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EpiCARE – a network for rare and complex epilepsies

HP-ERN-2017 European Reference Networks / Framework Partnership Agreement (FPA 739537)

DV.3. Identification of candidate treatments prioritized for testing in selected patient cohorts

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Contributors: *28 EpiCARE leads*

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1 Version log

Version	Date	Released by	Nature of Change
Version 1	2 Jan 2019	E. Perucca (Fondazione Istituto Neurologico, Pavia, Italy) and R. Nabbout (Hopital Enfant Malade, Necker, Paris, France)	First version

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2 Definition and acronyms

Acronyms	Definitions
ACTH	Adrenocorticotrophic hormone
AED	Antiepileptic drug
ASO	Antisense oligonucleotide
CSWS	Continuous spike-wave during sleep
FCD	Focal cortical dysplasia
fMRI	Functional magnetic resonance imaging
JME	Juvenile myoclonic epilepsy
GAD	Glutamic acid decarboxylase
GRIN2A	Glutamate ionotropic receptor NMDA type subunit 2A
KCNT1	Potassium sodium-activated channel subfamily T member 1
mTOR	Mammalian target of rapamycin
NMDA	N-methyl-D-aspartate
WP V TF	EpicARE Workpackage V (Clinical Trials) Task Force

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3 Introduction

The present work was developed by an ad hoc Task Force (WP V TF) assembled in consultation with the EPICARE coordinator to address one of the goals of the EpiCARE network, i.e. the promotion/facilitation of clinical trials in rare and complex epilepsies. The overarching objective is to promote the acquisition of high-quality data guiding management decisions, particularly treatment decisions, in epilepsy syndromes where evidence is scarce or completely lacking.

Because currently EpiCARE receives no funding for research activities, it is understood that EpiCARE members are expected to pursue separate funding opportunities for the conduction of clinical trials. Against this background the WP V TF felt that it would be important to consult with EpiCARE members to define emerging candidate treatments for which evidence from clinical trials is particularly needed. This initiative was considered to be of value in fostering collaborative research within the network and the epilepsy community at large, and in establishing priorities when seeking grants for therapeutic research.

The ultimate goal was to provide a comprehensive list of candidate molecules, or non-drug treatment strategies, that stakeholders should consider as priorities for future clinical trials, particularly when seeking funding for collaborative clinical research in Europe.

The WP V TF includes the following members: Rima Nabbout (Paris, France) and Emilio Perucca (Pavia, Italy) as TF Chairs, Helen Cross (London, UK as EpiCARE coordinator), Geraldine Boylan (Cork, Ireland), Lieven Lagae (Leuven, Belgium), Sylvain Rheims (Lyon, France), Vicente Villanueva (Valencia, Spain).

4 Activities carried out and results

4.1 Activities carried out

WP V TF members met regularly by teleconference and two face-to-face meetings were held on March 9, 2018 in London, as part of the Annual EpiCARE members meeting, and on August 29, 2018 in Vienna, Austria, in conjunction with the European Congress of Epileptology. In November 2018, the WP V TF conducted a survey among EpiCARE members soliciting feedback on up to three treatments to be prioritized for clinical trials, together with suggestions on specific patient populations to be targeted by these treatments, the underlying rationale and a proposed trial design.

Suggestions received during these activities were shared among WP V TF members in December 2018. The TF Chairs prepared a draft summary report, which listed all suggestions received, categorized them by therapeutic areas, and included a critical assessment. The document was circulated among WP V TF members on December 26, 2018 and a teleconference with WP V TF members was held on January 8, 2019 to

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receive further input and to finalize the current report, which represents deliverable DV.3.

4.2 Results

A total of 17 respondents among EpiCARE members provided suggestions for 35 different candidate treatments and/or related epilepsy conditions to be prioritized for future clinical trials. A detailed list of all suggestions received is provided in Table 1.

The sections below provide a critical summary of the survey results, with candidate treatments classified into specific broader categories based on the input received by respondents and review by WP V TF members.

4.2.1 Treatments targeting CNS immune-mediated and inflammatory mechanisms

There is now sound evidence that autoimmune and inflammatory mechanisms play an important role in the pathogenesis and progression of several severe epilepsy syndromes, and that agents targeting these mechanisms can have antiseizure and potentially disease modifying effects in these conditions (Mirabelli-Badenier et al, 2012; Ramanathan et al, 2014; Dubey et al, 2015; Toledano et al, 2014; Aronica et al, 2017; Mirabelli et al, 2018; Mazunder et al, 2018). Autoimmune epilepsies are a group of disorders where unmet therapeutic needs are large, and not surprisingly clinical trials with immune-modulating treatments such as steroids, rituximab and mycofenolate mofetil were highlighted as priorities for testing in patients with these conditions.

The growing interest for clinical trials targeting the cause, rather than the symptoms, of epilepsy also resulted in several respondents proposing clinical trials of everolimus in epilepsies related with mTOR dysfunction, including epilepsies associated with focal cortical dysplasia and with mTOR pathway mutations. Other treatments highlighted as being worth testing include adrenocorticotrophic hormone (ACTH) for continuous spike-wave in sleep syndrome (CSWS), and anakinra, an interleukin-1 receptor antagonist, for seizure clusters associated with Dravet syndrome.

There was consensus within the WP V TF that experimental data and, in some cases, anecdotal reports do support the conduction of the suggested clinical trials. As a whole, autoimmune epilepsies represent a priority area for clinical research, which could benefit from advances made in the treatment of other CNS conditions where immune and inflammatory mechanisms play a fundamental role.

4.2.2 Precision treatments for rare epilepsies

In recent years, progress in next generation sequencing (NGS) techniques has led to identification of several mutations, particularly *de novo* mutations, which cause many severe epilepsy syndromes with onset in early age. Elucidation of the underlying epileptogenic functional abnormalities, which can be corrected with targeted treatments (Poduri, 2017), often using repurposed drugs (Mirza et al, 2017).

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Precision treatments targeting severe genetic epilepsies and identified by the survey as priorities for testing include quinidine for gain-of-function KNCT1-related early onset epileptic encephalopathies, memantine for GRIN2 related encephalopathies and ASO (or gene) therapies for Dravet syndrome.

Table 1. List of candidate treatments to be prioritized for clinical trials based on responses received in the survey conducted among EpiCARE members.

Candidate treatment	Target indication/population	Suggested trial design
ACTH (i.m.)	Continuous spike-wave in sleep (CSWS)	Steroids (oral)
Anakinra	Dravet syndrome (tonic-clonic seizure clusters)	Exploratory
Brivaracetam	Juvenile myoclonic epilepsy (JME)	Controlled versus valproate
Bromides	Dravet syndrome	Add-on controlled vs placebo
Cannabidiol	Angelman s. (myoclonic seizures)	Controlled add-on vs placebo
Cannabidiol	Hypothalamic amartoma	Exploratory
Cannabidiol	CSWS	
Cannabidiol	Focal seizures	Exploratory
Cannabidiol	Juvenile myoclonic epilepsy	Add-on controlled vs placebo
Cannabidiol	Ring chromosome 20 s.	Exploratory
Cannabidiol	Refractory epilepsy in adults	Controlled add-on vs placebo
Cannabidiol plus THC	Dravet and Lennox-Gastaut syndrome	Add-on controlled vs cannabidiol alone
Carbamazepine	Neonatal seizures	Exploratory
Disease modifiers (e.g. ASOs, gene therapy)	Dravet syndrome	Controlled (type of control to be discussed)
Everolimus (suggested by 3 responders)	Refractory focal epilepsy due to non-surgically treatable cortical dysplasia (e.g. type 2 FCD)	Exploratory or controlled add-on vs placebo
Everolimus (or other mTOR inhibitors) (2 suggestions)	Epilepsies related to mTOR pathway mutations	Controlled add-on vs placebo
Fenfluramine	Refractory epilepsy in adults	Controlled add-on vs placebo
Focused ultrasound	Hypothalamic hamartoma	Exploratory
Ketamine	Encephalopathy with refractory CSWS	Controlled add-on vs standard of care
Ketogenic diet	Eyelid myoclonias with absences	Controlled versus standard therapy (valproate, levetiracetam, ethosuximide)
Ketogenic diet	Ring chromosome 20 syndrome	Exploratory
Laser ablation guided by pre-study fMRI	Hypothalamic hamartoma	Controlled vs conventional laser ablation
Memantine	Epilepsy due to GRIN2A mutations	Exploratory
Micophenolate	Autoimmune (anti-GAD) epilepsy	Controlled vs standard therapy
Perampanel	Established status epilepticus	Exploratory
Perampanel	Progressive myoclonic epilepsies	Exploratory
Perampanel	Refractory absence seizures	Controlled, versus lamotrigine
Phenobarbital	Dravet syndrome (tonic-clonic seizure/clusters)	Controlled vs standard therapies
Quinidine (suggested by two respondents)	Epilepsy due to KCNT1 mutations	Exploratory or controlled vs placebo
Rituximab	Autoimmune (anti-NMDA) epilepsy	Controlled vs i.v. immunoglobulins
Stereotactic thermocoagulation	Hypothalamic hamartoma	Exploratory (compare outcomes from centers using alternative techniques)
Steroids	Unverricht-Lundborg syndrome	Exploratory
Steroids	Epilepsy due to limbic encephalitis	Controlled versus i.v. immunoglobulins
Steroids	Autoimmune epilepsies	Controlled vs IgG and/or other trearments
Topiramate	Dravet syndrome	Controlled versus standard therapy (valproate + clobazam + stiripentol)

There were also suggestions to consider clinical trials of non-pharmacological 'precision treatments' in rare epilepsies not necessarily related to gene defects,

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examples being focused ultrasound, fMRI-guided laser ablation and stereotactic thermocoagulation for hypothalamic hamartoma.

The WP V TF considered these suggestions well founded, particularly for conditions where anecdotal evidence from case reports provides further support to the theoretical rationale, as in the case of quinidine for KCNT1-related early onset epileptic encephalopathies (Abdelnour et al, 2018), and memantine for GRIN2 related encephalopathies (Pierson et al, 2014). Because of the rarity of these conditions, the EpiCARE network would be especially suitable for the design and conduction of these trials.

4.2.3 Cannabinoids

In recent years there has been exponential increase in the interest among physicians and the general public about the potential of cannabinoids, cannabidiol in particular, for the treatment of epilepsy (Perucca, 2017). Class I evidence is now available indicating that cannabidiol added on to other antiepileptic drugs (AEDs) improves seizure control in patients with Dravet syndrome (Devinsky et al. 2017) and Lennox-Gastaut-syndrome (Devinsky et al, 2018; Thiele et al, 2018), but high-quality evidence for its potential usefulness in the management of other epilepsy syndromes is still lacking. The results of the present survey show that exploration of the potential value of cannabidiol in a wide range of other seizure types and epileptic syndromes remains a high priority in the epilepsy community. It has also been suggested that the combination of cannabidiol and tetrahydrocannabidiol could bring antiseizure benefits superior to those associated with cannabidiol alone (McCoy et al, 2018), and assessment of the potential added value of this combination was also recommended by one survey participant.

The WP V TF concurred that high quality trials on the value of cannabinoids in epilepsy are worth pursuing. There was consensus that any such trial should make use of pharmaceutical-grade formulations, because there is evidence that some commercially available artisanal products may not contain the stated amount of cannabinoids, and may even contain harmful contaminants (Perucca, 2017).

4.2.4 Additional indications for conventional or innovative epilepsy treatments

Some respondents identified as priority areas for clinical trials the exploration of potential additional indications for old-generation AEDs (e.g., carbamazepine for neonatal seizures, phenobarbital for Dravet syndrome); for recently approved AEDs (e.g., topiramate for Dravet syndrome, brivaracetam for juvenile myoclonic epilepsy, perampanel for established status epilepticus, progressive myoclonic epilepsies and refractory absence seizures); for medications used in other conditions but already investigated in epilepsy (e.g. fenfluramine for refractory focal epilepsies; ketamine for encephalopathy associated with CSWS); and for dietary treatments (e.g. the ketogenic diet for eyelid myoclonias with absences and Ring chromosome 20 syndrome).

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5 Conclusions

The survey conducted within the EpiCAre network identified a wide range of treatments/syndromes which should be prioritized for future clinical trials. Given the heterogeneity of the epilepsies, it is not surprising that the number of priorities suggested was relatively large. However, some common denominators could be identified, the most relevant being a tendency to investigate treatments which are no longer directed at the symptoms, but target the underlying causes of epilepsies such immune and neuroinflammatory mechanisms, or functional abnormalities associated with specific gene defects.

It is hoped that this report will be useful to the EpiCARE network members and the epilepsy community at large for planning future trials and preparing funding applications. In fact, some of the treatments/indications identified in this report are currently being pursued as c4c (Connect4Children) funding applications The treatments prioritized for clinical trials are all targeting rare and/or complex epilepsies, which makes the EpiCARE network an ideal setting for the planning, design and execution of such trials.

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