Applying the latest data to move beyond seizure control for people with severe epilepsy

A touchLIVE MEETING webinar recorded in June 2021

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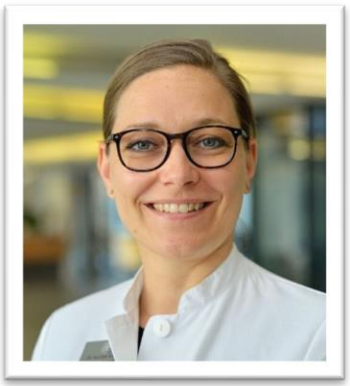
Welcome and Introduction

Ley Sander

Expert panel

Ley Sander

National Hospital for Neurology & Neurosurgery, Queen Square, London, UK



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Faculty disclosures

Ley Sander

- Has taken part in virtual & presential events sponsored by Arvelle Therapeutics, Eisai, Novartis, UCB & Zogenix
- Has served on advisory boards for Arvelle Therapeutics, UCB & Zogenix
- Has not, nor has any members of his family, owned shares or equities in pharmaceutical or medical device companies
- Has, or his Department has, undertaken, or are undertaking, studies funded by research grants from Medtronic & UCB

Kerstin Alexandra Klotz

- Has received speaker fees and served on advisory boards for Eisai, GW Phamarceuticals, Neurazpharm, PTC Threrapeutics GmbH Germany, and Zogenix.

Pasquale Striano

- Has received speaker fees and served on advisory boards for BioMarin, GW Pharmaceuticals, and Zogenix, and has received research funding from Eisai, Enecta BV, GW Pharmaceuticals, and Kolfarma Srl.

Agenda

Webinar open and introductions	**Ley Sander (chair)**
1 **PRESENTATION:** What are the key unmet medical needs remaining for people with severe epilepsy	**Kerstin Alexandra Klotz**
2 **PANEL DISCUSSION:** How can we improve the management of people with severe epilepsy?	**Ley Sander**
3 **CASE STUDY DISCUSSION:** Improving quality of life for people with severe epilepsy: Applying the latest findings in daily practice	**Pasquale Striano**
Audience questions and close	**All Faculty**

What are the key unmet medical needs remaining for people with severe epilepsy?

Kerstin Alexandra Klotz

Needs of people with epilepsy beyond clinical seizure control

Subclinical seizures

- Seizures with rhythmic ictal discharges which lack any objective or subjective alteration in behaviour or consciousness.[1]
- People may experience subclinical seizures, particularly during sleep.[2–5]
- How common these seizures are in people with severe epilepsy and their impact remains uncertain.[5,6]

Comorbidities

- Cognitive, behavioural, communication and movement difficulties are common.[7,8]
- Independent impact on people with epilepsy and family QoL.[8]
- AEDs can worsen certain comorbidities including mood disorders.[9]
- Drugs for treating comorbidities including behavioural issues can interact with AEDs.[7]

AED, antiepileptic drug; QoL, quality of life

1. Sperling MR, O'Connor MJ. Ann Neurol 1990;28(3):320-8; 2. Connolly MB, et al. Can J Neurol Sci 2016;43 Suppl 3:S3-8; 3. Genton P, et al. Epilepsia. 2011;52 Suppl 2:44-9.; 4. Bureau M, et al. Epilepsia. 2011;52 Suppl 2:13-23; 5. Jin B, et al. Int J Neurosci 2017;127(8):651-658; 6. Farooque P, Duckrow R. Epilepsy Res. 2014;108(10):1790-6; 7. Wheless JW, et al. Pediatr Neurol. 2020;107:28-40; 8. Nickels KC, et al. Nat Rev Neurol. 2016;12(8):465-76; 9. Kanner AM, et al. Nat Rev Neurol. 2016;12(2):106-16.

Needs of people with epilepsy beyond clinical seizure control

QoL

- Significantly worse in people with epilepsy, particularly due to communication and motor limitations.[1–4]
- Significantly worse in caregivers and family due to impact on relationships and work.[3–5]
- QoL is only indirectly associated with seizure frequency.[1,2]

Activities of daily living

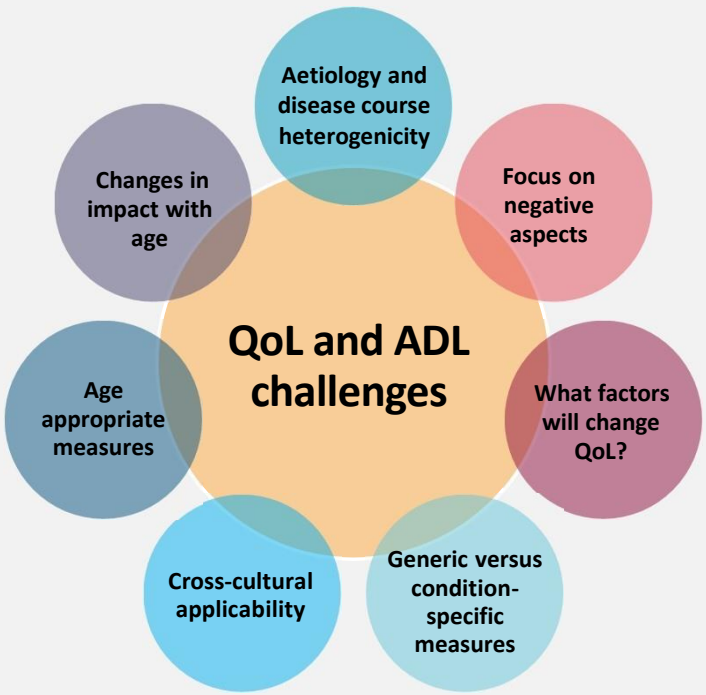
- 70–90% of caregivers reported an adverse impact of severe epilepsy on daily activities.[3–5]
- 90% of caregivers experience disruption of their work-life.[3–5]
- Caregivers have their social activities disrupted in 70–90% of cases, with the majority of caregivers reporting having <1 hour/day to themselves.[3–5]

QoL, quality of life;

1. Sinoo C, et al. Epilepsy Behav. 2019;90:217-227; 2. Brunklaus A, et al. Epilepsia, 2001;52(8):1476–1482; 3. Nabbout R, et al. Dev Med Child Neurol. 2019;61(10):1229-1236; 4. Gallop K, et al. Seizure 2009;18:554-8; 5. Lagae L, et al. Seizure 2019;65:72-79.

Challenges that remaining in evaluating QoL and activities of daily living

- Many generic and epilepsy-specific QoL measures for children and adults exist
- In children, measures include the CHQ, PedsQL, KINDL, ELDQOL, HRQOLCE, ICND, QOLIE-AD-48 and QOLCE
- Measures used in adults include the WPSI, ESI-55, QOLIE-89/31/10 and Liverpool QoL Batteries
- Many challenges remain in evaluating the impact of severe epilepsy



ADL, activities of daily living; CHQ, Child Health Questionnaire; ELDQOL, Epilepsy and Learning Disabilities Quality of Life questionnaire; ESI-55, Epilepsy Surgery Inventory; HRQOLCE, Health-Related Quality of Life in Children with Epilepsy; ICND, Impact of Childhood Neurologic Disability Scale; KINDL, Questionnaire for measuring HRQOL in children and adolescents; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; QOLCE, Quality of Life for Children with Epilepsy; QOLIE-89/31/10, Quality of Life in Epilepsy 89-item, 31-item and 10-item measures; WPSI, Washington Psychosocial Inventory; QOLIE-AD-48, Quality of Life in Epilepsy Inventory for Adolescents.

Jacoby A, et al. Expert Rev Neurother. 2013;13(12):1355-69.

Limitations with current AEDs

Lack of efficacy

- 30–40% of people with epilepsy have disease that is refractory to treatment[1,2]

Side effects

- Including drowsiness, unsteadiness, visual disturbances, cognitive dysfunction and mood disturbances[3]

Worsening of comorbidities

- Certain AEDs can mimic mood disorders and increase risk of cardio and cerebrovascular disease[4]

Burden of polypharmacy

- People with epilepsy frequently require multiple drugs for seizure and comorbidity management[5,6]

1. Laxer KD, et al. Epilepsy Behav. 2014;37:59–70; 2. Jain P, et al. Epilepsy Res Treat. 2013:501981; 3. Perucca P & Gilliam FG. Lancet Neurol. 2012;11(9):792-802; 4. Kanner AM, et al. Nat Rev Neurol. 2016;12(2):106-16; 5. Terman SW, et al. Epilepsy Behav. 2020;111:1072616; 6. Bunschoten JW, et al. Seizure. 2020;81:104-110.

Therapeutic targets

Cannabidiol

- Plant-derived purified CBD solution[1]
- Precise MoA of anti-convulsant activity is unknown[2]
- Reduces neuronal hyper-excitability via GPR55 and TRPV-1 channels and modulating adenosine signalling[2,3]

Fenfluramine

- Amphetamine derivative[1]
- Precise MoA of anti-convulsant activity is unknown[4]
- Disrupts 5-HT storage and synaptic reuptake, in addition to other MoA[1]

Gene replacement therapies

- These approaches include **AAV** (replacement of the entire gene), **ASO** (influencing translation, splicing and protein degradation), **NMD** (promoting specific gene expression) and **CRISPR** (activation of specific gene promoters)[5,6]

AAV, adeno-associated vector; AED, anti-epileptic drugs; ASO, antisense oligonucleotide; CDB, cannabidiol; CRISPR, clustered regularly interspaced short palindromic repeats; MoA, mechanism of action; NMD, nonsense mediated decay; RCT, randomized controlled trial.

1. Verrotti A, et al. Expert Rev Neurother. 2021;1:1-4; 2. GW Pharma Ltd. Epidyolex (cannabidiol) summary of product characteristics. www.medicines.org.uk/emc/product/10781#gref (accessed May 2021); 3. Morano A, et al. Neuropsychiatr Dis Treat. 2020;16:381-396; 4. Fintepla (fenfluramine) prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2020/212102s000lbl.pdf (accessed May 2021); 5. Carvill G. Gene modifying therapy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762553 (accessed 18 Jan 2021); 6. McTague A. Medical modification of disease expression and encephalopathy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762531 (accessed 7 Jan 2021).

How can we improve the management of people with severe epilepsy?

Panel Discussion

Improving quality of life for people with severe epilepsy: focus on comorbidities

Pasquale Striano

Epilepsy and comorbidities (1)

Medical, psychiatric and cognitive comorbidities are common

- Of individuals with epilepsy, 27–84% have at least one medical comorbidity[1]
- Of individuals with epilepsy, 6–64% have at least one psychiatric comorbidity[1]

Comorbidities influence prognosis and QoL

- Comorbidities can cause drug-resistant epilepsy[2]
- Treating comorbidities can improve epilepsy[3]
- The presence of comorbidities leads to different therapeutic choices[3]

Choice of antiseizure drugs has changed from “disease-oriented” to “patient-oriented”

QoL, quality of life

1. Seidenberg M, et al. Future Neurol. 2009;4:663-668; 2. Pérez-Pérez D, et al. Epilepsy Behav. 2021;121(Pt B):106430; 3. Keezer MR, et al. Lancet Neurol. 2016;15(1):106-15.

Epilepsy and comorbidities (2)

Medical Comorbidities	Neurological Comorbidities	Psychiatric Comorbidities
Obesity	Migraine	Depression
Gastrointestinal disorders	Cerebrovascular accidents	Generalised Anxiety Disorder
Respiratory system disorders	Alzheimer's disease/dementia	Panic Disorder
Chronic pain disorders	Intellectual Disability	Suicidal Ideation
Neoplasia	Fibromyalgia	Psychosis
Arthritis/rheumatism	Neuropathic Pain	Interictal dysphoric disorder
Musculoskeletal system disorders	ADHD	Interictal behaviour disorder
Diabetes		Autism spectrum disorder
Infections		
Fractures		
Allergies		

ADHD, Attention-deficit hyperactivity disorder

Seidenberg M, et al. Future Neurol. 2009;4:663-668; Kanner AM, et al. Nat Rev Neurol. 2016;12(2):106-16.

Examples of neurological comorbidities

Migraine

- Migraines are more than twice as common in people with epilepsy compared to without epilepsy
- The risk of developing migraine versus tension-type headache is increased 4.5-fold in children with epilepsy
- Headache initiation is usually in the same year or year after epilepsy diagnosis and occurs mostly in association with genetic/non-lesional epilepsy

Sleep problems

- Sleep problems, including parasomnias, sleep fragmentation, daytime drowsiness, and parent/child interaction during the night are common
- Children with refractory seizures have more sleep problems than seizure-free children
- People with epilepsy have an abnormal Stage 1 sleep percentage and latency to REM sleep versus controls
- Periodic leg movement, REM latency, length of apnoea, correlate with depression, inattentiveness/hyperactivity, and/or oppositional behaviour
- Persistent daytime drowsiness in people with epilepsy is not always due to the side effects of therapy

REM, random eye movement

Wei S-H, et al. J Formos Med Assoc. 2015;114:1031-1038.

Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment

Epilepsia. 2009 Mar;50(3):579-82. doi: 10.1111/j.1528-1167.2008.01813.x.

The NINDS epilepsy research benchmarks

Melinda S Kelley [1], Margaret P Jacobs, Daniel H Lowenstein, NINDS Epilepsy Benchmark Stewards

- Identify and characterise the full range and age specificity of comorbidities in people with epilepsy
- Identify predictors and underlying mechanisms that contribute to comorbidities
- Determine the optimal treatments for the neuropsychiatric and cognitive comorbidities in people with epilepsy

Kelley MS, et al. Epilepsia. 2009;50:579-582.

Physical comorbidities caused by specific drugs in people with epilepsy

- The most well-known adverse effects of treatment, including allergic reactions, cytopenia, electrolyte imbalance, and renal or hepatic impairment, are reversible after ceasing drug use
- Some physical comorbidities related to drugs, including disturbances of hormonal balance, may potentially have a long-term impact on the medical health and QoL of people with epilepsy

Comorbidities	Type of AEDs
Bone loss	TPM,[a] VPA, LMT, PB
Immunological disturbances	CBZ, VPA
Hypothyroidism	CBZ, VPA
Polycystic ovary syndrome	VPA
Weight gain	VPA,[a] GBP, PGB, VGB
Weight loss	TPM, FBM, ZNS
Dyslipidemia	CBZ, PB
Carnitine deficiency	VPA,[a] OXC. CBZ, PHT, PB

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[a]More significant than the other drugs.
CBZ, carbamazepine; FBM, felbamate; GBP, gabapentine; LMT, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; QoL, quality of life; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.
Wei S-H, et al. J Formos Med Assoc. 2015;114:1031-1038.

Choice of ASMs related to comorbidities in epilepsy

Comorbidities	Choose	Avoid
Obesity ≠ DM	TPM, ZNS	GBP, PGB, VPA, PRP
Migraine	TPM, GBP, PGB, ZNS, VPA	
Skin rashes	LEV, GBP, PGB, TPM, VPA, PER, LCM	CBZ, LTG, OXC, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT, LTG	
Depression ≠ behavioral dis	LTG, CBZ, OXC, VPA, PGB	LEV, PB, TPM, ZNS, PER
Cognitive dysfunction	LTG, LEV, OXC, LCM	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, LCM, ZNS	Enzyme-inducers or inhibitors
Cancer	LEV, VPA, PER	Enzyme-inducers
Cardia arrhythmia		Sodium channel blockers
Glaucoma		TPM
Gait disturbances		CBZ, PHT, PER
Heat stroke		TPM, ZNS
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	Drugs excreted by renal excretion	VPA
Renal disease	Drugs excreted by hepatic metabolism	GBP, PGB, LEV
Hyponatremia		OXC, ESL, CBZ
Osteoporosis	LTG, LEV	Enzyme inducers, TPM, VPA, ZNS
Restless leg syndrome	GBP, PGB, CZP, PER	
Parkinson disease	ZNS	
Tremor	TPM, PB, PRM	

ASM, anti-seizure medication; CBZ, carbamazepine; CZP, clonazepam; DM, diabetes mellitus; GBP, gabapentine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PRM, primidone; PER, perampanel; PGB, pregabalin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide;

Lee BI, et al. Epilepsy Res. 2019;156:106165.

Perspective strategies and recommendations

- Neurological and non-neurological comorbidities are common in people with epilepsy, and sometimes **even more disabling than the seizures themselves**
- Management strategies focus not only on controlling seizures, but also on **early diagnosis and therapy of comorbid conditions,** which should be assessed as integral part of management in people with epilepsy
- **Clinicians should screen and assess the comorbidities,** both in patients with newly diagnosed epilepsy and those with regular follow-up after treatment
- Many factors may contribute to the development of physical morbidities, such as the detrimental effects of chronic seizures and therapies; when a physical comorbidity is suspected to result from a specific medication, alternatives should be considered
- Because of a significant impact of epilepsy on affected people, further work should also focus on the **educational strategies of psychosocial support** to reduce burden and familial stress

Panel Discussion

Audience Questions

Thank you

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