, providing safe and effective methods for gene therapy. These are being used extensively in haematological disorders and have great potential in neurological disease. Focal epilepsy is an obvious target, as it is often drug resistant and surgery is possible for very few (often with a signficant associated morbidity). A number of gene therapy approaches have been considered for epilepsy and I will present one such approach, which is to use gene therapy to modify the intrinsic excitability of neurons. Within this, we have used three different strategies.

1) We have successfully used a lentiviral vector to overexpress an endogenous gene that encodes the potassium channel Kv1.1 and have cured epilepsy in a model of focal neocortical epilepsy.
2) A different approach is to express proteins that can be modulated on demand. We have used optogenetic (the expression of channels and ion pumps that are activated by coloured light) in order to increase or decrease neuronal excitability in specific neurons. Using a system in which an implanted light is activated when a seizure is detected, it is possible through optogenetics to suppress seizure activity.
3) Rather than using light sensitive proteins, receptors have been developed that are activated by specific drugs – Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). Using gene therapy to express in specific neurons a DREADD that is sensitive to an otherwise inert synthetic ligand, clozapine-N-oxide (CNO), we have been able to suppress seizure activity by the administration of CNO.
Although human trials are some way off, there is a clear route to translation and it is likely that trials of gene therapy in the treatment of epilepsy will occur within the next decade.

EEG-BASED SEIZURE DETECTION SYSTEMS IN EPILEPSY

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Automatic seizure detection has been primarily developed as an aid during long-term epilepsy monitoring because it is practically impossible to constantly observe the patient and the EEG. Many methods have been published since the 1980's, relying on a variety of features extracted from the EEG. No specific feature has proven overwhelmingly dominant. Whereas earlier methods tended to be validated with datasets that were not very extensive, recent methods have been validated on dozens of patients, sometimes more than a hundred, hundreds of seizures and thousands of hours or recording. The performance is usually in the range of 80 to 90% sensitivity and one false detection every 3 to 6 hours, making such methods useful to help in the epilepsy monitoring process. A few systems have also been developed as seizure warning device, giving a signal when a seizure has just started. This can be useful in the monitoring unit to improve the clinical observation of patients early in the seizure, and could be useful if it were implemented as a wearable or implantable device to warn the patients or caregivers in cases of seizures without an aura or warning. Such systems are tuned to the particular seizure pattern of a patient and can give a warning 10 to 12 seconds after EEG onset. Finally much effort has gone into the prediction of seizures. After early encouraging results, it became clear that the problem is more complex than originally thought and in particular its statistical validation requires large amounts of data and careful procedures. It appears that seizures can be predicted in some patients with statistical significance. It is not clear yet if this can have an impact on patients' lives.

Introduction

Automatic seizure detection developed with the advent of long-term video and EEG monitoring in the 1970s. Until then, the usual 30 min to 2-hour EEG recording sessions only captured seizures accidentally. One of the main purposes of long-term monitoring is to capture seizures but it became quickly apparent that this was not an easy task. The level of patient observation by qualified staff varies greatly from hospital to hospital and it is obvious that even close observation cannot be 100% observation. Furthermore there are seizures with no apparent or very minimal clinical signs and these can be missed unless the EEG is observed continuously, a further level of observation that is rarely undertaken in epilepsy monitoring units. In this context, automatic seizure detection should be conceived as an aid in capturing seizures.

Automatic seizure detection can also be placed in a context other than that of this hospital diagnostic setting. In patients who are not aware of the onset of their seizures, a device that could be carried by the patient and that could provide an alarm as soon as a seizure started might be useful for the patient or caregivers to take precautionary measures and avoid that the patient gets hurt. It would even be better if the device could predict that a seizure was likely to occur in the near future.

TRANSCUTANEOUS VAGUS NERVE STIMULATION (tVNS)

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Background: Various brain stimulation techniques are in use to treat epilepsy. These methods usually require surgical implantation procedures. Transcutaneous vagus nerve stimulation (tVNS, NEMOS, cerbomed) is a non-invasive technique to stimulate the left auricular branch of the vagus nerve at the ear conch and which received CE-marking in Europe.

Objective: To explain how the device is constructed and used, and to report on the results of a randomized, double-blind controlled trial (cMPsE02) implemented to assess efficacy and safety of tVNS vs. control stimulation in patients with drug-resistant epilepsy (Bauer S et al. Brain Stimulation 2016).

Methods: Primary objective was to demonstrate superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n=39) versus active control (1 Hz, n=37) in reducing seizure frequency over 20 weeks. Secondary objectives comprised reduction in seizure frequency from baseline to end of treatment, subgroup analyses and safety evaluation.

Results: Treatment adherence was 84% in the 1 Hz group and 88% in the 25 Hz group, respectively. Stimulation intensity significantly differed between the 1 Hz group (1.02 ± 0.83 mA) and the 25 Hz group (0.50 ± 0.47 mA; p=0.006). Mean seizure reduction per 28 days at end of treatment was -2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p=0.146). In contrast to controls, we found a significant reduction in seizure frequency in patients of the 25 Hz group who completed the full treatment period (20 weeks; n=26, 34.2%, p=0.034). Responder rates (25%, 50%) were similar in both groups. Subgroup analyses for seizure type and baseline seizure frequency revealed no significant differences. Adverse events were usually mild or moderate and comprised headache, ear pain, application site erythema, vertigo, fatigue, and nausea. Four serious adverse events were reported including one sudden unexplained death in epilepsy patients (SUDEP) in the 1 Hz group which was assessed as not treatment-related.

Conclusions: TVNS had a high treatment adherence and was well tolerated. Superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this relatively small study, which might be attributed to the higher stimulation intensity in the control group. Efficacy data revealed results that justify further trials with larger patient numbers and longer observation periods (Bauer S et al. Brain Stimulation 2016).

TRIGEMINAL NERVE STIMULATION IN EPILEPSY

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Trigeminal nerve stimulation (eTNS) is an emerging noninvasive neuromodulation therapy for epilepsy. It is approved for use in Europe, Canada, and Australia and is investigational in the United States. eTNS has been reported to be a safe and effective treatment for drug-resistant epilepsy. Clinical data from a phase I trial in 13 subjects showed a 66% reduction in seizures at 3 months, with a long-term 50% responder rate of 42% at 6 and 12 months. Results from a phase II randomized controlled trial in 50 subjects with drug-resistant epilepsy indicated that eTNS treatment was associated with a significant within-group improvement in responder rate to 40.5% after 18 weeks of treatment (p= 0.01).
We have followed up 17 patients with refractory epilepsy treated with eTNS from 4 to 37 months. Stimulation was set at 3-5 mAmps during 8-12 hours/day at night. We studied efficacy by looking at responder rates (50% reduction in seizure frequency), tolerability, and retention rate. Responder rates were 29% at 6 months, 24% at 12 months, 18% at 24 months, and 18% at 36 months. Retention rates were 47% at 12 months, 29% at 24 months, and 29% at 36 months. TNS was easy to implement in all patients. Adverse effects were very mild in intensity and included mild transient headache and skin irritation.
eTNS appears to be an effective and almost side-effect free method to reduce seizure frequency in drug-resistant epilepsy. A large multicenter phase III randomized controlled trial and a larger follow-up study are necessary to confirm the safety and efficacy of eTNS as well as to assess long-term effectiveness.

DEEP BRAIN STIMULATION AND MRI GUIDED LASER ABLATION TECHNOLOGY

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The Circuit of Papez has been widely studied as a neural network, due to its demonstrated involvement in seizure generation and propagation, and its critical role in learning and memory. This network has been targeted for therapeutic intervention with Deep Brain Stimulation (DBS) in patients with epilepsy (Fisher et al., 2010; Salanova et al, 2015), and more recently investigated in pilot studies of MRI-guided LASER ablation technology (Willie et al., 2014; Kang et al., 2016).

In order to better understand the effects of DBS within this network, we have developed a large animal model to study stimulation induced changes of neural activity (Stypulkowski et al, 2014). Using a human grade DBS system that allows for both stimulation and chronic local field potential (LFP) recording - termed "brain radio" or "Medtronic Activa PC+S" - leads were implanted within the anterior nucleus of the thalamus (ANT) and hippocampus (HC) and tuned for monitoring. Effects of remote (ANT) and direct (HC) stimulation paradigms (evoked potentials, cycled thalamus DBS, direct hippocampal DBS) were investigated in awake, behaving animals, with the goal of identifying biomarkers for cortical excitability changes. The results of this work are presented, along with preliminary preclinical data on Medtronic's next generation rechargeable platform (Activa RC+S) incorporating brain and motion sensing features for epilepsy.

A status update of Medtronic's epilepsy therapy development program will also be provided. This includes: (1) Data collection activities related to a European epilepsy cohort being treated with DBS and followed in the Medtronic Registry for Epilepsy (MORE); (2) Proof of concept approaches related to minimally invasive sub-cutaneous brain monitoring for seizure diagnosis; and, (3) Planned clinical activities related to MRI-guided LASER ablation technology as a possible treatment for mesial temporal lobe epilepsy (MTLE). These technologies will be discussed in reference to elements of a proposed epilepsy portfolio with emphasis on the care continuum.

CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use

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BRAIN-RESPONSIVE NEUROSTIMULATION FOR THE TREATMENT OF DRUG RESISTANT PARTIAL ONSET SEIZURES: CLINICAL RESPONSE AND INSIGHTS FROM LONG-TERM AMBULATORY ELECTROCORTICOGRAPHIC MONITORING

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The first responsive brain neurostimulator (RNS® System, NeuroPace) is approved by the U.S. FDA for treatment of partial onset seizures in adults. In contrast to open-loop stimulation devices, responsive (or closed-loop) neurostimulation devices modulate or adapt therapy in response to physiological signals, in addition to clinically overt symptoms. The RNS System includes a neurostimulator placed in the skull that continuously monitors electrocorticographic activity recorded from 2 4-electrode containing leads placed at 1 or 2 seizure foci. When previously defined abnormal electrographic activity is detected (generally the type of activity that precedes an electrographic seizure), then brief pulses of stimulation are delivered to any number of the electrode contacts. Detection and stimulation parameters are modifiable by the physician according to that patient's electrocorticographic data and the clinical response. The quantitative data regarding the frequency and type of epileptiform activity and the electrographic response to treatment, as well as recordings of the electrocorticogram are combined with reports of clinical seizures to individualize treatment for each patient. Seizure reductions of 44% at one year increase to 60 to 66% at 3 to 6 years of treatment and are accompanied by improvements in quality of life overall and in areas related to attention, language, memory, as well as work and social function. There is no negative impact on mood or cognition, and some patients experience improvements in aspects of language and memory. The risk is similar to other implanted medical devices and the neurostimulator can be programmed so that therapeutic stimulation is not perceived.

Neuromodulation, including brain-responsive neurostimulation, has proven an important treatment option for patients with pharmacoresistant partial epilepsy. Brain responsive stimulation permits personalization of therapy and achieves long-lasting reductions in seizures with good tolerability in patients with drug resistant epilepsy.

Morrell MJ, Halpern C. Responsive Direct Brain Stimulation for Epilepsy. Neurosurg Clin N Am. 2016 Jan;27(1):111-21.

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ABSTRACTS:

POSTER PRESENTATIONS

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ANTIICTOGENIC AND ANTIEPILEPTOGENIC PROPERTIES OF PERAMPANEL IN MATURE AND IMMATURE RATS

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OBJECTIVE: Perampanel (PER) is a non-competitive AMPA antagonist approved as antiepileptic drug for both focal seizure and primary generalized seizure. We explored anti-ictogenic and anti-epileptogenic effects of PER in rats at different stages of development. METHODS: Using a rapid kindling model in P14, P21, P28 and P60 rats, we studied two doses of PER: 1mg/kg and 2mg/kg injected intra-peritoneally 30 minutes before afterdischarge assessment.
RESULTS: PER 2 mg/kg significantly increased the afterdischarge threshold (ADT) at P28, P21 and P14 while PER at 1 mg/kg increased ADT in P21 rats only. PER 2m/kg also shortens the afterdischarge duration (ADD) at P28 and P14. At P28, P21 and P14, PER increased the number of stimulations required to develop a stage 4-5 seizure in a dose-dependent manner with almost complete elimination of stage 4-5 seizures in all immature animals (P28, P21 and P14). In contrast, at P60 PER had no effect on the number of stage 4-5 seizures.
SIGNIFICANCE: PER anti-ictogenic and anti-epileptogenic effects differing according to brain maturation. The antiepileptogenic effect of PER was stronger in younger animals.

UTILIZATION AND REPORTED ADVERSE EFFECTS OF THE NEWEST ANTIEPILEPTIC DRUGS IN NORWAY

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Purpose: In recent years, several new AEDs have become available in Norway as add-on therapy in patients with epilepsy. The documentation of adverse effects in short or long-term use is often lacking. The aim of this study was to investigate changes in utilization of the newest AEDs in epilepsy and study the reported adverse effect.

Methods: Data regarding the utilizations of the newest AEDs consisted of all prescriptions of AEDs from the Norwegian Prescription Database (NorPD) from 2009 to 2014. Aggregated numbers from the Eudravigilance database was used as the source of adverse effects data. The data contains reports from Norway in the period 2004-2013.

Results: The use of the newest AEDs (eslicarbazepine acetate, lacosamide, rufinamide, stiripentol, perampanel) has increased by 410% from 237 patients in 2009 to 1209 patients in 2014 (0.023 to 0.19 DDDs/1000 inhabitants/day). A total of 18 adverse effects were reported; 11 for for perampanel, 4 for lacosamide, 2 for eslicarbazepine and one for retigabine. Three cases of sudden unexplained death in epilepsy were reported, while non-mandatory reports included neurological adverse effects such as dizziness. No adverse effects were reported for rufinamide and stiripentol. A clear reduction in the use of retigabine was seen from 2012 to 2014 due to restrictions because of serious adverse effects reports, although no cases of discoloration/pigment abnormalities was reported from Norway.

Conclusion: The use of NorPD in addition to adverse effect reports is useful to study the changes and follow the utilization of antiepileptic drugs over time. Awareness of the increased exposure of AEDs to new groups of patients followed by data regarding safety aspects is of great importance and contributes to improved pharmacovigilance.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS AFTER VARIOUS ROUTES OF ADMINISTRATION OF SEC-BUTYLPROPYLACETAMIDE (SPD), A NEW CNS DRUG POSSESSING A UNIQUE ACTIVITY AGAINST STATUS EPILEPTICUS

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Purpose: Benzodiazepines are first-line therapy for status epilepticus (SE) but they lose their efficacy when given in a delayed setting. sec-Butylpropylacetamide (SPD) is a one-carbon homologue of valnoctamide, a chiral constitutional isomer of valproic acid (VPA) corresponding amide; valpromide. SPD possess a unique and broad-spectrum antiseizure profile superior to that of VPA and blocks behavioral- and electrographic-SE induced by pilocarpine and the organophosphate soman. SPD activity on SE is superior to that of benzodiazepines in terms of ability to block SE when given 20 to 60 min after seizure onset. However, i.p. administration to rats cannot be extrapolated to humans. Consequently, in the current study a comparative pharmacokinetic (PK)-Pharmacodynamic (PD)-analysis of SPD was conducted following i.p., i.m. and i.v. administrations to rats including estimating SPD´s plasma and brain bioavailability after each mode of administration.

Method: SPD brain and plasma levels were quantified at various times after dosing following i.p. (60 mg/kg), i.v. (60 mg/kg) and i.m. administrations (120 mg/kg) to rats and SPD major PK parameters were estimated after each administration. The antiseizure (SE) efficacy of SPD and its individual stereoisomers was assessed in the pilocrapine-induced SE model following i.p. and i.m. administrations to rats at 30 min after seizure onset.

Results: SPD absolute bioavailability following i.p. and i.m. administration was 76% (i.m.) and 108% (i.p.) and its clearance and half-life were 2-3 L/h/kg and 1h, respectively. SPD-brain-to-plasma-(AUC)-ratio was 2.3 (i.v.), 2.4 (i.p.) and 0.75 (i.m.). Nevertheless, the ED50 values of SPD and its individual stereoisomers were almost identical in the rat-pilocrapine-induced-SE model-following i.p. and i.m. administrations.

Conclusion: In rats SPD is completely or almost completely absorbed following i.p., and i.m. administration, respectively and readily penetrates into the brain. Consequently, in spite of PK differences SPD unique activity in the BZD-resistant SE model is similar following i.m. and ip. administrations.

NOVEL ULTRA-LONG TERM SUBCUTANEOUS EEG MONITORING SYSTEM

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Objectives: Various research groups have recently outlined the future within portable EEG equipment. They agree that small, portable and convenient systems for instantaneous and continuous EEG monitoring are essential. We present a novel subcutaneous monitoring system developed for unobtrusive, continuous, ultra-long term EEG applications. Evidence of high signal quality is provided for 12 patients monitored continuously night and day for more than a month.

Methods: The system consists of an implantable and an external part. The implantable part of the device consists of a housing and a protruding lead, which is placed in the subcutaneous layer of the skin behind the ear. The lead has three platinum-iridium electrodes located 30mm apart with the middle being the reference. The implant housing contains a coil for inductive power transmission and data communication to a similar coil in the external device. The external device furthermore consist of a small box (9x4x1.5 cm) for storage of approximately 30 days of EEG, 3-axial accelerometry and ambient light intensity. Data were collected from 12 healthy volunteers for up to 45 days. To investigate the signal quality longitudinally over time, the signal was decomposed into standard physiological frequency bands (δ: 0-4 Hz, θ: 4-8 Hz, α: 8-13 Hz, βlow: 13-20 Hz, and βhigh: 20-30 Hz). The average power of each frequency band was computed over 10 second non-overlapping epochs.

Results: By visually inspecting the average power of the frequency bands over time, no trend was observed. In a previous publication, we showed that the EEG data quality of subcutaneous measurements made 10 days after implantation of the implantable device is comparable to the data quality of standard scalp EEG. The present analysis has shown that the average power in the five standard frequency bands do not change over a time course of more than one month.

Conclusion: The stable measurements indicate that the previously documented good data quality obtained 10 days after implantation can be expected throughout ultra-long term subcutaneous EEG measurements. We believe that we can present a novel, portable and user-friendly device well suited for ultra-long term EEG monitoring with applications in epilepsy research where continuous and instantaneous EEG measurements are needed.

EARLY-LIFE CLONAZEPAM EXPOSURE LEADS TO PERSISTENT INCREASE OF SEIZURE SUSCEPTIBILITY

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Rationale: Early exposure of the immature brain to benzodiazepines leads to enduring behavioral disturbances and morphologic alterations. There are however only limited data on effects of such treatment on brain excitability and seizure susceptibility later in life. The present study aimed to examine whether early clonazepam (CZP) exposure results in enduring changes in seizure susceptibility.
Methods: CZP in a dose of 1 mg/kg/day (suspension in saline) was administered intraperitonealy for five consecutive days beginning on postnatal day (P) 7. Seizure susceptibility was assessed in adult animals using models of (1) pentylenetetrazole (PTZ) –induced seizure activity and (2) single-pulse evoked hippocampal potentials and electrically-induced hippocampal afterdischarges (ADs). PTZ (20mg/kg i.p.) was administered three times with 20-min intervals to rats with chronically implanted cortical electrodes and development and duration of rhythmic PTZ activity and myoclonic seizures was evaluated. Hippocampal excitability was determined with single pulse stimulation with intensities increasing from 0.1 to 2.0 mA and one week later using electrically elicited hippocampal afterdischarges.
Results: Early CZP exposure resulted to an enduring increase in PTZ sensitivity, which was seizure type specific. Exposure to CZP resulted in an increased frequency of PTZ-induced spike-and-wave discharge episodes, but had no effect on development of myoclonic seizures. Also, hippocampal excitability was increased in CZP exposed rats compared to controls. The duration of both the N1-P2 amplitude and ADs was significantly longer, and incidence of recurrent ADs was 3.7 times higher in CZP exposed animals than in corresponding controls.
Conclusion: Our data demonstrate increased seizure susceptibility in animals exposed to CZP early in postnatal development.
This study was supported by grant No. P304/12/G069 of the Czech Science Foundation and Research Project RVO 67985823.

SURVEILLANCE OF ESLICARBAZEPINE ACETATE, OXCARBAZEPINE AND CARBAMAZEPINE IN NORWAY

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Purpose: The rationale behind development of new antiepileptic drugs (AEDs) is to improve efficacy and/or tolerability. The aim of this study was to study the surveillance of three related AEDs, eslicarbazepine acetate (ESL), oxcarbazepine (OXC) and carbamazepine (CBZ) by reported adverse effects in Norway.

Methods: Data regarding the utilization of these AEDs consisted of all prescriptions of AEDs from the Norwegian Prescription Database (NorPD). Aggregated numbers from the Eudravigilance database from Norway to the European Medicines Agency were used as the source of adverse effects data. All data were collected in the period 2004-2013.

Results: Based on NorPD, the use of CBZ decreased by 37% from 22457 to14190 patients, while OXC increased by 48% from 1701 to 2523 patients (2004-13). The use of ESL increased from 205 to 250 patients (2010-13). The gender distribution was similar and equal for all drugs. During this period, there were 240 reports on carbamazepine, mean age 39 years, 31/17 women/men, including e.g. 16 rash, 6 sudden unexplained deaths, 2 Stevens-Johnson syndrome, and 2 hyponatremia. There were 24 reports for OXC, mean age 21 years, 10/7 women/men, including 6 rash, 4 sudden unexplained deaths, 3 hypersensitivity reactions, 1 Stevens-Johnson syndrome, 1 hyponatremia and 9 other reports. There were only 2 reports for ESL, both sudden unexplained death. When comparing the utilization of these drugs, there is an extensive under-reporting of adverse effects in Norway. Limitations include that only fatal outcomes are mandatory to report. The reports do not reflect our clinical experience, where moderate adverse effects are common, as hyponatremia and skin reactions.

Conclusion: Surveillance of AEDs may be followed by combination of NorPD and adverse effect reports. Even if Norway has a close surveillance of drug utilization, there are important limitations in the reporting of adverse effects. Focus on reporting adverse effects is especially important for the newest drugs. The present study is important regarding safety aspects of AEDs and calls for improved international collaboration of pharmacovigilance.

PHOTOSENSITIVITY MODEL: STABILITY OF THE PHOTOPAROXYSMAL EEG RESPONSE OVER THE DAY

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Introduction

Intermittent photic stimulation (IPS) can evoke repeatedly, over time, epileptiform EEG discharges in susceptible epilepsy patients. Change in this so-called Photo-Paroxysmal Response (PPR) is used in clinical practice and (Proof of Concept) trials evaluating AED efficacy. The utility of the PPR as a valid efficacy marker in PoC AED trials depends on the assumption of PPR stability throughout the day. We sought to demonstrate PPR stability across the day.

Methods

We retrospectively data-mined from # 19 clinical PoC AED trials, published and unpublished (Ethics approval, Informed Consent were obtained in all). Adult epilepsy patients taking stable doses of up to 2 other AED's with generalized PPRs had been evaluated via a standardized PPR protocol (Kasteleijn-Nolst Trenite et al., 2012) 7 times during each test day: 7-9am, 9-10 am, 10-11am, 11am-12md, 1-2pm, 3-4pm, and 5-7pm. Patients were dosed with placebo plus their standard AEDs (some trials did not add placebo) on the baseline day. At each time point the PPR test included IPS on-eye closure, with eyes closed and with eyes open. This also allowed intra-patient comparison of PPR response at each eye condition for each patient. EEG's were read blind and the resulting PPR data were standardised and recorded as "standardized photoparoxysmal responses" (SPR's). NONMEM statistical methods were utilised in data analysis.

Results

We evaluated 2,058 EEG PPR tests in 98 patients with PPRs at every time point and in all 3 eye conditions. The SPR's were plotted for each eye condition at each time point with 95% C.I.'s. See Figure 1.These results demonstrate that the PPR is stable across the waking day, are not dependent on time of day, and that the eye closure condition had the greatest reproducibility.

Conclusions

The photically evoked epileptiform activity in epilepsy patients (PPR and derived SPR) values are reproducible over the waking day, without diurnal variation. IPS

during eye closure is the most reproducible PPR-test. This has implications for the utility Photosensitivity Model in the PoC evaluation of (new) AEDs.

EFFECT OF ALISKIREN, A DIRECT RENIN INHIBITOR, ON THE ANTICONVULSANT ACTIVITY OF ANTIEPILEPTIC DRUGS AGAINST MAXIMAL ELECTROSHOCK-INDUCED SEIZURES IN MICE

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The brain renin-angiotensin system (RAS) could be involved in the regulation of seizure susceptibility. RAS inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors (e.g. captopril, enalapril) and angiotensin AT1 receptor antagonists (e.g. losartan) have been documented to decrease seizure severity in rodent models of seizures and epilepsy. Some of them have positively affected the anticonvulsant action of antiepileptic drugs (AEDs) against maximal electroshock-induced seizures (MES) in mice, too. In the current study, the effect of aliskiren, a direct renin inhibitor and a novel antihypertensive drug, on the anticonvulsant activity of AEDs in the MES test was assessed. Additionally, adverse effects of the combined treatment with aliskiren and AEDs were evaluated in the rota-rod and passive avoidance test. The study was performed on adult Swiss mice. All drugs were administered intraperitoneally (i.p.).

Aliskiren up to a dose of 75 mg/kg did not affect the threshold for electroconvulsions. In the MES test, aliskiren was combined with the following AEDs: carbamazepine (CBZ), valproate (VPA), clonazepam (CLO), phenobarbital (PB), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM) and pregabalin (PGB). Aliskiren (75 mg/kg) enhanced the protective action of VPA in the MES test, decreasing its ED50 value from 248.3 to 187.5 mg/kg ($p < 0.05$). Additionally, aliskiren (75 mg/kg) potentiated the anticonvulsant action of CLO, lowering its ED50 value from 35.1 to 22.6 mg/kg ($p < 0.01$). Aliskiren at the lower dose of 50 mg/kg was ineffective. On the other hand, the combined treatment with aliskiren (75 or 50 mg/kg) and CLO (22.6 mg/kg) led to motor coordination impairment in the rota-rod test ($p < 0.01$ and $p < 0.05$, respectively). The activity of VPA and other AEDs in the rota-rod test was not significantly affected by aliskiren. In the passive avoidance test, only combination of aliskiren (75 mg/kg) with PB (25.5 mg/kg) caused long-term memory deficits ($p < 0.05$).

This study shows that there are no negative interactions between aliskiren and the examined AEDs as concerns their anticonvulsant activity. Aliskiren even enhanced the anticonvulsant action of VPA and CLO, however, in the case of CLO combined with aliskiren, the significant motor incoordination was observed.

AN ANTAGONIST OF AMPA RECEPTORS PERMEABLE FOR CALCIUM AS A POSSIBLE ANTIEPILEPTIC DRUG

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AMPA receptors without editied GluA2 subunit permeable to calcium ions are represented mostly in immature brain. Specific antagonist of these receptors IEM1460 might thus be a potential age-specific antiepileptic drug.
Anticonvulsant action of IEM1460 was tested in rats 12, 18 and 25 days old in two models – pentetrazol induced convulsive seizures and cortical epileptic afterdischarges. The same age groups were used for checking of possible effects of IEM1460 on motor performance and spontaneous locomotion. Animals were pretreated intraperitoneally with IEM1460 in doses of 10 or 20 mg/kg, 30 minutes later the testing was performed. A different time schedule was used in the cortical epileptic afterdischarges model – stimulation was repeated six times with 10-min intervals and IEM1460 was injected 5 min after the first afterdischarge.
Generalized tonic-clonic seizures were suppressed by the higher dose in 25-day-old rats. Unfortunately, there are no data for development of subunit composition of AMPA receptors in the brainstem, i.e.in structure generating this type of seizures.
In contrast, cortical afterdischarges were suppressed in the youngest group what is in agreement with development of GluR2 subunit of AMPA receptors in the cerebral cortex (Szczurowska et al. – submitted).
Motor performance was not affected by the lower dose, the 20-mg/kg dose compromised motor abilities in some but not all tests mainly in 12-day-old rats.
Selective antagonism of calciuim-permeable AMPA receptors resulted in age-dependent anticonvulsant action specific for different types of epileptic seizures. Side effects of the higher dose of IEM1460 on motor abilities are only moderate.

DIFFERENTIAL EFFECTS OF ANTIEPILEPTIC DRUGS IN A MOUSE MODEL OF MESIAL TEMPORAL LOBE EPILEPSY

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Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of drug-refractory epilepsy. To better understand and treat this syndrome, the use of predictive animal models is mandatory. The MTLE mouse model induced by unilateral intrahippocampal injection of kainate reproduces most of the morphological and electroclinical features of human MTLE. Here, we present a comprehensive pharmacological characterization of the response of the MTLE mouse to the major antiepileptic drugs (AEDs) currently on the market.

Using depth EEG recordings, we tested the dose-response effects of nine AEDs with different mechanisms of action on the occurrence of hippocampal paroxysmal discharges (HPD) in the mouse model of MTLE. AEDs effects on ictal and interictal power spectra were as well studied using quantitative EEG methods.

The MTLE mouse displayed a wide range of sensitivity to the tested AEDs. Depending on their effects on our model, AEDs can be classified in three categories. 1) Valproate, carbamazepine, lamotrigine dose-dependently suppressed HPDs in a dose-dependent way with the modification of the general behaviour and/or EEG activity. 2) Phenobarbital, tiagabine, vigabatrin and diazepam decreased in a dose-dependent manner the occurrence of HPDs without obvious behavioural changes or interictal EEG perturbations. Finally, levetiracetam and pregabalin suppressed the occurrence of HPDs at high doses but without any behavioural nor interictal EEG changes.

These data show that this mouse model of MTLE displays a differential sensitivity to AEDs with a greater sensitivity to drug acting on the GABAergic system. This model provides a critical tool to identify new treatments for pharmacoresistant forms of focal epilepsy.

NONCONVULSIVE STATUS EPILEPTICUS: CASE REPORT

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Nonconvulsive status epilepticus (NCSE) is a condition of ongoing or intermittent seizure activity without recovery of consciousness, with no interval of normal mental activity between attacks lasting more than 30 min. There is two types: absence and partial complex nonconvulsive status epilepticus. Symptoms of nonconvulsive status epilepticus are more subtle than convulsive status epilepticus which delays diagnosis. EEG is needed to confirm the clinical diagnosis.

We report the case of a 51-year-old male patient without previous family recorded history of epilepsy. He has epilepsy since he was 12 years old. He used many medications, included valproat, phenobarbiton, carbamazepine, topiramat, but without improvement. He used oxcarbazepine (600 mg, 0, 600 mg) and levetiracetam (500 mg, 0, 1000 mg). He arrived in our emergency service with symptoms of interrupted consciousness. Neurogical examination showed clonic movements of facial muscles, bradyphrenia and he was able to answer only simple question and doing automatic actions. Standard EEG showed iregular 2,5-3,5 Hz generalizated spike – wave interictal discharges. He was treated with diazepam 10 mg intravenous, levetiracetam 3000 mg intavenous, but EEG still showed iregular 2,5-3,5 Hz generalizated spike – wave interictal discharges, nonconvulsive status epilepticus. After lacosamide 100 mg per oral, standard EEG showed paroxysmal electrical discharges with stereotyped pattern of 2-3 Hz spike- wave complexes interruped with normal background activity. Two days after EEG was markedly improved. Medications was corrected and now patient is using lacosamide (100 mg, ,0 100 mg), levetiracetam (500 mg, 500 mg, 1000 mg) and valproat (0 mg, 0 mg, 250 mg). Number and intensity of seizures has decreased.

CLINICAL AND MRI MORPHOMETRY EFFECTS OF ANTIEPILEPTIC DRUGS IN TEMPORAL LOBE EPILEPSY IN UZBEKISTAN

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Background: We examined the relationship between brain MRI and clinical characteristics and patterns of antiepileptic drug (AED) response in patients with mesial temporal lobe epilepsy (MTLE).
Methods: A total of 165 MTLE patients were divided into seizure-free with AED (AED responders, n = 50), pharmacoresistant (n = 87), and remitting-relapsing seizure control group (n = 28). All groups were evaluated regarding age, frequency of seizures, and age at epilepsy onset, duration of epilepsy, febrile seizures, presence and side of hippocampal atrophy (HA), and initial precipitating injuries. For gray matter (GM) MRI voxel-based morphometry (VBM) we selected only patients with unilateral HA on visual MRI analysis (n = 100). Comparisons were made between all groups and 75 healthy controls.
Results: Age at epilepsy onset was lower (p=0,005) and initial freequency of seizures was higher in the pharmacoresistant compared with the other 2 groups (p=0,018). All groups showed GM atrophy compared to controls in ipsilateral hippocampus, bilateral parahippocampal gyri, frontal, occipital, parietal, and cerebellar areas.In the AED responders group, such findings were more restricted to areas ipsilateral to the epileptic focus and more widespread in the pharmacoresistant and remitting-relapsing groups. VBM pairwise comparisons showed areas with GM volume reduction in the pharmacoresistant and remitting-relapsing groups compared with AED responders in bilateral periorbital frontal (p=0,01), cingulum (p<0,05), and temporal lobe contralateral to the epileptic focus (p<0,05).
Conclusions: Pharmacoresistant and remitting-relapsing groups presented a similar pattern of GM atrophy, which was more widespread compared with AED responders. Conversely, age at epilepsy onset was lower and initial seizure frequency was higher in pharmacoresistant patients.

DECANOIC ACID, WITHIN THE MCT KETOGENIC DIET, DIRECTLY INHIBITS AMPA RECEPTOR ACTIVITY AS A THERAPEUTIC MECHANISM OF ACTION

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The medium chain triglyceride (MCT) ketogenic diet provides a highly effective and commonly used approach for treating drug resistant epilepsy. Due to the restrictive nature of the diet and compliance issues, it is mainly used in children. The diet is associated with elevated levels of ketone bodies and two MCT-derived fatty acids, decanoic and octanoic acid. As a therapeutic mechanism, we have identified a role for decanoic acid and a range of novel related chemicals in seizure control in multiple acute in vitro and in vivo models. We have further shown that a principal mechanism of decanoic acid is through direct inhibition of AMPA receptors, a key excitatory neurotransmitter receptor widely recognized as a therapeutic target for seizure control. These data suggest a therapeutic mechanism of the MCT ketogenic diet through a direct fatty acid-dependent mechanism, independent of ketosis. This discovery will enable the development of an improved and, potentially, better tolerated diet and the generation of a corresponding pharmaceutical approach. We also suggest that the diet should be more correctly termed the MCT diet, as the consequent ketosis may not be necessary for seizure control.

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