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Novel treatment approaches and pediatric research networks in status epilepticus

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ABSTRACT

This paper contains five contributions which were presented as part of the novel therapies section of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. These illustrate recent advances being made in the management and therapy of status epilepticus. The five contributions concern: genetic variations in Na + channel genes and their importance in status epilepticus; the European Reference Network for rare and complex epilepsies EpiCARE; the North American Pediatric Status Epilepticus Research Group (pSERG); Fenfluramine as a potential therapy for status epilepticus' and the valproate derivatives, valnoctamide and sec-butylpropylacetamide (SPD), as potential therapies for status epilepticus.

This article is part of the Special Issue "Proceedings of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures"

As part of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, 5 papers were presented, which were concerned with the aspects of novel treatment, and these are presented jointly here.

1. Status epilepticus and genetic variations in Na^+ channel genes

Ulrike B.S. Hedrich, Holger Lerche

Status epilepticus (SE) is the most severe and often a life-threatening form of an epileptic seizure. It is defined as an ongoing seizure activity surpassing a conventional length, which is usually 3–5 min for a bilateral tonic–clonic (convulsive) seizure and 20–30 min for a nonconvulsive focal seizure. Since bilateral convulsive SE is a life-threatening condition needing immediate treatment, it is important to know about the conditions that can lead to a status and to know as much as possible about the underlying cause in order to determine the best treatment options.

There is increasing evidence that specific medications are necessary and effective in the treatment of severe genetic epilepsies showing a high degree of pharmacoresistance. These diseases are

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often accompanied by developmental delay or regression and by a persisting intellectual disability and are therefore called developmental and epileptic encephalopathies (DEEs) [1]. Many of the DEEs are caused by variants in ion channels, and since most of the available antiseizure drugs (ASDs) target voltage- or ligand-gated ion channels, specific consequences for treatment increasingly emerge for those syndromes. This can be either a high efficacy or a specific pharmacoresistance even with deterioration of patient's seizures, depending on the functional deficits that are caused by the variants [2, 3]. Since it is important to know about these specific conditions in clinical practice, we here review the neuronal Na^+ channelopathies as a common example among the genetic epilepsies, i.e., their most important clinical features, appearance of SE, and consequences for treatment. We focus on the three most important Na^+ channel genes of the mammalian brain, *SCN1A*, *SCN2A*, and *SCN8A*, since those are common, whereas little is known so far about epilepsies associated with variants in *SCN3A*, which is expressed mainly during early development. *SCN1A*, *SCN2A*, and *SCN8A* encode the main (alpha-)subunits of the voltage-gated Na^+ channels $Na_V1.1$, $Na_V1.2$, and $Na_V1.6$. Whereas $Na_V1.1$ is the main channel in inhibitory interneurons, $Na_V1.2$ is mainly expressed in excitatory neurons with two different expression maxima during development: early on around birth in myelinated nerve fibers and later on around postnatal day 20 (P20) in unmyelinated fibers, which is related to different clinical syndromes. $Na_V1.6$ is expressed later than $Na_V1.2$ in principal (excitatory) pyramidal neurons but also found abundantly in inhibitory neurons [4, 5] (Fig. 1).

Variants in *SCN1A* cause a large variety of mild to severe epilepsy syndromes, from simple febrile seizures to the most severe form, which is Dravet syndrome (DS). Only for DS, a high incidence of SE has been described. Dravet syndrome is characterized by febrile, often prolonged seizures starting in the first or second year of life, and by afebrile myoclonic and generalized or hemitonic or -clonic seizures, accompanied by developmental delay or regression. Status epilepticus is common in DS ranging from 74 to 92% of observed cases. It presents mainly as febrile SE in the first or second year (often clonic, asymmetric, also alternating sides), and after the second year, as afebrile generalized clonic, asymmetric tonic, or multifocal migrating SE [6–8]. The outcome is unfavorable after frequent SE in terms of seizures [7], cognition [9], and residual syndromes, e.g., three cases with tetraparesis were described [8]. In addition, the mortality is high: in 100 cases of DS, 87 of which due to *SCN1A* variants, 17 deaths occurred, 10 due to Sudden Unexpected Death in Epilepsy (SUDEP) four due to SE, two due to drowning, and one due to asphyxia [10]. A literature-search for deaths in DS revealed 177 deaths, of which 87 were due to SUDEP (49%), 56 due to SE (32%), 14 due to drowning/accident (8%), and 20 for other reasons (11%) [11]. In addition, a severe form of cerebral edema after febrile SE, with herniation and death, was described in five cases, which may be one reason for mortality after SE in DS [12].

Treatment response was analyzed in a survey of 109 cases [6]: Stopping of ongoing SE was achieved for 75–100% of cases with barbiturates, for 69% with midazolam, for 54% with diazepam, but only for 21% with lidocaine, and only 15% with phenytoin. Prophylaxis for SE was well obtained with bromide (41%) but not with phenytoin (2,6%) or carbamazepine (0%). These observations fit well the known problem to treat DS with Na^+ channel blockers [13]. However, beneficial effects of lamotrigine or provoked seizures after withdrawal of lamotrigine were reported in older patients [14], in which SE is more rare, seizures are less severe, and cognitive decline usually stops.

The pathophysiology of *SCN1A*-related syndromes including DS is commonly thought to be built on a deficit of interneuron firing because of a reduced expression or reduced function of $Na_V1.1$ channels in interneuron axon initial segments [15–17]. However, the reduced expression seems to be compensated in mouse models later in development [18], which correspond to the aforementioned changes of the pharmacoresponse and severity in older age.

SCN2A-related epilepsy syndromes also cover a wide phenotypic spectrum from mild to severe disease. Nevertheless, SE is generally a very rare condition in these syndromes. There are two different age periods of onset, one in the neonatal–infantile period and another one later on, which are also related to the pathophysiology and treatment response. Early onset syndromes (<3 months of age) include benign familial neonatal–infantile epilepsy, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, and unspecific encephalopathy with early infantile onset epilepsy. The later onset syndromes (>3 months) include West syndrome, epilepsy with myoclonic–atonic seizures, Lennox–Gastaut syndrome, unspecific encephalopathy with infantile/childhood onset epilepsy, and intellectual disability or autism without epilepsy. In more than 200 cases, only six cases of ESES (electrical SE during sleep)-like syndromes and two cases of SE occurred, of which the two early onset cases (1 ESES, 1 SE) responded to Na^+ channel blockers. For the late onset cases, one SE was induced by lamotrigine, and of three ESES cases treated with Na^+ channel blockers, none responded and some deteriorated. This principle of pharmacoresponse does also apply to the epilepsy syndromes: The early onset cases, which are caused by gain-of-function (GOF) variants, respond well to Na^+ channel blockers, whereas the late onset cases, which are caused by loss-of-function (LOF) variants, do not respond well to Na^+ channel blockers [19]. The aforementioned different early and late expression patterns may explain these differences, since early expression of GOF variants in pyramidal neurons can well explain the early onset epilepsies, whereas later expression of LOF variants in unmyelinated fibers, which at least in the case of mossy fibers in the hippocampus largely project to inhibitory neurons, could explain later onset seizures with and lack of response to Na^+ channel blockers, similar as in *SCN1A*-related disease [19, 20].

SCN8A-related epilepsy is less well described than the two other Na^+ channelopathies so far, but it is clear from the current literature that the associated epilepsy syndromes are less specific and that SE is a common phenomenon in severe cases. Benign cases with benign familial infantile (BFIE) do not develop SE [21], but nonconvulsive SE (NCSE) was found in 16/22 cases in patients with severe DEE due to *de novo* variants, 14 of which had recurrent NCSE. Treatment responses were not well documented, but it emerges that the early onset DEEs are due to GOF variants that respond quite well to Na^+ channel blockers [22], similar in *SCN2A*-related disease, whereas developmental delay, intellectual disability, or autism without epilepsy have LOF mutations [23–25].

In summary, SE is a common and threatening condition in DS and in *SCN8A*-related DEE, but not in *SCN2A*-related syndromes. In *SCN1A*- and *SCN2A*-related late onset diseases due to loss-of-function variants, Na^+ channel blockers should be avoided, whereas these drugs are beneficial in early onset *SCN2A*- and *SCN8A*-related syndromes that are caused by gain-of-function variants.

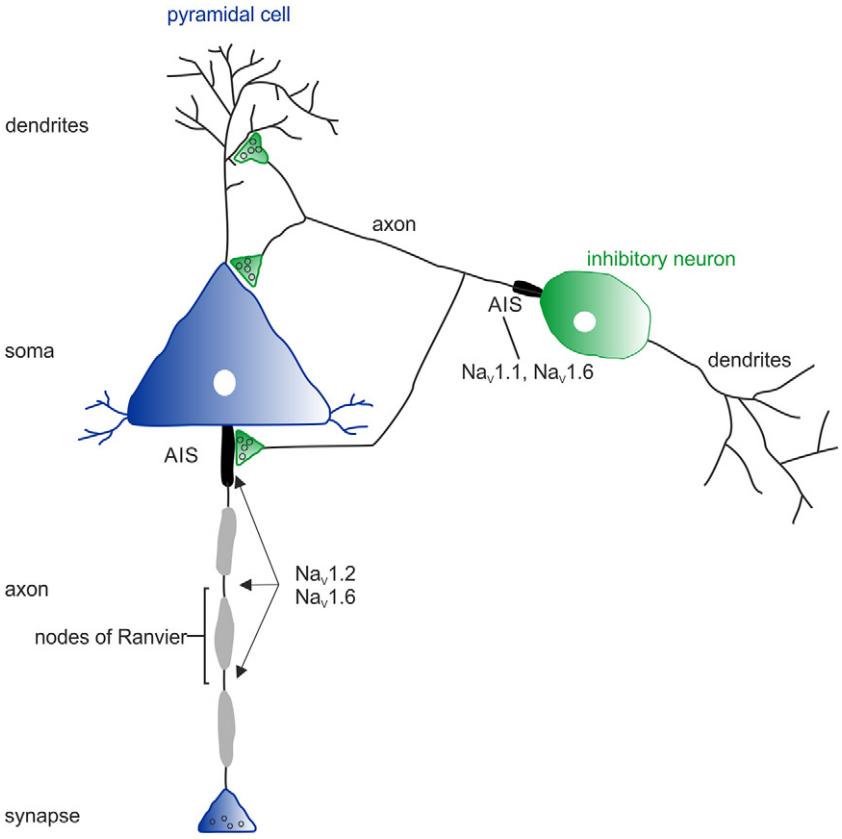

Fig. 1. Localization of the voltage-gated sodium channels $Na_V1.1$, $Na_V1.2$ and $Na_V1.6$. Scheme of an excitatory pyramidal cell (blue) and an inhibitory neuron (green) and their synaptic connections. $Na_V1.1$ is mainly expressed at axon initial segments of inhibitory neurons. $Na_V1.2$ is localized at the axon initial segment and nodes of Ranvier of excitatory pyramidal cell. $Na_V1.6$ is found at axon initial segments (AIS) and nodes of Ranvier as well as at lower abundance in the soma and dendrites of pyramidal neurons and also at axon initial segments of inhibitory neurons.

References

[1] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58: 512–521.

[2] Weber YG, Nies AT, Schwab M, Lerche H. Genetic biomarkers in epilepsy. Neurotherapeutics 2014;11: 324–33.

[3] Orsini A, Zara F, Striano P. Recent advances in epilepsy genetics. Neurosci Lett 2018;667: 4–9.

[4] Catterall WA. Sodium channel mutations and epilepsy. In: th, Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's basic mechanisms of the epilepsies. Bethesda (MD); 2012.

[5] Lorincz A, Nusser Z. Cell-type-dependent molecular composition of the axon initial segment. J Neurosci 2008;28: 14329–40.

[6] Tanabe T, Awaya Y, Matsuishi T, Iyoda K, Nagai T, Kurihara M, Yamamoto K, Minagawa K, Maekawa K. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome)—a nationwide questionnaire survey in Japan. Brain Dev 2008;30: 629–35.

[7] Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia 2010;51: 1043–52.

[8] Chipaux M, Villeneuve N, Sabouraud P, Desguerre I, Boddaert N, Depienne C, Chiron C, Dulac O, Nabbout R. Unusual consequences of status epilepticus in Dravet syndrome. Seizure 2010;19: 190–194.

[9] Wolff M, Casse-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. Epilepsia 2006;47 Suppl 2: 45–8.

[10] Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, Ganesan V, Gill D, Kivity S, Lerman-Sagie T, McLellan A, Pelekanos J, Ramesh V, Sadleir L, Wirrell E, Scheffer IE. Mortality in Dravet syndrome. Epilepsy Res 2016;128: 43–47.

[11] Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. Epilepsy Behav 2016;64: 69–74.

[12] Myers KA, McMahon JM, Mandelstam SA, Mackay MT, Kalnins RM, Leventer RJ, Scheffer IE. Fatal cerebral edema with status epilepticus in children with Dravet syndrome: report of 5 cases. Pediatrics 2017;139.

[13] Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39: 508–12.

[14] Dalic L, Mullen SA, Roulet Perez E, Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. Dev Med Child Neurol 2015;57: 200–2.

[15] Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci 2006;9: 1142–9.

[16] Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, Takeuchi T, Itohara S, Yanagawa Y, Obata K, Furuichi T, Hensch TK, Yamakawa K. Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J Neurosci 2007;27: 5903–14.

[17] Hedrich UB, Liautard C, Kirschenbaum D, Pofahl M, Lavigne J, Liu Y, Theiss S, Slotta J, Escayg A, Dihne M, Beck H, Mantegazza M, Lerche H. Impaired action potential initiation in GABAergic interneurons causes hyperexcitable networks in an epileptic mouse model carrying a human Na(V)1.1 mutation. J Neurosci 2014;34: 14874–89.

[18] Favero M, Sotuyo NP, Lopez E, Kearney JA, Goldberg EM. A Transient developmental window of fast-spiking interneuron dysfunction in a mouse model of Dravet syndrome. J Neurosci 2018;38: 7912–7927.
[19] Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, Lesca G, Ville D, Milh M, Villard L, Afenjar A, Chantot-Bastaraud S, Mignot C, Lardennois C, Nava C, Schwarz N, Gerard M, Perrin L, Doummar D, Auvin S, Miranda MJ, Hempel M, Brilstra E, Knoers N, Verbeek N, van Kempen M, Braun KP, Mancini G, Biskup S, Hortnagel K, Docker M, Bast T, Loddenkemper T, Wong-Kisiel L, Baumeister FM, Fazeli W, Striano P, Dilena R, Fontana E, Zara F, Kurlemann G, Klepper J, Thoene JG, Arndt DH, Deconinck N, Schmitt-Mechelke T, Maier O, Muhle H, Wical B, Finetti C, Bruckner R, Pietz J, Golla G, Jillella D, Linnet KM, Charles P, Moog U, Oiglane-Shlik E, Mantovani JF, Park K, Deprez M, Lederer D, Mary S, Scalais E, Selim L, Van Coster R, Lagae L, Nikanorova M, Hjalgrim H, Korenke GC, Trivisano M, Specchio N, Ceulemans B, Dorn T, Helbig KL, Hardies K, Stamberger H, de Jonghe P, Weckhuysen S, Lemke JR, Krageloh-Mann I, Helbig I, Kluger G, Lerche H, Moller RS. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 2017;140: 1316–1336.
[20] Liao Y, Deprez L, Maljevic S, Pitsch J, Claes L, Hristova D, Jordanova A, Ala-Mello S, Bellan-Koch A, Blazevic D, Schubert S, Thomas EA, Petrou S, Becker AJ, De Jonghe P, Lerche H. Molecular correlates of age-dependent seizures in an inherited neonatal-infantile epilepsy. Brain 2010;133: 1403–14.
[21] Gardella E, Becker F, Moller RS, Schubert J, Lemke JR, Larsen LH, Eiberg H, Nothnagel M, Thiele H, Altmuller J, Syrbe S, Merkenschlager A, Bast T, Steinhoff B, Nurnberg P, Mang Y, Bakke Moller L, Gellert P, Heron SE, Dibbens LM, Weckhuysen S, Dahl HA, Biskup S, Tommerup N, Hjalgrim H, Lerche H, Beniczky S, Weber YG. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. Ann Neurol 2016;79: 428–36.
[22] Boerma RS, Braun KP, van de Broek MP, van Berkestijn FM, Swinkels ME, Hagebeuk EO, Lindhout D, van Kempen M, Boon M, Nicolai J. Remarkable phenytoin sensitivity in 4 children with SCN8A-related epilepsy: a molecular neuropharmacological approach. Neurotherapeutics 2016;13: 192–197.
[23] Liu Y, Schubert J, Sonnenberg L, Helbig KL, Hoei-Hansen CE, Koko M, Rannap M, Lauxmann S, Huq M, Schneider MC, Johannesen KM, Kurlemann G, Gardella E, Becker F, Weber YG, Benda J, Moller RS, Lerche H. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. Brain 2019;142: 376–390.
[24] Wagnon JL, Barker BS, Hounshell JA, Haaxma CA, Shealy A, Moss T, Parikh S, Messer RD, Patel MK, Meisler MH. Pathogenic mechanism of recurrent mutations of SCN8A in epileptic encephalopathy. Ann Clin Transl Neurol 2016;3: 114–23.
[25] Trudeau MM, Dalton JC, Day JW, Ranum LP, Meisler MH. Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a patient with cerebellar atrophy, ataxia, and mental retardation. J Med Genet 2006;43: 527–30.

2. The European Reference Network for rare and complex epilepsies EpiCARE and its role in status epilepticus

J Helen Cross, MD

It has become increasingly apparent that epilepsy is not a single condition, but a symptom of a group of rare diseases. Rare epilepsies maybe, therefore, defined as those with incidence <5 in 10,000 population, either defined as an epilepsy syndrome or etiologically driven epilepsy. Traditionally, treatments have been targeted at the seizures with little understanding of the underlying cause; advances in structural brain imaging as well as molecular and metabolic diagnostics have determined there to be an increasing number of causes resulting in the description of in excess of 130 rare diseases. With an understanding of underlying cause, treatments can be more targeted. The relative prevalence of each disease means that a coordinated approach is required across key centers of expertise, with the development of e-tools to enable complex diagnostic and therapeutic interventions in a wider number of patients across Europe. Only then can we increase the possibility for new treatments that can be integrated into the clinical care pathway.

In 2013, E-pilepsy, one of two pilot European reference networks, was given funding to be developed over a period of three years. The aim of this network was to raise awareness and availability of epilepsy surgery across Europe. This was initially a network of 13 partners and a further 15 affiliated centers that ultimately achieved participation of 52 centers across Europe; a website was developed with information translated into 13 languages and an eligibility tool for physicians to guide referral in 3 languages. Monthly case discussions were established, and development of web-based tools for postprocessing Magnetic Resonance Scan (MRI) and neuropsychology assessment were initiated. Systematic reviews and surveys formed the basis of work toward guideline development and an electronic case record form (eCRF)-documented patients moving through presurgical evaluation. In 2016, DG Sante called for proposals for the development of European Reference Networks (ERNs) for rare diseases. Twenty-four networks were agreed by the board of member states including EpiCARE, an ERN for rare and complex epilepsies.

The EpiCARE network (www.epi-care.eu), for the clinical care and management of individuals across Europe with rare and complex epilepsies, was developed as an extension from the pilot reference network, E-pilepsy. EpiCARE is a network of 28 centers with expertise in the rare and complex epilepsies, developed to enhance diagnosis and ultimate management of this group of disorders, and located across 13 countries. Complex epilepsies are those requiring multidisciplinary management through a care pathway or for comorbidity, with or without known etiology, for example, the surgically treatable epilepsies requiring a high level of multidisciplinary expertise and diagnostic resource (including video-electroencephalography (EEG) analysis, functional and/or structural neuroimaging). It is recognized that delivery of such expertise can be enhanced through the use of e-tools, minimizing the need for patients to travel and ensuring the delivery of optimal healthcare at a local level. The objective, structure, and function of EpiCARE is built on the four objectives of the third program of the EUs action in the field of health (2014–2020), particularly the protection of Union citizens from serious cross-border health threats through e-health discussion and local delivery where possible; contribution to innovative, efficient, and safer health systems and facilitation of access to better and safer healthcare for Union citizens through networking of expertise, and harmonization of care as well as education and training.

E-pilepsy continues as the surgical therapeutic arm of EpiCARE and has continued with case discussion at the European level. However, there are now both 5 diagnostic (laboratory diagnostics, neurophysiology, neuroimaging, neuropsychology, and neuropathology) and a further 3 therapeutic work packages (neonatal seizures, targeted medical therapies, and dietary therapies), all established and working toward harmonization and availability of diagnosis and care of the rare and complex epilepsies. There are also cross-cutting themes including registry and guideline development, education and training, research, and clinical trials. The network has also built on the established neonatal network for recognition and treatment of neonatal seizures and the European Epilepsy Brain Bank. With the aim of enhancing clinical care in the first two years of its existence, we have initiated regular review and discussion of nonsurgical cases with a clear care pathway as well as maintaining the surgical discussions on a monthly basis. A knowledge of current standards of care has been established across all areas, and further progress has been made with regard to the development of a registry to suit both clinical and research purposes. Patient support groups through Patient Advisory Group (ePAG) have been present at

all levels of discussion and will be the key as we move forward in further development of the network.

The primary aim of the ERNs is to enhance clinical care of individuals with rare disease; inevitably, however, from this will stem further research. Collaboration across several platforms are likely to enhance this. EpiCARE has been integral to the successful European Joint Programme with participation at several levels, is partnering with the Human Brain Project, and will likely leverage utilization of the European Union (EU) and Innovative Medicines Initiative (INI)-funded C4C (Connect 4 Children) aiming to facilitate clinical trials in children across Europe. The development of a registry to determine where patients with relevant rare diseases are geographically located is a key objective and is in the early stage of development.

It is anticipated that EpiCARE will be able to contribute to the care and management of individuals with status epilepticus at several levels. Status epilepticus requiring intensive care is one rare/complex disease named as an entity for which the network was developed with monitoring of the number of cases treated in each center. It is anticipated that the care pathway will enable discussion of complex cases at a European level both in the search for diagnosis and ongoing management using either WebEx or the clinical patient management system as developed by the EU; further, it would be anticipated that documentation through a registry would highlight cohorts of patients from which pilot information on management could be drawn. Ultimately, we hope to formulate a platform through which standardized protocols could be utilized with documentation of outcomes, and work building toward clinical trial readiness and activation.

3. Pediatric Status Epilepticus Research Group (pSERG)

Tobias Loddenkemper, MD

Many aspects of care in Status Epilepticus (SE) and pediatric SE, in particular in refractory and super-refractory cases, are based on expert opinion or isolated case series. Upon review of the literature, gaps continue to present in risk factors, clinical care, and treatment, as well as short-term and long-term outcomes (1).

In order to address these gaps, multiple centers in North America joined to prospectively collect and share information on clinical presentation, test results, care and treatment, as well as outcomes, and also, jointly investigate a subgroup of patients' biological specimens. Utilizing variability in clinical presentation and care across patients and centers, this group attempts to identify optimal management and intervention strategies with regard to outcomes, and large patient numbers as well as prospectively collected data granularity allow for confounder adjustment (1). Inclusion criteria focus on pediatric patients (1 month–21 years) presenting with convulsive seizures at SE onset. Only patients whose seizures failed 2 or more antiepileptic drug (AED) classes or needed continuous infusions to terminate convulsive SE were included (2,3,4).

Among the first 81 patients enrolled, we evaluated timing to treatment. First, second, and third antiseizure medication doses were given at median times of 28, 40, and 59 min after seizure onset, respectively. Upon review of medication classes and timing, the first and second non-benzodiazepine antiseizure medication treatments occurred at 69 and 120 min, respectively (2), and these times were longer than more recent treatment suggestions. In a subsequent analysis, in 219 patients with refractory convulsive pediatric SE, intermittent convulsive SE (as compared with continuous convulsive seizures), and out-of-hospital SE onset proved to be risk factors for receiving later first-line treatment (3).

In this larger patient group, we analyzed the relationship between timing to treatment and outcome (4), selecting death during the related hospital admission as primary outcome and the need for continuous infusion as secondary outcome. The group was split into patients who were initially treated in less than or greater than 10 min. Multivariate analysis revealed that patients receiving first treatment later than 10 min had higher odds of death and of receiving continuous infusion. Timing of first-line, second-line, and third-line therapy correlated with each other. Results raise the question of whether time to treatment and outcomes may be causally related and whether shorter times to treatment may improve outcomes (4).

Longer treatment times were not only seen in this study. A review of 15 articles and 2212 patients with SE revealed 42 min as the average treatment time. Only half of all patients received treatment by emergency medical services (EMS), and 12% received treatment by caregivers or families prior to EMS arrival (5).

Next steps may focus on attempts to improve morbidity and mortality from refractory SE, and one potentially feasible consideration to adjust care may include sooner medication application and escalation. Future interventions in this area may therefore build on implementation research and quality improvement techniques and may also leverage technologies in improved seizure and refractory status epilepticus (RSE) detection and evaluation (5, 6).

References

[1] Sánchez Fernández I, Abend NS, Agadi S, An S, Arya R, Carpenter JL, Chapman KE, Gaillard WD, Glauser TA, Goldstein D, Goldstein JL, Goodkin HP, Hahn CD, Heinzen EL, Mikati MA, Peariso K, Pestian JP, Ream M, Riviello JJ, Tasker RC, Williams K, Loddenkemper T. Gaps and opportunities in refractory status epilepticus research in children: a multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure (2014) 23(2):87–97.

[2] Sánchez Fernández I, Abend, NS Agadi S, An S, Arya R, Brenton JN, Carpenter JL, Chapman KE, Gaillard WD, Glauser TA, Goodkin HP, Kapur K, Mikati MA, Peariso K, Ream M, Riviello Jr J, Tasker RC, Loddenkemper T, on behalf of the pediatric Status Epilepticus Research Group (pSERG). Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology (2015) 84(23):2304–11.

[3] Sánchez Fernández I, Gaínza-Lein M, Abend NS, Anderson A, Arya R, Brenton JN, Carpenter JL, Chapman KE, Clark J, Gaillard WD, Glauser TA, Goldstein JL, Goodkin HP, Helseth AR, Jackson MC, Kapur K, Lai Y-C, McDonough TL, Mikati MA, Nayak A, Peariso K, Riviello JJ Jr, Tasker RC, Tchapyjnikov D, Topjian AA, Wilfong A, Williams K, Loddenkemper T, on behalf of Pediatric Status Epilepticus Research Group (pSERG). Factors associated with treatment delays in pediatric refractory convulsive status epilepticus. Neurology (2018) 90 (19):e1692–e1701

[4] Gaínza-Lein M, Sánchez Fernández I, Jackson M, Abend NS, Arya R, Brenton JN, Carpenter JL, Chapman KE, Gaillard WD, Glauser TA, Goldstein JL, Goodkin HP, Kapur K, Mikati MA, Peariso K, Tasker RC, Tchapyjnikov D, Topjian AA, Wainwright MS, Wilfong A, Williams K, Loddenkemper T, on behalf of Pediatric Status Epilepticus Research Group (pSERG). Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurology (2018) 75(4): 410–418.

[5] Gaínza-Lein M, Fernández IS, Ulate-Campos A, Loddenkemper T, Ostendorf AP. Timing in the treatment of status epilepticus: from basics to the clinic. Seizure (2019) 68: 22–30.

[6] Ramgopal S, Thome-Souza S, Jackson M, Kadish NE, Sánchez Fernández I, Klehm J, Bosl W, Reinsberger C, Schachter S, Loddenkemper T. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. Epilepsy Behav. 2014 Aug;37:291–307.

4. Fenfluramine as a treatment option for acute repetitive seizures and status epilepticus?

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Before 1997, fenfluramine was used in combination with phentermin as an appetite suppressor, but because of cardiac side effects (valvular hypertrophy and pulmonary hypertension), when used in high dosages, it was banned as a therapeutic drug in 1997 (Schoonjans et al., 2017). Fenfluramine has a high affinity for serotonin receptors in the brain (especially 5HT 2A and 2C), leading to a higher brain serotonin concentration, and also, is a positive modulator of the sigma 1 receptor (Sourbron et al., 2017). In the past, several case reports described that fenfluramine in low dosages could stop self-induced syncopes and intermittent light-induced paroxysmal events in children with behavioral problems. Because it could also abolish photosensitivity on the EEG in some patients, it was hypothesized that fenfluramine should be tested as an antiepileptic drug (Gastaut, 1984, Aicardi and Gastaut, 1985). Boel and Casaer published in 1996 a first paper showing that low-dose fenfluramine was highly beneficial in children with refractory epilepsy (Boel and Casaer, 1996). In this case series, all children had intellectual disability and early onset epilepsy with drug-resistant self-induced seizures that were classified as generalized seizures. The effect of fenfluramine was remarkable, with a long-lasting seizure freedom in 7/11 children. A retrospective analysis on the effect of fenfluramine in children and adolescents with Dravet syndrome (Ceulemans et al., 2012) showed that 7/10 patients were seizure-free for at least 1 year (mean: 6 years and 7 months). Now, data from 2 prospective, double-blind, placebo-controlled trials are available, and they both confirm the efficacy and safety of low-dose fenfluramine in Dravet syndrome (Lagae et al., 2017 and 2018, presentations at American Epilepsy Society meetings). In a first study, children with Dravet syndrome whose seizures were refractory to standard-of-care treatment, but who were not taking stiripentol, were included. Two dosages (0,2 and 0,8 mg/kg/day) were tested against placebo. At both fenfluramine dosages, the effect was significantly higher than in the placebo group. The number of 50% responders in the 0,8 and 0,2 group was 70% and 41%, respectively, whereas this was only 7,5% in the placebo group. In the 0,8-mg/kg/day group, 25% of the children were seizure-free or only had 1 seizure during the 14-week trial. These findings were also seen in the second trial, now also including children who were on stiripentol at the time of inclusion. All primary and secondary end points were also met in this study, with fenfluramine being 54% better than placebo. Here, the number of 50% responders was 53,5% in the fenfluramine arm compared with 4,5% in the placebo arm. In another very refractory epilepsy syndrome, the Lennox–Gastaut syndrome, similar effect sizes of add-on fenfluramine were found (Lagae et al., 2018). In 6/13 children, a seizure frequency reduction of at least >60% was found.

Both Dravet and Lennox–Gastaut syndromes are prototypes of severe epileptic encephalopathies. In both syndromes, seizures are notoriously difficult to treat, and the large majority of these children have severe intellectual disability. In a recent survey, it was shown that only 6,3% of 574 children with Dravet syndrome were seizure-free in the last 3 months, with even lower numbers in infancy and preschool years (Lagae et al., 2018). Especially in Dravet syndrome, long-lasting convulsive and nonconvulsive seizures are typical (Dravet, 2011). In particular, focal long-lasting (>10 min) febrile seizures before the age of 1 year are the typical presenting seizure types in Dravet syndrome. In view of the promising results of fenfluramine in all studies, an obvious question is whether fenfluramine has an effect on long-lasting seizures and status epilepticus.

There are no specific data available yet that look at the effect of fenfluramine on long-lasting seizures types. However, looking in more detail into the data of the 2012 retrospective Dravet study, we can observe that 5/12 children had a status epilepticus episode in the year before inclusion. Four of these 5 children with Dravet syndrome became seizure-free after the introduction of add-on fenfluramine. This is indirect evidence of a preventive fenfluramine effect on long-lasting seizures. A typical example is case 12 in that publication: this child was 22 months at inclusion and had suffered already from 15 episodes of status epilepticus, with 2 times an intensive care hospitalization. She became seizure-free after add-on fenfluramine, and now only rarely has short-lasting seizures and no long-lasting convulsive seizures anymore. Similar indirect evidence can be found in the Lennox–Gastaut paper. Three out of thirteen children had at least one documented status epilepticus in the 6 months preceding the start of fenfluramine. In the core add-on trial lasting 5 months (with no changes in the concomitant antiepileptic drug (AEDs)), 2/3 did not have a status epilepticus anymore. At this moment, however, it is too early to consider fenfluramine as an agent in the intensive care unit as an acute treatment option in established refractory status epilepticus. In a case of super-refractory status epilepticus, a 21-year-old female with Dravet syndrome was successfully treated with fenfluramine 4 weeks after the start of the status epilepticus. A higher dose of 0.8 mg/kg had to be administered, and after weaning and revalidation, she remains with overall significant less seizures (Dr David Millett, personal communication).

In conclusion, we have indirect evidence that fenfluramine is able to prevent status epilepticus in patients with refractory epilepsy. It remains to be studied whether fenfluramine will become a treatment option in acute status epilepticus situations.

References

Aicardi J, Gastaut H. Treatment of self-induced photosensitive epilepsy with fenfluramine. N Engl J Med. 1985;313:1419.

Boel M, Casaer P. Add-on therapy of fenfluramine in intractable self-induced epilepsy. Neuropediatrics. 1996;27:171–3.

Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, Lagae L. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 2012;53:1131–9.

Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011;53 Suppl 2:1–6.

Gastaut H. Efficacy of fenfluramine for the treatment of compulsive behavior disorders in psychotic children. Presse Med. 1984;13:2024–5.

Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol. 2018; 60:63–72

Lagae L, Schoonjans AS, Gammaitoni AR, Galer BS, Ceulemans B. A pilot, open-label study of the effectiveness and tolerability of low-dose ZX008 (fenfluramine HCl) in Lennox–Gastaut syndrome. Epilepsia. 2018; 10:1881–1888.

Schoonjans AS, Marchau F, Paelinck BP, Lagae L, Gammaitoni A, Pringsheim M,Keane MG, Ceulemans B. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population. Curr Med Res Opin. 2017;33:1773–1781.

Sourbron J, Smolders I, de Witte P, Lagae L. Pharmacological analysis of the anti-epileptic mechanisms of fenfluramine in scn1a mutant zebrafish. Front Pharmacol. 2017;8:191.

5. Valnoctamide and *sec*-butylpropylacetamide (SPD): Potential follow-up Compounds to valproic acid (VPA)

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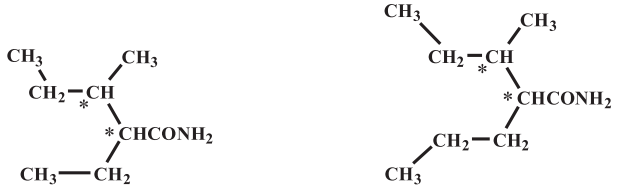

Valnoctamide (VCD) **sec-Butylpropylacetamide (SPD)**

Fig. 2. Chemical structures of valnoctamide (VCD) and sec-butylpropylaceamide (SPD).

Valproic acid (VPA) is a major antiepileptic drug (AED) with efficacy in multiple types of epilepsies (seizures) as well as other nonepileptic central nervous system (CNS) disorders. As a consequence of VPA's notorious teratogenicity that includes declined Intelligence quotient (IQ) in fetuses exposed to VPA coupled with autism spectrum (ASD) and hyperactivity disorders, Food and Drug Administration (FDA) [1] and European Medicines Agency (EMA) [2] issued warning against the use of VPA in women of childbearing age. Consequently, there is a substantial need to develop second-generation CNS drugs and VPA follow-up compounds that are better and safer than the parent compound [3–5].

Valnoctamide (VCD; Fig. 2) is a CNS-active chiral constitutional isomer of valpromide (VPD; Fig. 2), the corresponding amide of VPA, with two stereogenic centers denoted with * in Fig. 2 [3–5]. Unlike VPD that, in human, acts as a prodrug to VPA [6], VCD acts as a drug on its own with minimal biotransformation to its corresponding acid valnoctic acid (VCA) [3,6–8]. Valnoctamide was used in Europe as an anxiolytic (1964–2005) and, in 2013–2014, underwent a phase IIb clinical trial in bipolar disorder [9].

sec-Butylpropylacetamide (SPD; Fig. 2) is a one-carbon chiral homolog of VCD, currently in preclinical stage, that has a unique activity against status epilepticus (SE) and organophosphate neuronal damage [9–14]. *sec*-Butylpropylacetamide and VCD possess a unique anticonvulsant activity in a wide array of animal models that is superior to that of VPA, and their ED_{50} values are 3–15 times more potent than those of VPA. *sec*-Butylpropylacetamide and VCD exhibit stereoselective pharmacokinetics (PK) in humans (VCD) and rats (VCD and SPD) [9–16]. In mice and rats, VCD's four individual stereoisomers exhibited similar anticonvulsant activity to one another as well as to racemic-VCD in the maximal electroconvulsive shock (MES), subcutaneous Metrazol (scMET), and 6-Hz tests [15].

5.1. VCD and SPD unique activity in various models for status epilepticus (SE) and organophosphate nerve damage

The activity of SPD and VCD has been assessed in six different models of SE in which seizures were induced by pilocarpine, soman, paraoxon, tetramethylenedisulfotetramine (TETS), sarin, and VX [9–20]. For comparison, VPA was also evaluated in most of these models.

In all above SE models, SPD, VCD, and VPA were administered to rats (ip or im) 20–40 min after seizure onset. Racemic-VCD administered with the standard medical countermeasures at treatment delays of 5 min, 20 min, and 40 min after seizure onset was capable of stopping soman-induced SE seizures with ED_{50} values of 26 mg/kg, 60 mg/kg, and 62 mg/kg, respectively. *sec*-Butylpropylacetamide stereoisomers, administered 30 min after seizure onset at the lithium–pilocarpine-induced SE model, prevented the expression of further convulsive seizures in a dose-dependent fashion with ED_{50} values ranging between 95 and 135 mg/kg. (2R,3R)-SPD was the least potent SPD stereoisomer (ED_{50} > 130 mg/kg) [12]. *sec*-Butylpropylacetamide and its individual stereoisomers when given 20 min after seizure onset were capable of stopping soman-induced SE seizures with ED_{50} values ranging between 40 and 71 mg/kg.

Treatment with SPD or its individual stereoisomer, (2S,3S)-SPD, 30 min after seizure onset significantly shortened paraoxon-induced SE and reduced the duration of recorded pathological activity after the SE was terminated. (2S,3S)-SPD was superior to racemic-SPD in diminishing delayed pathological epileptiform activity within the first 8 h after SE [17].

In the TETS model, SPD (54 and 100 mg/kg) terminated SE within ~4 and ~2 min, respectively, and protected 65% and 100% of animals from mortality for >7 days. Valnoctamide (50 and 100 mg/kg) terminated SE within ~7 and ~2 min, respectively, and protected 62.5 and 90% of animals from mortality. Both SPD and VCD produced sedation in treated animals, which was especially pronounced at the dose of 100 mg/kg. Valproic acid (100 mg/kg) terminated TETS SE transiently in 80% of animals, and only 20% animals survived. A high VPA dose (200 mg/kg) terminated SE within ~8.8 min and protected 80% of animals from mortality [19]. Thus, both SPD and VCD effectively terminate TETS-induced behavioral SE, protect animals from mortality, and are more potent and more rapidly acting than VPA [19].

Children are likely to be among the casualties in a civilian nerve agent exposure, as recent events in Syria have demonstrated. Pediatric population is particularly susceptible to seizures when compared with adults [21–23]. Consequently, the efficacy of SPD and VCD, in comparison with phenobarbital, was studied in pediatric rats, utilizing a model recently developed by McDonough et al., for nerve agent-induced SE in both pediatric and adult rats [24]. Female and male postnatal days (PNDs) 21 and 28 and PND 70 adult control rats were surgically implanted with stainless steel electroencephalographic (EEG) screw electrodes and headpieces and were exposed to seizure-inducing doses of the nerve agents sarin or VX. These PND ages represent 3–6-year, 8- to 10-year old, and 15- to 18-year-old human equivalent ages, accordingly [20,25]. Five minutes after seizure onset, animals were treated with SPD, VCD, or phenobarbital. The up–down method was used over successive animals to determine the anticonvulsant ED_{50} of each drug [26].

The SPD-ED_{50} values in the VX model were as follows: PND 21, 53 mg/kg (male) and 48 mg/kg (female); PND 28, 108 mg/kg (male) and 43 mg/kg (female); PND 70, 102 mg/kg (male), and 40 mg/kg (female). The SPD-ED_{50} values in the sarin model were as follows: PND 21, 36 mg/kg (male) and 49 mg/kg (female); PND 28, 79 mg/kg (male) and 34 mg/kg (female); PND 70, 53 mg/kg (male) and 53 mg/kg (female). The VCD-ED_{50} values in the VX model were as follows: PND 21, 36 mg/kg (male) and 43 mg/kg (female); PND 28, 166 mg/kg (male) and 59 mg/kg (female); PND 70, 87 mg/kg (male) and 91 mg/kg (female). The VCD-ED_{50} values in the sarin model were as follows: PND 21, 45 mg/kg (male) and 53 mg/kg (female), PND 28, 233 mg/kg (male) and 79 mg/kg (female); PND 70, 97 mg/kg (male) and 79 mg/kg (female). The phenobarbital-ED_{50} values in the VX model were as follows: PND 21, 43 mg/kg (male) and 18 mg/kg (female); PND 28, 48 mg/kg (male) and 97 mg/kg (female). The phenobarbital-ED_{50} values in the sarin model were as follows: PND 21, 32 mg/kg (male) and 32 mg/kg (female); PND 28, 58 mg/kg (male) and 97 mg/kg (female): PND 70, 65 mg/kg (female) [20].

The VX and sarin study shows that anticonvulsant ED_{50} values varied with age and sex.

sec-Butylpropylacetamide, VCD, and phenobarbital are more effective in PND 21 rats. Phenobarbital has been effective in pediatric rats, but its ED_{50} values could not be determined in adult rats because of higher doses required that were accompanied with toxicity.

5.2. VCD activity in patients with acute mania

Women of childbearing age with epilepsy or bipolar disorder face a dilemma when pregnant, as VPA and most of the mood stabilizers have teratogenic potential to the unborn fetus [1–5,9,27–29]. Intense research initiatives have been aimed to design nonteratogenic CNS-active VPA derivatives that possess the antiepileptic and mood stabilizing properties of VPA [3–5]. In a head-to-head comparison between VCD and VPA, VCD, in contrast to VPA, was found to be nonteratogenic in three species: mice, rats, and rabbits [9,13,14]. Consequently, the efficacy and safety of VCD was evaluated as an add-on drug to risperidone in patient with acute mania [30]. Valnoctamide was found to be effective from week 3 to the end of the study at week 5 [30]. Subsequently, VCD activity was evaluated in a phase IIb monotherapy trial in comparison with placebo in the treatment of patients in an acute manic episode. Risperidone was used as an active control to verify the validity of the trial [9,13,14,31]. In an interim analysis of the study, VCD showed superiority over placebo in the completer cohort but not in the intentional-to-treat (ITT) cohort. Because of the ITT interim analysis results, the study sponsor (Stanley Medical Research Institute (SMRI)) decided to stop the study [9,13,14,31].

Valnoctamide was well tolerated at 1500 mg/day but lacked efficacy as a monotherapy in the treatment of symptoms in patients with acute mania. This outcome is in contrast to the results of the add-on phase IIa

study, which found that dual therapy of VCD and risperidone was better than risperidone monotherapy in severely ill patients [13,14,30,31].

5.3. The potential of VCD and SPD as New AEDs

As VCD (SPD's homolog) reached phase IIb, SPD has a potential as a new antiepileptic and CNS (with potential in pain and migraine) drug beyond its parenteral antinerve gas and anti-SE activity. The SPD-ED_{50} values in the rat-MES and -scMet tests are identical following ip and oral admonitions, indicating complete oral bioavailability. The lack of significant differences between SPD and VCD and their individual stereoisomers suggest that their unique and broad anticonvulsant activity is due to multiple mechanisms of action in addition to their documented GABAergic activity [32,33].

sec-Butylpropylacetamide's broad anticonvulsant spectrum of activity, better potency than VPA, and its unique activity at six different animal models for benzodiazepine-resistant SE coupled with its strong (composition of matter) valid patent makes it as an attractive candidate for development as a new molecular entity.

The good tolerability of a high VCD dose (up to 1500 mg/day) in patients with acute mania, coupled with the unmet need for a nonteratogenic VPA derivative, emphasizes the potential of VCD in epilepsy as a nonteratogenic CNS-active follow-up compound to VPA suitable for women of childbearing age as well as for therapy-resistant patients with epilepsy.

Declaration of competing interest

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Tobias Loddenkemper serves as founder and consortium PI of the pediatric status epilepticus research group (pSERG), and as a member of the NORSE Institute. He is part of intellectual property and patent applications to detect and predict clinical outcomes, and to manage, diagnose, and treat neurological conditions, epilepsy, and seizures. He received research grants from Upsher-Smith and Sage. In the past, he served as a consultant for Zogenix, Upsher Smith, Engage, and UCB.

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References

[1] FDA drug safety communication: valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children; 2013 http://www.fda.gov/Drugs/DrugSafety/ucm350684.htm. Accessed Jan 26 2019.
[2] European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. EMA/375438/2018. https://www.ema.europa.eu/documents/referral/valproate-article-31-referral-new-measures-avoid-valproate-exposure-pregnancy-endorsed_en-0.pdf. Updated Jul 6 2018. .
[3] Bialer M, Yagen B. Valproic acid — second generation. Neurotherapeutics 2007;4:130–7.
[4] Bialer M. Chemical properties of antiepileptic drugs (AEDs). Adv Drug Deliv Rev 2012;64:887–95.
[5] Bialer M, White HS. Key factors in the discovery and development of new antiepileptic drugs (AEDs). Nat Rev Drug Discov 2010;9:68–83.
[6] Bialer M. Clinical pharmacology of valpromide. Clin Pharmacokinet 1991;20:114–22.
[7] Bialer M, Haj-Yehia A, Barzaghi N, Pisani F, Perucca E. Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. Eur J Clin Pharmacol 1990;38:289–91.
[8] Barel S, Yagen B, Schurig V, Soback S, Pisani F, Perucca E, et al. Stereoselective pharmacokinetic analysis of valnoctamide in healthy subjects and in patients with epilepsy. Clin Pharmacol Ther 1997;61:442–9.
[9] Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the twelfth Eilat Conference (EILAT XII). Epilepsy Res 2015;111:85–141.
[10] White HS, Alex AB, Pollock A, Hen N, Shekh-Ahmad T, Wilcox KS, et al. A new derivative of valproic acid amide possesses a broad-spectrum antiseizure profile and unique activity against status epilepticus and organophosphate neuronal damage. Epilepsia 2012;53:134–46.
[11] Pouliot W, Bialer M, Hen N, Kaufmann D, Yagen B, Ricks K, et al. Electrographic analysis of the effect of *sec*-butyl-propylacetamide on pharmacoresistant status epilepticus. Neuroscience 2013;231:145–56.
[12] Hen N, Shekh-Ahmad T, Yagen B, McDonough JH, Finnell RH, Wlodarczyk B, et al. Stereoselective pharmacodynamic and pharmacokinetic analysis of *sec*-propylbutylacetamide (SPD), a new CNS-active derivative of valproic acid with unique activity against status epilepticus. J Med Chem 2013;56:6467–77.
[13] Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the thirteenth Eilat Conference (EILAT XIII). Epilepsia 2017;58:181–221.
[14] Bialer M, Johannessen SI, Koepp MJ, Levy RH, Perucca E, Tomson T, et al. Progress report on new antiepileptic drugs and devices: a summary of the fourteenth Eilat Conference (EILAT XIV). II. Drugs in more advanced clinical development. Epilepsia 2018;59:1842–66.
[15] Shekh-Ahmad T, Hen N, Yagen B, McDonough JH, Finnell RH, Wlodarczyk B, et al. Stereoseclctive analyses of valnoctamide, a non-teratogenic CNS-active derivetive of valproic acid with potential in epielpsy. Epilepsia 2014;55:1944–52.
[16] Shekh-Ahmad T, Mawasi H, McDonough JH, Yagen Bialer M. The potential of sec-propylbutylacetamide (SPD) and valnoctamide and their individual stereoisomers in status epilepticus. Epilepsy Behav 2015;15:298–301.
[17] Bar-Klein G, Swissa E, Kamintsky L, Shekh-Ahmad T, Hubary H, Short S, et al. *sec*-Butyl-propylacetamide (SPD) and two of its stereoisomers rapidly terminate paraoxon-induced status epilepticus in rats. Epilepsia 2014;55:1953–8.
[18] Mawasi H, Bibi D, Shekh-Ahmad T, Shaul C, Blotnik S, Bialer M. Pharmacokinetic and pharmacodynamic analysis after various routes of administration of sec-butylpropylacetamide (SPD), a new CNS drug possessing a unique activity against status epilepticus. Mol Pharmaceutic 2016;13:2492–6.
[19] Zolkowska D, Bialer M, Rogawski MA. Effects of valproic acid derivatives valnoctamide and *sec*-butylpropylacetamide on tetramethylenedisulfotetramine-induced status epilepticus in mice. American Epilepsy Society Annual Meeting, Washington DC, 2017 Abstract 2.269. https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/403367, Accessed date: 30 January 2018.
[20] Haine KM, Matson LM, Dunn EN, Ardinger CE, Lee-Stubbs Bibi D, McDonough JH, et al. Comparative efficacy of valnoctamide and *sec*-butylpropylacetamide (SPD) in terminating nerve agents-induced seizures in pediatric rats. Epilepsia 2019;00:1–7. https://doi.org/10.1111/epi.14530.
[21] Haut SR, Veliskova J, Moshe SL. Susceptibility of immature and adult brains to seizure effects. Lancet Neurol 2004;3:608–17.
[22] Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat Rev Neurol 2009;5:380–91.
[23] Sidell FR, Newmark J, McDonough JH. Nerve agents. In: Tuorinksy SD, editor. Medical aspects of chemical warfare. Washington DC: Department of the Army, The Office of the Surgeon General at TMM Publications, Bordon Institute, Walter Reed Army Medical Center; 2008. p. 155–219.
[24] Scholl EA, Miller-Smith SM, Bealer SL, Lehmkuhle MJ, Ekstrand JJ, Dudek EF, et al. Age-dependent behaviors, seizure severity and neuronal damage in response to nerve agents or the organophosphate DFP in immature and adult rats. Neurotoxicol 2018;66:10–21.
[25] Sengupta P. The laboratory rat: relating its age with humans. Int J Prev Med 2013;624-630(2013):4.
[26] Dixon WJ, Massey F. Introduction to statistical analysis. New York: McGraw-Hill; 1983; 426–41.
[27] Wlodarczyk BJ, Ogle K, Ying L, Lin M, Bialer M, Finnell RH. Comparative teratogenicity analysis of valnoctamide, risperidone and olanzapine in mice. Bipolar Disord 2015;17:615–25.
[28] Ying L, Bialer M, Cabera RH, Ogle K, Finnell RH, Wlodarczyk BJ. Teratogenicity of valproic acid and its constitutional isomer amide derivative valnoctamide in mice. Birth Defe Res 2018;92:1–11.
[29] Nguyen HT, Shamra V, McIntyre RS. Teratogenesis associated with antibipolar agents. Adv Ther 2009;26:281–94.
[30] Bersudsky Y, Applebaum J, Gaiduk L, Sharony L, Mishory A, Podberezsky A, et al. Valnoctamide as valproate substitute with low teratogenic potential in mania: a double-blind controlled, add-on clinical trial. Bipolar Disord 2010;12:376–82.
[31] Weiser M, Levi L, Levine SZ, Bialer M, Shekh-Ahmad T, Matie Viugan A, et al. A randomized, double-blind, placebo and risperidone-controlled study on valnoctamide for acute mania. Bipolar Disord 2017;19:285–94.
[32] Kaufmann D, West PJ, Smith MD, Yagen B, Bialer M, Devor M, et al. *sec*-Butylpropylacetamide (SPD), a new amide of valproic acid analogue for the treatment of neuropathic and inflammatory pain. Pharmacol Res 2017;17:129–39.
[33] Kaufmann D, Bahr S, Bates EA, Yagen B, Bialer M, Saunders GH, et al. The anti-migraine potential of a novel amide of valproic acid derivative: *sec*-butylpropylacetamide (SPD). Cephalagia 2016;36:924–35.