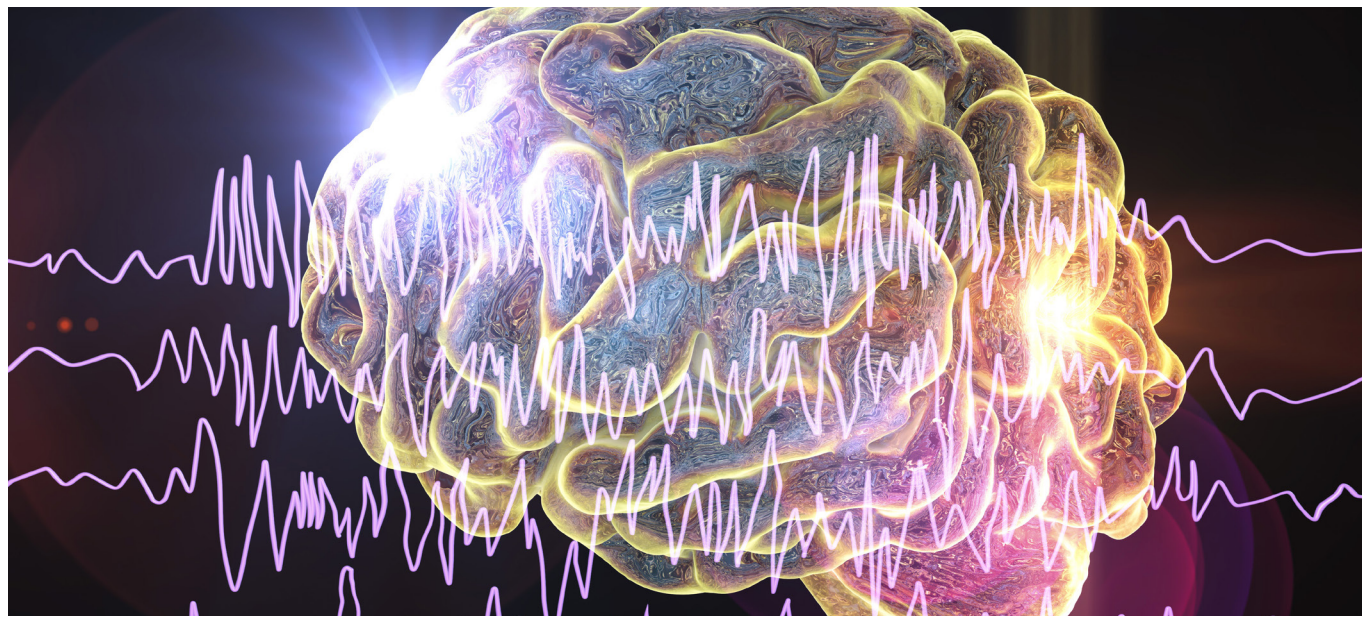


ADDRESSING UNMET NEEDS TO IMPROVE OUTCOMES FOR PEOPLE WITH EPILEPSY

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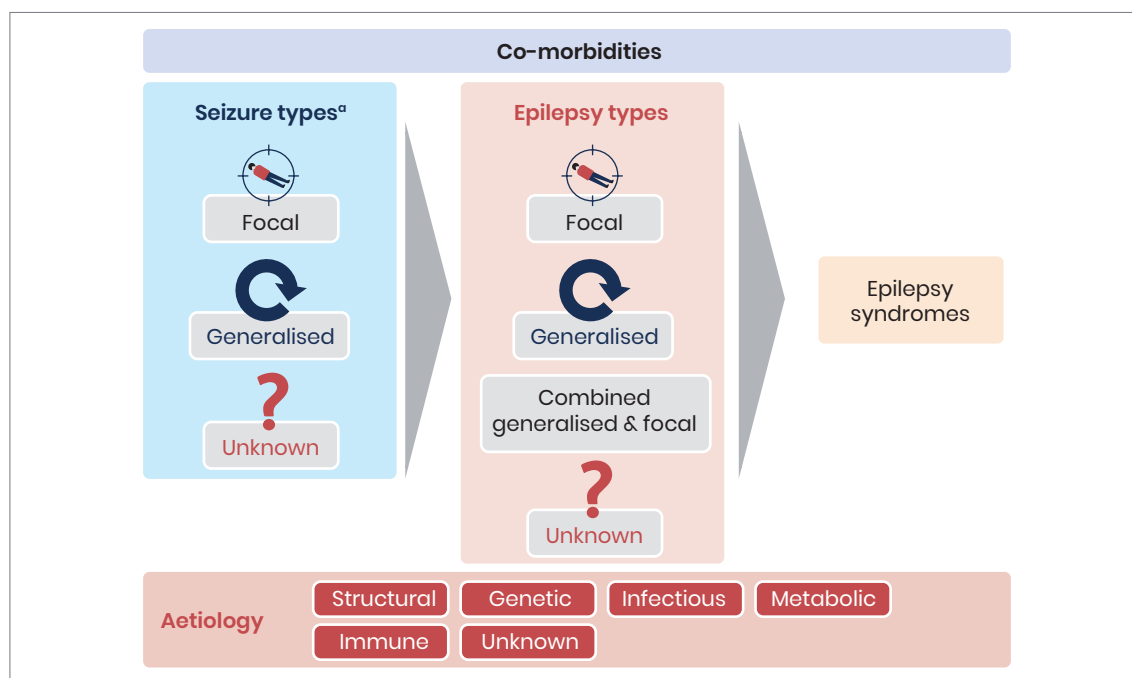


The COVID-19 pandemic has not only raised challenges and barriers to the effective diagnosis and management of epilepsy, but also highlighted the need for appropriate support for people with epilepsy and their caregivers. Here we discuss the key unmet medical needs that still exist for people with severe epilepsy, how recent clinical trial findings and therapeutic developments help to address these unmet needs, and the impact of the COVID-19 pandemic on diagnostic, therapeutic and coping strategies.

Key unmet medical needs for people with epilepsy

‘One of the most important factors for a good prognosis in epilepsy is an early diagnosis and appropriate treatment’. – Patricia Smeyers

In epilepsy, particularly in childhood-onset epilepsies, early diagnosis, treatment and monitoring are essential as delays can result in poorer seizure outcomes.¹ An accurate determination of epilepsy type is also critical for prognostication and treatment selection.² Diagnosis can sometimes be challenging as there is considerable overlap between different seizure types: many focal seizures may lack lateralising features; more than half of people with what look to be generalised epilepsy can have a focal syndrome; three-quarters of people with focal epilepsy are amnesic for some seizures; and over half of people with epilepsy do not have an aura preceding their seizures.² In recognition of this, the International League Against Epilepsy revised its definitions of epilepsy in 2014 to encourage prompt diagnosis and treatment,³ and further expanded the classification of seizure and epilepsy types in 2017 to include aetiologies, which may aid treatment selection (**Figure 1**).^{4,5} Despite this improved diagnostic framework and the availability of a wide variety of anti-seizure medications, it is estimated that 30–40% of all people with epilepsy still fail to respond to treatment.⁶ Certain paediatric conditions are particularly refractory to anti-seizure medications, including epileptic encephalopathies such as West’s syndrome, Dravet’s syndrome,

Figure 1: ILAE frameworks for the classification of epilepsies and seizures^{4,5}

^aDenotes onset of seizures.

ILAE = International League Against Epilepsy.

Lennox–Gastaut’s syndrome, Ohtahara syndrome and early myoclonic encephalopathy.⁷ This highlights the clear unmet medical need that still exists for some people with epilepsy.

Recently, new treatments have been developed that may address these unmet medical needs: cannabidiol and fenfluramine. Cannabidiol belongs to a novel class of epilepsy therapies, the cannabinoids, which can reduce neuronal hyper-excitability by modulating intracellular calcium and adenosine-mediated signalling.⁸ In four randomised, double-blind, placebo-controlled clinical trials, cannabidiol (20 mg/kg/day) plus clobazam was shown to reduce seizures by 31–43% versus placebo in people with Dravet’s syndrome, and 46–54% versus placebo in people with Lennox–Gastaut’s syndrome.⁹ As a result, cannabidiol is currently indicated as adjunctive therapy (with clobazam in the European Union) for seizures associated with Lennox–Gastaut’s syndrome or Dravet’s syndrome in people 2 years of age or over.⁹ Fenfluramine is a serotonin agonist indicated to treat seizures in people with Dravet’s syndrome (as add-on therapy in the European Union).^{9–11} In two randomised, double-blind, placebo-controlled trials, fenfluramine (0.2–0.7 mg/kg/day added to 1–4 existing anti-seizure medications) was shown to reduce convulsive seizures by 32–70% versus placebo.¹⁰

The impact of COVID-19 on people with epilepsy

‘The first months of the [COVID-19] pandemic changed the entire healthcare world’. – Pasquale Striano

In addition to the current unmet medical needs for people with severe epilepsy, the COVID-19 pandemic has raised new challenges and barriers to the effective diagnosis and management of the condition. While there is no direct evidence that COVID-19 can directly trigger a seizure, it is known that infection, fever (especially in children) and sleep deprivation can be triggers.¹² Indirect factors, such as increased stress, reduced physical activity and isolation, may also impact the health of people with epilepsy.^{13–15} Psychological stress is a known factor that induces seizures in people with epilepsy. The COVID-19 pandemic can increase psychological stress in a variety of ways, including fear, worry, sadness and frustration (e.g. about health, financial situations, jobs, loved ones); changes in sleeping patterns; changes in appetite, energy, desires and interests; worsening of chronic health or mental health conditions (depression, anxiety); or increased use of tobacco, alcohol or other substances.^{13,16,17} People with epilepsy are also known to have low levels of physical activity, which can negatively affect their physical and

mental health.¹³ In addition, periods of social isolation and quarantine during the COVID-19 pandemic are likely to increase sedentary behaviours and reduce physical activity.¹³ As such, coping strategies to maintain psychological and physical fitness during the pandemic would seem key aspects of epilepsy management. They could consist of light, regular, home-based physical exercise guided by health experts; meditative techniques; emotional support and counselling; a healthy, well-balanced nutritious diet; regular sleep; and spiritual/religious pursuits dependent on the preference of the individual.^{13,17}

The pandemic has also raised barriers against the effective diagnosis and management of epilepsy, with social distancing and self-isolation measures introducing several limitations. Some of these, highlighted by experts, include fewer physical examinations and face-to-face appointments, a reduction in the level of direct support for people with epilepsy (potentially increasing the risk of seizures), and fear and anxiety towards travel, making people reluctant to attend necessary hospital or physician appointments or even to collect prescriptions for anti-seizure medications (personal communication; Pasquale Striano). To overcome these barriers, service users and physicians have had to adapt their practices, such as utilising telemedicine to conduct remote appointments or assessments;¹⁸ providing increased education on the signs and symptoms of an individual's condition to promote self-monitoring; and online services for advice and prescription deliveries.¹²

Summary

'This [treating epilepsy] is a dynamic process, and we should never give up'. – Josemir W Sander

Overall, while unmet needs and challenges in diagnosing and treating severe epilepsies still exist, especially during the COVID-19 pandemic, promising new treatment options and new methods of diagnosis and disease monitoring provide us with strategies for meeting these needs and improving the lives of people with severe epilepsy.

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Reference

- Khan A, Lim H, Almubarak S. Importance of prompt diagnosis in pediatric epilepsy outcomes. *Seizure*. 2020;80:24–30.
- Bank AM, Kuzniecky RI. Diagnosis and management of new onset epilepsy in adults. *US Neurology*. 2020;16:32–7.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55:475–82.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58:522–30.
- Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58:512–21.
- Laxer KD, Trinka E, Hirsch LJ, et al. The consequences of refractory epilepsy and its treatment. *Epilepsy Behav*. 2014;37:59–70.
- Jain P, Sharma S, Tripathi M. Diagnosis and management of epileptic encephalopathies in children. *Epilepsy Res Treat*. 2013;2013:501981.
- GW Pharmaceuticals plc. Cannabidiol (Epidyolex) summary of product characteristics. Available at: www.medicines.org.uk/emc/product/10781#gref (accessed 27 January 2021).
- European Medicines Agency (EMA). Fintepla (fenfluramine). 2021. Available at: www.ema.europa.eu/en/medicines/human/summaries-opinion/fintepla (accessed 27 January 2021).
- Zogenix, FINTEPLA (fenfluramine). US prescribing information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/212102s000lbl.pdf (accessed 27 January 2021).
- European Medicines Agency (EMA). Fintepla (fenfluramine) summary of product characteristics. 2021. Available at: www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf (accessed 03 February 2021).
- Sander I, Epilepsy Society: Epilepsy and the coronavirus (COVID19) FAQs. 2020. Available at: www.epilepsysociety.org.uk/epilepsy-and-coronavirus-covid-19-faqs (accessed 27 January 2021).
- Vancini RL, de Lira CAB, Andrade MS, et al. CoVID-19 vs. epilepsy: It is time to move, act, and encourage physical exercise. *Epilepsy Behav*. 2020;107:154.
- Hall G, Laddu DR, Phillips SA, et al. A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? *Prog Cardiovasc Dis*. 2020;S0033-0620:30077–3.
- Rosengard JL, Donato J, Ferastraoaru V, et al. Seizure control, stress, and access to care during the COVID-19 pandemic in New York City: The patient perspective. *Epilepsia*. 2021;62:41–50.
- Li S, Wang Y, Xue J, et al. The impact of COVID-19 epidemic declaration on psychological consequences: A study on active Weibo users. *Int J Environ Res Public Health*. 2020;17:2032.
- Center for Disease Control and Prevention (CDC). COVID-19: Coping with stress. 2020. Available at: www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/managing-stress-anxiety.html (accessed 27 January 2021).
- Zuberi S, Patel N, Shetty J, et al. Multi-centre pilot of an interactive, secure, cloud-based, patient to clinician, smartphone video transfer service for epilepsy management during the COVID-19 pandemic. Abstract 507; presented at the virtual AES 2020. Available at: www.aesnet.org/meetings_events/annual_meeting_abstracts/view/2422849 (accessed 02 February 2021).