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Epilepsy: Mitochondrial connections to the 'Sacred' disease

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ABSTRACT

Over 65 million people suffer from recurrent, unprovoked seizures. The lack of validated biomarkers specific for myriad forms of epilepsy makes diagnosis challenging. Diagnosis and monitoring of childhood epilepsy add to the need for non-invasive biomarkers, especially when evaluating antiseizure medications. Although underlying mechanisms of epileptogenesis are not fully understood, evidence for mitochondrial involvement is substantial. Seizures affect 35%-60% of patients diagnosed with mitochondrial diseases. Mitochondrial dysfunction is pathophysiological in various epilepsies, including those of non-mitochondrial origin. Decreased ATP production caused by malfunctioning brain cell mitochondria leads to altered neuronal bioenergetics, metabolism and neurological complications, including seizures. Iron-dependent lipid peroxidation initiates ferroptosis, a cell death pathway that aligns with altered mitochondrial bioenergetics, metabolism and morphology found in neurodegenerative diseases (NDDs). Studies in mouse genetic models with seizure phenotypes where the function

Abbreviations: ADDM, CDC Autism and Developmental Disabilities Monitoring Network; ADHD, attention deficit hyperactivity disorder; AHS, Alpers-Huttenlocher syndrome; ALA, α-lipoic acid; ASD, antiseizure drug; BCE, before current era; CcO, cytochrome *c* oxidase; CDC, Centers for Disease Control and Prevention; CDD, *CDKL5* deficiency disorder; CE, current era; CNS, central nervous system; CT, computerized tomography scan; DHLA, dihydrolipoic acid; EEG, electroencephalogram; EPC, epilepsia partialis continua; ESI, electrical source imaging; ETC, mitochondrial electron transport chain; FA, Friedreich's ataxia; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FPN, ferroportin; *FXN*, frataxin gene; GPX, glutathione peroxidase; HSP, heat shock protein; ILAE, International League Against Epilepsy; LIAS, lipoic acid synthetase; LS, Leigh syndrome; MEG, magnetoencephalography; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MEMSA, myoclonus epilepsy, myopathy and sensory ataxia; MERRF, myoclonic epilepsy with ragged red fibers; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NARP, neuropathy, ataxia, and retinitis pigmentosa; NDD, neurodegenerative disease; NF-kB, nuclear factor kappa B; NINDS, National Institute of Neurological Disorders and Stroke; Nrf2, nuclear factor erythroid 2-related factor 2; P2X, ligand-gated ion channel purinergic receptor; P2Y, G protein-coupled purinergic receptor; PBM, photobiomodulation; PDH, pyruvate dehydrogenase complex deficiency; PET, positron emission tomography; *POLG*, DNA polymerase subunit gamma; ROS, reactive oxygen species; SCAE, spinocerebellar ataxia with epilepsy; SE, status epilepticus; SPECT, single-photon emission computerized tomography; SPM, statistical parametric mapping; SUDEP, sudden unexpected death in epilepsy; TLE, temporal lobe epilepsy; TMS, transcranial magnetic stimulation; tPBM, transcranial PBM; VNS, vagus nerve stimulation.

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of an essential selenoprotein (GPX4) is targeted suggest roles for ferroptosis in epilepsy. GPX4 is pivotal in NDDs, where selenium protects interneurons from ferroptosis. Selenium is an essential central nervous system micronutrient and trace element. Low serum concentrations of selenium and other trace elements and minerals, including iron, are noted in diagnosing childhood epilepsy. Selenium supplements alleviate intractable seizures in children with reduced GPX activity. Copper and cuproptosis, like iron and ferroptosis, link to mitochondria and NDDs. Connecting these mechanistic pathways to selenoproteins provides new insights into treating seizures, pointing to using medicines including prodrugs of lipoic acid to treat epilepsy and to potential alternative therapeutic approaches including transcranial magnetic stimulation (transcranial), photobiomodulation and vagus nerve stimulation.

1. Introduction

1.1. The falling sickness from heaven, a 'Sacred' disease

Epilepsy (Devinsky et al., 2018), a complex brain network disease characterized principally by an enduring predisposition to unprovoked seizures, is an illness known since antiquity (Ali et al., 2016; Karoly et al., 2021; Niesvizky-Kogan et al., 2022; Panteliadis et al., 2017; Patel and Moshé, 2020; Wilson and Reynolds, 1990). Cognitive and behavioral alterations associated with epilepsy often are subtle, presenting with or without revealing overt abnormal signs (Devinsky et al., 2018; Löscher and Stafstrom, 2023; Matias et al., 2023). In the distant past, diseases were attributed to the spiritual whims of gods who had control over human health, life and death (Ali et al., 2016; Rektor et al., 2013). The ancient Greeks believed epilepsy (*επιληψία*) was caused by a poisonous miasma (*μίασμα*) that Selene (*Σελήνη*) (Grimal, 1986), the Goddess of the Moon (whom the Romans called *Luna*), cast on offending sinners (*lunatics*) (Bou Nasif et al., 2021; Eloge et al., 2020; Khalil et al., 2020; Magiorkinis et al., 2010). To the Babylonians and Assyrians, epilepsy was an ominous disease feared as the *falling sickness from heaven* (Panteliadis et al., 2017; Reynolds, 2020; Wilson and Reynolds, 1990). However, the Greek physician-philosopher, Alcmaeon of Croton (~500 BCE (Bowder, 1982)), rejecting the religious attributes, questioned the prevailing dogma. He believed the brain is the anatomical site where thoughts originate and memory is kept and, thus, also the most probable source of epileptogenesis (Rektor et al., 2013; Toncheva et al., 2023). This concept was further advanced by Hippocrates of Kos (460–380 BCE (Bowder, 1982)) in his treatise *On the Sacred Disease*, where he methodically detailed the first rational and scientific approach to epilepsy, describing and treating the illness as a dysfunction of the brain (Ali et al., 2016; Hamblin, 2023; Magiorkinis et al., 2010; Mavrogenis et al., 2019; Panteliadis et al., 2017; Patel and Moshé, 2020). Fig. 1 depicts a timeline of the history of epilepsy causes and treatments (Kaculini et al., 2021; OUPblog, 2015; Wolf, 2023).

1.2. Epilepsy, seizures, comorbidities and diagnostics

Epilepsy is a prevalent neurological disease affecting more than 65 million people worldwide (Hamblin, 2023; Kanner and Bicchi, 2022) with increasing incidence in the elderly (Del Pozo et al., 2022; van Vliet and Marchi, 2022). While our understanding of the underlying causes and associated risk factors has advanced considerably since the time of Hippocrates (Blank and Jette, 2023; Panteliadis, 2021), the classification of seizures and epilepsy syndromes remains enigmatic (Duncan, 2022; Hilal et al., 2022; Patel and Moshé, 2020; Shlobin and Sander, 2022; Steriade et al., 2022). An expanding list of causes, risk factors and conditions that induce seizures to occur is a nexus of a wide variety of epilepsy-associated comorbidities (Arulsamy and Shaikh, 2022; Löscher and Stafstrom, 2023; Steriade et al., 2022; Zilberter et al., 2022).

Seizures increase the probability of sudden unexpected death in

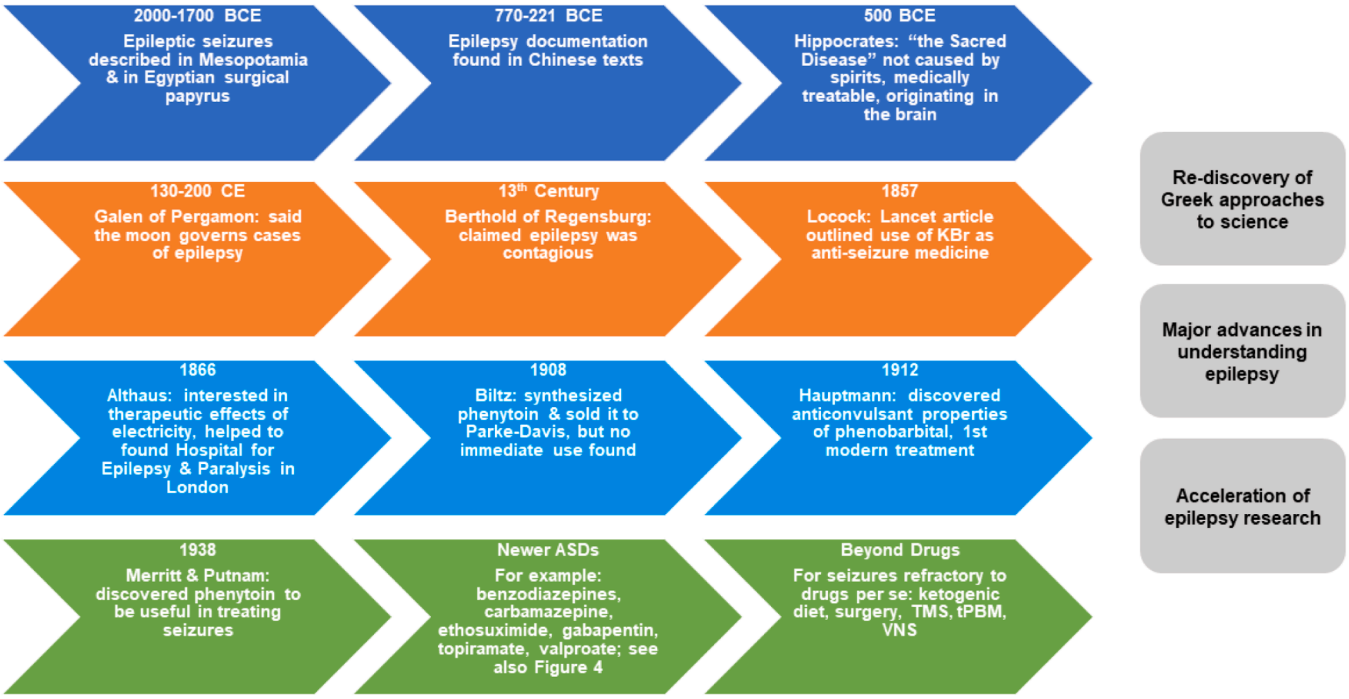

Fig. 1. A timeline of the history of epilepsy causes and treatments. Abbreviations: BCE, before current era; CE, current era; TMS, transcranial magnetic stimulation; tPBM, transcranial PBM; VNS, vagus nerve stimulation.

epilepsy (SUDEP) (Arulsamy and Shaikh, 2022; Hamdy et al., 2022a; Hamdy et al., 2022b; Li et al., 2022a; Löscher and Stafstrom, 2023; O'Neal et al., 2022). Seizures also occur in autism spectrum disorders (Chakraborty et al., 2022; Davis, 2023; Hirota and King, 2023; Jia et al., 2022b; Liu et al., 2022b; Löscher and Stafstrom, 2023; Shao et al., 2022b; Watkins et al., 2022). (Note that there is a growing preference for "autism spectrum disorders" to be referred to as "autism" or "person with autism" (Keating et al., 2023; Zamzow, 2023).) And, more frequently, seizures are being linked to neurological complications concomitant with the novel coronavirus infectious disease first identified in 2019, better known today as COVID-19. COVID-19 is the second severe acute respiratory syndrome coronavirus (SARS-CoV-2) to cause worldwide concern in the last couple of decades (Ben Mohamed et al., 2023; Davis et al., 2023; Dunn et al., 2023; Kizilkilic et al., 2022; Kurokawa et al., 2023; Taquet et al., 2023; Yea et al., 2023).

The lack of validated and specific biomarkers for the myriad forms in which epilepsy present can make an accurate diagnosis of the underlying cause challenging and consequential (Bandopadhyay et al., 2021; Blank and Jette, 2023; Devinsky et al., 2018; Graifman et al., 2023; Ismail et al., 2022; Johannesen, 2023; Khamis et al., 2023; Ma et al., 2023; Martinez and Peplow, 2023; McKnight et al., 2022; Perucca and Gotman, 2022; Pitkänen et al., 2016; The Lancet Neurology, 2022; Zweiphenning et al., 2022). See Table 1 for a partial list of the tests and diagnostic tools used. The traditional use of non-invasive scalp EEGs (the principal diagnostic test used in the ILAE classification of seizures (Asadi-Pooya et al., 2023; Kleen and Guterman, 2023; Tveit et al., 2023)) can be a cumbersome diagnostic procedure, which may require collecting data over a period of a few minutes to several days (Karoly et al., 2021). Diagnosis and monitoring of epileptic activity in children add additional levels of importance to the need for non-invasive markers (Barsh and Wusthoff, 2023; McKee et al., 2023), especially for evaluating the therapeutic efficacy of antiseizure medications (Kasteleijn-Nolst Trenite and Reed, 2023; Whitlock et al., 2022).

Salivary analysis is attracting much attention as a promising diagnostic technique (Almukainzi, 2023; Aro et al., 2017; Bindila et al., 2022; De Bartolo et al., 2023; Huang et al., 2023; Kodukula et al., 2017; Li et al., 2015; Urbizu et al., 2023; Whitlock et al., 2022; Wolgin et al., 2022). A study by Shahar et al. that analyzed and compared saliva samples from 33 epileptic children (11 with intractable epilepsy and 22 with non-intractable epilepsy) with the corresponding results from saliva samples collected from 16 healthy controls found differences in the salivary composition between healthy and epileptic children, irrespective of the pathology (Shahar et al., 2014). Diagnostic decisions on the probable prognosis and response to treatment are based on seizure type (Hakeem et al., 2022; Löscher and Klein, 2021; Myers and Scheffer, 2022). Seizure types are determined according to the most recent (2017) instruction manual for the "International League Against Epilepsy" (ILAE), which classifies seizure types operationally (Fisher et al., 2017; Kanner and Bicchi, 2022). Epilepsy syndromes that begin in infants or neonates are further subcategorized by the ILAE (Gribkoff and Winquist, 2023; Zuberi et al., 2022). Once the seizure type has been delineated, epilepsy is categorized as focal, generalized, both or unknown (Table2) (Duncan, 2022; Kanner and Bicchi, 2022; Myers and Scheffer, 2022; Patel and Patel, 2022).

Table 1
Diagnostic tools.

Tests (abbreviation)	
Blood tests, including genetics	Computerized tomography scan (X-ray; CT)
Electrical source imaging	Electroencephalograms (EEGs)
Magnetic resonance imaging (MRI)	Magnetoencephalography (MEG)
Neurological exams	Neuropsychological tests
Positron emission tomography	Statistical parametric mapping (SPM)
Single-photon emission computerized tomography (SPECT)	

Table 2
Types of epilepsy.

Generalized epilepsy
Focal epilepsies (such as those that are idiopathic location-related, including the frontal, temporal, parietal or occipital lobes)
Combined generalized and focal epilepsy
Unknown epilepsy

Interestingly, based on interpretations of the behavioral description of Socrates (469–399 BCE (Bowder, 1982)) in historical writings, a present-day pathographical, retrospective diagnosis posits that Socrates suffered from temporal lobe epilepsy (TLE) (Muramoto, 2018). Muramoto outlines some of the legitimate criticisms and pitfalls one faces in making a retrospective diagnosis and couches his theory as a medical explanation based on clinical diagnostic reasoning, pointing out that a clinical diagnosis is to some degree speculative even today (Patrikelis et al., 2023). A high-profile example illustrating the inaptness of anyone (healthcare professionals or laypeople) extrapolating a medical diagnosis in the absence of an in-person examination is the Muhammad Ali case (Okun et al., 2023). In Muramoto's reasoning, the recurrent voices and peculiar behavior—the signature characteristic features of Socrates—were a manifestation of two associated types, namely, simple and complex partial seizures (Muramoto, 2018).

TLE, the most prevalent form of focal epilepsy in adults and a common childhood neurological disorder, accounts for one third of all diagnosed epileptic patients (Martinez and Peplow, 2023). Although the exact incidence of TLE has not been ascertained, in children the incidence of new-onset epilepsy is reported in a study by Nickels et al. to be 33–82 per 100,000 annually. In these children, roughly half- to two-thirds presented with focal-onset seizures. This suggests that, in this cohort, TLE accounted for 13% of the focal seizures and 8% of pediatric epilepsy overall. (Nickels et al., 2012).

To put this in perspective, according to the latest estimates from the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network, about 1 in 36 children in the United States has been identified with autism (Maenner et al., 2023), while in the United States and Western Europe, seizures caused by fever (febrile seizures) affect up to 5% of children aged 6 months–5 years, peaking at 12–18 months (Leung et al., 2018).

1.3. *Epilepsy, seizures and mitochondrial disease*

Although the underlying mechanisms of epileptogenesis are not well understood, evidence for the involvement of mitochondrial dysfunction is substantial (Cardoso et al., 2022; Del Pozo et al., 2022; Hikmat et al., 2017; Kahn-Kirby et al., 2019; Kalra, 2023; Khurana et al., 2013; Matricardi et al., 2019; Patergnani et al., 2022; Rho and Boison, 2022; Saneto, 2017; Singh and Singh, 2021; Singh et al., 2021; Smith et al., 2022; Valiente-Pallejà et al., 2022; Vishwakarma et al., 2022; Wesół-Kucharska et al., 2021; Wu et al., 2021; Yao et al., 2021; Zsurka and Kunz, 2015). Furthermore, many of the commonly used drugs, including antiseizure drugs (ASDs), can have detrimental effects on mitochondrial function and are not recommended in patients with confirmed mitochondrial diseases (Zanotti et al., 2022). However, there are disease situations where anti-inflammatory drugs, ASDs, chemotherapeutics, immunomodulators, statins, and steroids, for example, may be needed in the treatment protocol, and their use in patients with mitochondrial disease may be unavoidable.

The primary mitochondrial diseases affect approximately 1 in 4000–5000 people, with an estimated prevalence in children to be from 4.7 to 15 per 100,000 (Bottoni et al., 2023). Between 20% and 60% of patients diagnosed with primary mitochondrial diseases are likely to develop seizures (Bartlett et al., 2022; Bindoff and Engelsen, 2012; Kang et al., 2013). Mitochondrial dysfunction (Monzel et al., 2023) is pathophysiological in a number of epileptic disorders with an incidence said

to range from 10% to 40%, and among pediatric patients it could be as high as 60% (Anitha et al., 2023; Wesół-Kucharska et al., 2021). This includes disorders that may originate non-mitochondrially, suggesting that a reciprocal association between impaired mitochondrial function and epilepsy is likely (Zsurka and Kunz, 2015). A recent large cohort mitochondrial disease study in adolescents and children where over 48% of patients experienced seizures is worth noting (Saneto, 2017). Ninety percent of the patients were not medically tractable and almost 70% were under 3 years of age. About one quarter of the patients had epilepsia partialis continua (EPC) (Mameniškienė and Wolf, 2017) and status epilepticus (SE). For those patients who suffered from MELAS or its overlap syndrome (Wei et al., 2021) most developed SE (Saneto, 2017). Status epilepticus, according to the ILAE definition (Trinka et al., 2015), varies from type of seizure semiology: 5 min, tonic-clonic; 10 min, focal; and 10–15 min, absence (Migdady et al., 2022; Pinto et al., 2022; Wang et al., 2023a). It is the leading cause of epilepsy-related deaths (Du et al., 2022).

In another study, 129 children affected by the onset of mitochondrial disease during their first year of life were followed for 5 years (Matricardi et al., 2019). Seizures occurred in approximately half the number of children in the study, and the primary epilepsy-associated diseases were pyruvate dehydrogenase complex deficiency and non-syndromic mitochondrial encephalopathy. The incidence of epilepsy correlated with perinatal manifestations, disease onset at younger ages and recognition of developmental delay and regression early in the patient's lives (Matricardi et al., 2019). Notable examples of inherited mitochondrial diseases, syndromes and disorders (Gorman et al., 2016) presenting with epilepsy can be found in Table 3 (Anitha et al., 2023; Arena et al., 2022; Emmanuele et al., 2022; Huang et al., 2022; Kalra, 2023; Li et al., 2021; Lopriore et al., 2022b; Parissis et al., 2022; Peng et al., 2022; Pickrell and Fry, 2023; Saneto, 2017; Valiente-Pallejà et al., 2022; Wesół-Kucharska et al., 2021; Zeviani and Viscomi, 2022; Zsurka and Kunz, 2015).

Table 3
Examples of primary (inherited) mitochondrial diseases, syndromes and disorders that may also present with epilepsy.

AHS	Alpers-Huttenlocher syndrome — represents a severe phenotype characterized by onset in childhood, intractable epilepsy, liver failure and progressive encephalopathy. Focal-onset seizures (which may also be myoclonic or tonic-clonic) are often the first sign of AHS. In children suffering with AHS, status epilepticus (~70% of AHS patients) is the number one cause of mortality.
LS	Leigh syndrome — one of the most prevalent childhood mitochondrial diseases, a rare hereditary disorder of neurometabolism affecting the central nervous system (CNS), characteristics of which include ataxia, developmental delay, dystonia, epileptic seizures, external ophthalmoplegia, lactic acidosis, psychomotor regression, vomiting and/or weakness. Death often follows LS within a year of the onset of disease.
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes — Focal and generalized seizures may occur. A migraine-like headache may be associated with or precede the seizures. Seizures during a stroke-like episode are most typical. Also common is focal status epilepticus accompanied by secondary encephalopathy. Status epilepticus develops in the majority of MELAS patients, both with and without overlap syndrome.
MEMSA	Myoclonus epilepsy, myopathy and sensory ataxia — formerly called spinocerebellar ataxia with epilepsy (SCAE) — part of a group of conditions called the polymerase gamma (*POLG*)-related disorders (*POLG* affects mtDNA replication). MEMSA generally manifests in young adulthood. Symptoms include repeated seizures together with progressive interictal encephalopathy.
MERRF	Myoclonic epilepsy with ragged red fibers — most commonly adult onset, but almost one third may occur in childhood. The phenotype includes progressive myoclonic epilepsy, and the seizures are frequently atonic, tonic, or clonic. Seizure have been reported in anywhere from one third to all patients. MERRF coincides with cardiac arrhythmias, cerebellar ataxia, dementia, diabetes, hearing loss, and myopathy.
NARP	Neuropathy, ataxia, and retinitis pigmentosa — a progressive disease with onset in childhood or early adulthood that may include one or more of the following: ataxia, dementia, developmental delay, epilepsy, muscle weakness, pigmentary retinopathy, sensory polyneuropathy.
PDH	Pyruvate dehydrogenase complex deficiency — infancy-onset epilepsy with one or more of these characteristics: ataxia, abnormal eye movements, axonal neuropathy, clonic seizures, developmental delay, dystonia, hyper- or hypotonia, infantile spasms, refractory focal epilepsy.

2. Perspective

2.1. Mitochondrial dysfunction, ferroptosis and epilepsy

The human brain is a highly metabolic, energy-demanding organ (Padamsey and Rochefort, 2023). It comprises less than 3% of total body weight and yet, to provide the ATP needed to meet the high energy demand, mitochondrial respiration in the brain consumes 20% of the body's oxygen supply (Anitha et al., 2023; Cheng et al., 2022; Hosseinian et al., 2022; Huisman et al., 2022; Rho and Boison, 2022; Wandt et al., 2021). Consequently, a decrease in ATP production caused by malfunctioning mitochondria in brain cells can lead to pathophysiological changes in neuronal bioenergetics and metabolism that frequently result in neurological complications, including recurrent spontaneous seizures, one of the telltale signs of the epilepsies (Chakraborty et al., 2022; Pacheu-Grau et al., 2018; Rho and Boison, 2022).

Mitochondrial dysfunction increases oxidative stress. Key players are reactive oxygen species (ROS), damaging lipids, mitochondrial DNA and proteins (Rho and Boison, 2022). A postmortem study on patients who suffered from neurodegenerative diseases identified iron as a key participant in neuronal cell death mediated by oxidative stress (Wandt et al., 2021). Lipid peroxidation that is iron-dependent initiates the regulated cell death pathway, ferroptosis (Cai and Yang, 2021; Du et al., 2022; Kang et al., 2023; Li and Jia, 2023; Li et al., 2022b; Ou et al., 2022; Ruan et al., 2023; Stockwell, 2022; Wandt et al., 2021; Xu et al., 2023). More and more literature supports the association between epilepsy and ferroptosis (Cai and Yang, 2021; Chen et al., 2020a; Qi et al., 2022; Sun et al., 2022; Xiang et al., 2021; Yao et al., 2021; Zhou et al., 2022). Glutathione peroxidase 4 (GPX4) is an essential phospholipid hydroperoxide-reducing enzyme that reduces glutathione.

Murine genetic models that have seizure phenotypes (Bolea et al., 2019; Bornstein et al., 2022; Egawa et al., 2021; Ingraham et al., 2009; Kim et al., 2014; Li et al., 2020; Pinkert, 2014; Rizwan et al., 2019; Stokes et al., 2022; van Erum et al., 2020), especially where the function of GPX4 was targeted, provide convincing evidence for ferroptosis playing a pathomechanistic role in epilepsy (Kahn-Kirby et al., 2019). Unfortunately, animal models for neurological complications tend not to recapitulate a given human disease phenotype (Löscher, 2017, 2021). While no given model has been characterized to adequately identify potential treatment paradigms, a number of animal models have been used to develop antiseizure therapeutic interventions (Campos et al., 2018) and some of the validated rodent models are listed on the National Institute of Neurological Disorders and Stroke webpage (NINDS, 2023). Here, various models are described for the identification phase (acute seizure models, behavioral tolerability screens and chronic seizure models), the differentiation phase (acute, and subchronic dosing and drug resistant epilepsy models), as well as testing paradigms and disease modeling.

Selenoproteins, which contain the trace element selenium, are involved in regulating oxidative stress, antioxidant defense, immune and inflammatory responses and other redox functions (Ye et al., 2022). Among the 25 selenoproteins identified in humans are: glutathione peroxidases (GPXs), iodothyronine deiodinases, methionine-*R*-sulfoxide reductase B1, selenophosphate synthetase 2, and thioredoxin reductases. A complete list of selenoproteins and their roles in immune cells and tissues has been reviewed by Avery and Hoffmann (2018) and by Minich (2022). In human brains, selenoproteins are largely expressed (Turovsky et al., 2022). GPX4 is possibly the most important of the 25 human selenoproteins (Chen et al., 2022b; Jiang et al., 2021; Li and Jia, 2023). In neurodegenerative diseases, it plays a pivotal role, utilizing selenium to protect interneurons from ferroptotic cell death (Friedmann

Angeli and Conrad, 2018; Guo et al., 2022; Ingold and Conrad, 2018; Ingold et al., 2018; Nicholson et al., 2022; Schomburg, 2022; Wandt et al., 2021; Zhang et al., 2022b; Zhou et al., 2022). Selenium (discovered in 1817 by Jöns Jacob Berzelius, who named it after the goddess Selene (Domínguez-Álvarez et al., 2022; Schomburg, 2022)), is an essential micronutrient and trace element that is critical to CNS development and function (Kieliszek and Bano, 2022; Naderi et al, 2021; Nunes et al., 2022).

Low serum concentrations of selenium and other trace elements and minerals, including iron, have been noted in the clinical diagnosis of children with epilepsy (Fig. 2) (Abdelbasir et al., 2023) and by supplementing selenium in the diet, intractable seizures in children with reduced GPX activity can be alleviated (Ralston, 2023). Remarkably, considering a time period lacking any knowledge about ferroptosis, Pedanius Dioscorides (~40–90 AD (Sebastian, 2018)), a personal physician to Emperor Nero (whose family members, Julius Caesar, Caligula, Gaius Caesar, Caesarion, Octavia and Britannicus, were rumored to suffer from epileptic seizures (Camargo and Teive, 2018)), recommended the use of medicinal plants such as onion and garlic (of the *Allium* family of plants rich in sulfur and selenium (Astaneh et al., 2019; Block et al., 2017; Rakshit et al., 2023)) to treat epilepsy (Diskin, 2002; Sethi et al., 2014; Sharifi-Rad et al., 2016).

2.2. Mitochondrial dysfunction and ferroptosis in Friedreich's ataxia

Although, as described above, ferroptosis may be observed in epilepsy, the evidence does not clearly support a causal relationship. For example, Friedreich's Ataxia (FA), the most common inherited form of ataxia (1 in 50,000 individuals), is an autosomal recessive trinucleotide expansion disorder with decreased expression of the frataxin gene (*FXN*) and its gene product, the mitochondrial protein frataxin (La Rosa et al., 2020). In FA, loss-of-function mutations in the *FXN* gene cause excess accumulation of iron in mitochondria. This is accompanied by impairments in Fe–S cluster biogenesis, iron metabolism and transport, and in the antioxidant defense apparatus concomitant with a decrease of glutathione (GSH) and GPX4 (Dusek et al., 2022; La Rosa et al., 2020; Pallardó et al., 2021; Tiberi et al., 2023). These are attributes that are consistently related to ferroptosis, suggesting ferroptosis could be a pathogenic mechanism underlying neurodegeneration in FA (La Rosa et al., 2020). However, cases of FA patients presenting with epilepsy and seizures are exceedingly rare (Golomb et al., 2005; Manea et al., 2015).

2.3. Mitochondria-targeted therapeutic opportunities in epilepsy

Since the pioneering studies on the brain's anatomy and function that were undertaken by Wilder Penfield and Brenda Milner at the Montreal Neurological Institute ("The Neuro") (Kanmounye et al., 2022; Kolb, 2021; Leblanc, 2021, 2022a, 2022b, 2023; Servick, 2022), surgery has been a mainstay and key treatment option for epilepsy (Ali et al., 2016; Hanjani et al., 2021), particularly for patients diagnosed with treatment-resistant epilepsy (Chung et al., 2023; Corona et al., 2023; Hsieh et al., 2023; Kanner and Bicchi, 2022; Kerezoudis et al., 2021; Liu et al., 2022a; Pepi et al., 2022), and for patients with focal epilepsy, the only treatment with curative potential (Duncan and Taylor, 2023; Hoppe et al., 2023; Zweiphenning et al., 2022). Examples of epilepsy treatment options are shown in Fig. 3.

Although ASDs (also known as anticonvulsants, antiseizure medications and antiepileptic drugs) (Hakami, 2021; Kanner and Bicchi, 2022; Löscher and Klein, 2021; Łukasiuk and Lasoń, 2023; Olson et al., 2021; Perucca, 2021; Rogawski, 2021; Urzì Brancati et al., 2023) are the preferred first-line treatment (Devinsky et al., 2018; Kanner and Bicchi, 2022; Liu et al., 2022a; Nevitt et al., 2022; Rho and Boison, 2022), they are not curative (Chen et al., 2020b; Löscher and Klein, 2021; Łukasiuk and Lasoń, 2023; Matias et al., 2023) and are ineffective in approximately 30% of patients (intractable, drug-resistant epilepsy) (Duncan and Taylor, 2023; Hakami, 2021; Kocaaga and Yimenicioglu, 2023; Liu et al., 2022a; Löscher and Klein, 2021; Prentice and Rizwan, 2023; Ríos et al., 2023). In addition, with the most commonly prescribed ASDs (Matias et al., 2023), such as carbamazepine, lamotrigine, levetiracetam and valproic acid (Fig. 4), there is increased concern about an association between patients taking these drugs and Parkinson's disease (Belete et al., 2023; Kostev et al., 2023; Shnayder et al., 2023) and/or other psychiatric side effects, which may include suicidality (Anam et al., 2016; Hakami, 2021; Kanner and Bicchi, 2022; Kanner et al., 2023; Mula, 2022). Moreover, of the ASDs approved by the U.S. and European regulatory bodies (respectively, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Anam et al., 2016; Hamed et al., 2023; Kośmider et al., 2023; Urzì Brancati et al., 2023),

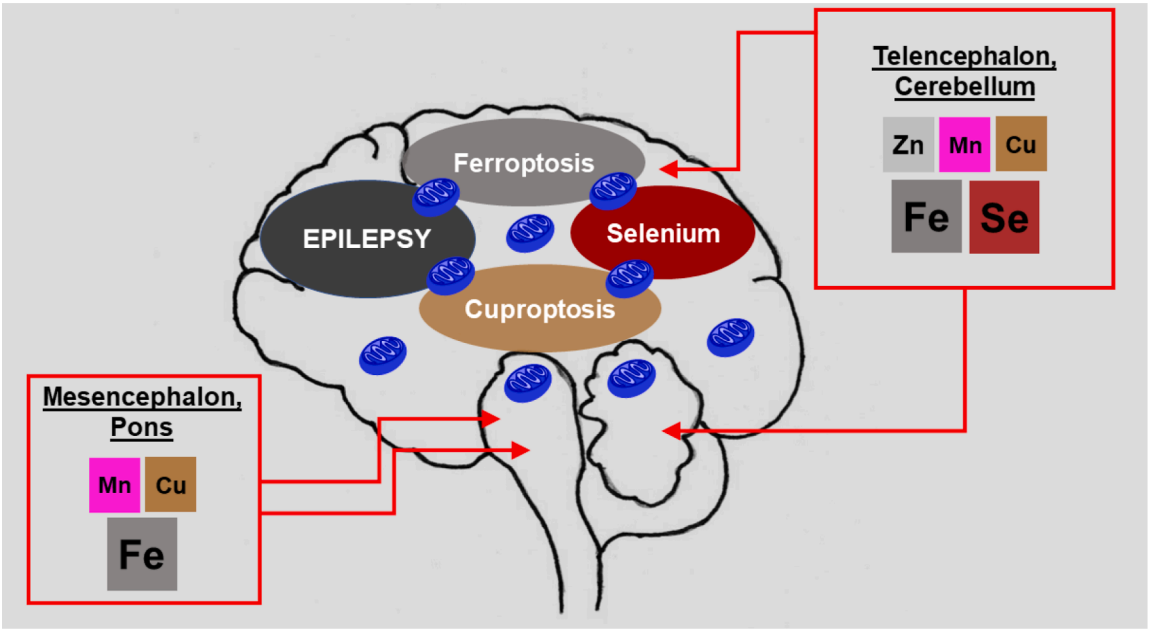

Fig. 2. Epilepsy is linked to mitochondrial diseases, to alterations in iron (ferroptosis) and copper (cuproptosis), and to a selenoprotein (GPX4) and serum levels of selenium and other trace elements.

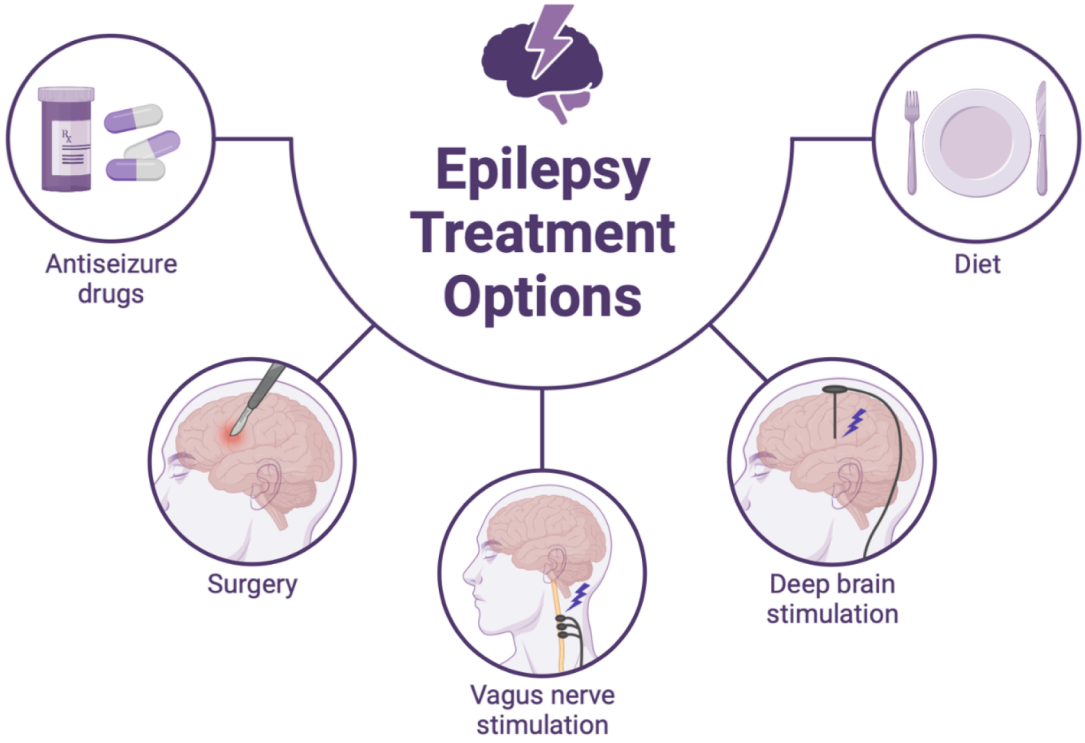

Fig. 3. Examples of epilepsy treatment options.

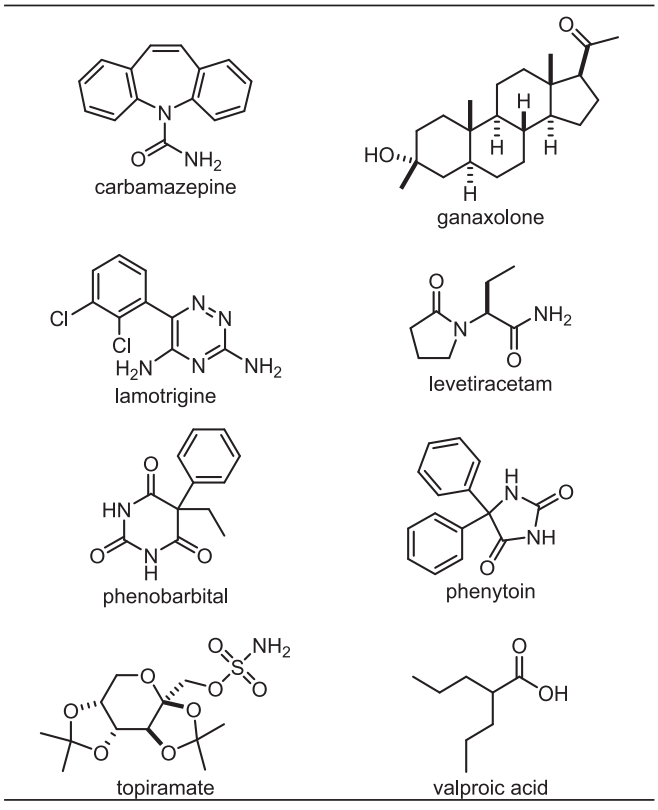

Fig. 4. Chemical structures for ganaxolone and some commonly used antiseizure drugs.

none has a broad indication for neonates (phenobarbital is not approved by the FDA and levetiracetam is approved for children with epilepsy at least one month old and adults with partial onset seizures) (Bättig et al., 2023; Chalia et al., 2022; Li et al., 2023a; Pressler and Lagae, 2020; Sewell et al., 2022; Sourbron et al., 2023; Treadwell et al., 2023; Xu et al., 2021), and this often leads to off-label drug use in these patients (Aeby et al., 2022; Chalia et al., 2022; Schiller et al., 2023; Sourbron et al., 2023; Trinka, 2023; Vawter-Lee et al., 2022). However, FDA-approved (March 18, 2022) (Do et al., 2022; Urquhart, 2022) ganaxolone, a γ-aminobutyric acid agonist neurosteroid for patients with *CDKL5* deficiency disorder (CDD)-associated refractory epilepsy (Benedetto Tiz et al., 2022; Knight et al., 2022; Olson et al., 2021; Yasmen et al., 2023), is potentially promising (Yawno et al., 2017). Neurosteroids (Sivcev et al., 2023) are an emerging class of neurotherapeutics having the ability to modulate neuronal activity that may help mitigate a wide range of neurological disorders. This includes anxiety, attention deficit hyperactivity disorder (ADHD), clinical depression, epilepsy, neurodegeneration, and West syndrome (infantile spasms) (Bassani et al., 2023; Bryson et al., 2023; Chakraborty et al., 2023; De Costa et al., 2023; Izumi et al., 2023; Riikonen, 2023; Singewald et al., 2023; Szczurowska et al., 2022).

Nonsurgical protocols for treating intractable epilepsy, drug-resistant epilepsy and mitochondrial and pediatric epileptic seizures rely largely on ketogenic-related diets (Dyńka et al., 2022; Kim et al., 2022; Kocatürk et al., 2022; Lopriore et al., 2022a; Mu et al., 2022; Rho and Boison, 2022; Saris and Timmers, 2022; Zhou et al., 2023; Zhu et al., 2022). Ketogenic-related diets, which include fasting and intermittent fasting have proven therapeutic value, especially in pediatric epilepsy syndromes (Perucca et al., 2023; Rho and Boison, 2022). Indeed, in selected children with drug-resistant epilepsy, strict adherence to dietary treatments can be as effective as ASDs in seizure control (Perucca et al., 2023). Moreover, ketogenic diets are often the first-line treatment in glucose transporter 1 deficiency syndrome and PDH (Falsaperla et al., 2021; Perucca et al., 2023). Fasting and intermittent fasting, which are reported to have first been used as a medical treatment for epilepsy by

Hippocrates (Grammatikopoulou et al., 2022; Lobo et al., 2022; Wheless, 2004, 2008; Zhu et al., 2022) are methods of treatment still used today (Lobo et al., 2022; Mattson et al., 2018; Rho and Boison, 2022; Zhu et al., 2022).

The impotence of a pharmaceutical intervention in the aforementioned indications presents an unmet medical need for new and more effective drugs that are safer, treat drug-resistant epilepsy and associated comorbidities, and importantly, prevent seizures. On the horizon, emerging concepts and mechanistic pathways are providing insights into new targets of therapeutic opportunity. In the CNS, iron is essential in the production of myelin, the synthesis and metabolism of neurotransmitters, oxidative phosphorylation and oxygen transport (Ren et al., 2020). Iron (Fe^{2+}) that is labile and in excess can accumulate abnormally in mitochondria (the principal sites in cells where iron is metabolized and utilized) is a critical element in triggering ferroptosis (Cheng et al., 2022; David et al., 2022; Guo et al., 2022; Moos et al., 2022; Shao et al., 2022a; Xiang et al., 2021). In fact, morphological indicators of ferroptotic cell death include mitochondrial fissures in outer membranes and cristae that are reduced in size or disappearing, as well as cells harboring mitochondria that are unusually small and that exhibit reduced density (Du et al., 2022; Fricker et al., 2018; Guo et al., 2022; McElroy et al., 2023; Sun et al., 2022; Xiang et al., 2021; Xie et al., 2016; Zhang et al., 2022a).

Klotho, an anti-aging protein, is a newly discovered therapeutic target for the diagnosis and treatment of neurodegenerative diseases and psychiatric disorders (Abraham and Li, 2022; Moos et al., 2020). In some patients with TLE, Klotho protein levels are subnormal and seizures in these patients tend to be less responsive to treatment with ASDs (Birdi et al., 2023). Induced overexpression of Klotho was found to inhibit ferroptosis and iron overload in an animal model of TLE with cognitive deficits and to have a neuroprotective effect in a rat model of TLE caused by administering lithium-chloride and the muscarinic receptor agonist, pilocarpine (Xiang et al., 2021).

In combination with fibroblast growth factor 21 (FGF21), Klotho promotes normalization of mitochondrial carbohydrate and lipid metabolism (Burtscher et al., 2023; Jia et al., 2022a; Moos et al., 2021). It helps mitigate injury from oxidative stress through upregulation of antioxidant responses that depend on nuclear factor erythroid 2-related factor 2 (Nrf2) (Prud'homme et al., 2022; Xiang et al., 2022), which can inhibit cellular ferroptosis by elevating the expression of ferroportin

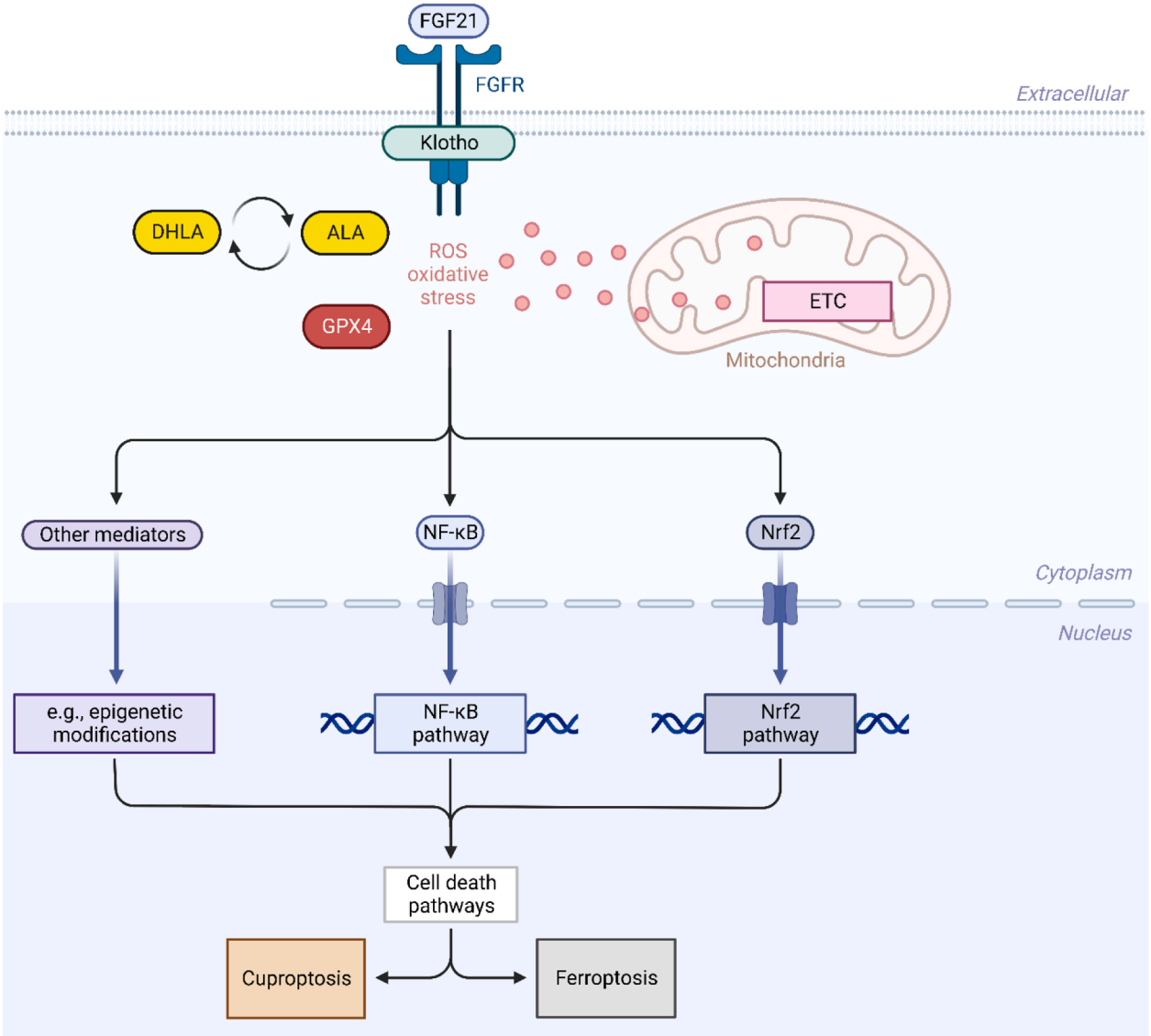

Fig. 5. Selected modulators and pathways involved in ferroptosis and cuproptosis. Abbreviations: ETC, mitochondrial electron transport chain; FGFR, fibroblast growth factor receptor; GPX4, glutathione peroxidase 4; NF-kB, nuclear factor kappa B.

(FPN) and suppressing intracellular Fe^{2+} levels (Song et al., 2022; Xiang et al., 2021). Importantly, by downregulating divalent metal transporter 1 expression and upregulating the expression of FPN, which are associated with iron accumulation in the hippocampus, Klotho inhibits ferroptosis and helps maintain neuronal iron metabolic balance and iron homeostasis (Jin et al., 2023; Xiang et al., 2021). ALA and/or its enzymatically-reduced form DHLA, play a central role in chelating Fe^{2+} and Cu^{2+}, scavenging free radicals (ROS), promoting the expression of Klotho, Nrf2 and antioxidants like catalase, GPX4 and superoxide dismutase, suppressing the expression of NF-kB, thus modulating cytokines like interleukin 1β, interleukin 6, and tumor necrosis factor α, thereby reducing inflammation. See Fig. 5 for a schematic representation of selected modulators and pathways involved in ferroptosis and cuproptosis (Ajith, 2020; Castelli et al., 2020; dos Santos et al., 2019; Poor and Chandel, 2023; Tan et al., 2015; Zhang et al., 2019).

(*R*)-α-Lipoic acid (ALA) is a required cofactor in five mitochondrial enzyme complexes (Warui et al., 2022). It is enzymatically synthesized in mitochondria from octanoic acid (Khan et al., 2022; Moos et al., 2017, 2018; Warui et al., 2022). Defects in the lipoic acid synthetase (LIAS) pathway or in the genes that encode enzymes which are intrinsic to biosynthesis of the mitochondrial iron-sulfur cluster (Warui et al., 2022) can lead to reductions in protein-bound ALA. This may lead to early infantile epileptic encephalopathy (Stowe et al., 2018). Under conditions of oxidative stress, ALA activates Nrf2-dependent antioxidant responses (Ajith, 2020; Khan et al., 2022; Moos et al., 2017; Stepanić and Kučerová-Chlupáčová, 2023; Zhang et al., 2023), which are important in regulating ferroptosis as well as lipid peroxidation (Liu et al., 2021; Moos et al., 2022; Stepanić and Kučerová-Chlupáčová, 2023; Zhang et al., 2023). In a rodent model of epilepsy induced by pentylenetetrazol via an Nrf2 pathway, treatment with ALA improved behavioral dysfunction and significantly reduced the number of epileptic seizures (Cheng et al., 2018). Unfortunately, as a drug candidate, ALA has poor pharmacokinetic properties that limit its therapeutic potential (Kumari et al., 2022; Salehi et al., 2019; Steliou et al., 2015; Usacheva et al., 2022). Ongoing efforts in design and chemical synthesis aim to overcome these deficiencies using ALA prodrugs prepared from analogues, derivatives or conjugates as potential therapeutics with more favorable pharmacological properties (Javaid et al., 2022; Kong et al., 2022; Kumari et al., 2022; Lv et al., 2022; Moos et al., 2022; Steliou et al., 2015; Wang et al., 2020; Zielonka et al., 2017). Various mitochondria-targeting strategies aimed principally at correcting dysfunctional mitochondria are also being explored (Åsander Frostner et al., 2022; Chinnery, 2023; Guo et al., 2023; Maurya et al., 2022; Zielonka et al., 2017).

2.4. Mitochondrial dysfunction, cuproptosis and epilepsy

Like iron, copper is an essential element in living systems (Jomova et al., 2022; Timoshnikov et al., 2022). It is required in the function and maintenance of cytochrome *c* oxidase (C*c*O), the terminal cuproenzyme (complex IV) of the mitochondrial respiratory chain (Tsang et al., 2021; Wikström et al., 2023). A dysregulated balance of intracellular copper concentration leads to the following: formation of free radicals, oxidative stress, and mitochondrial dysfunction caused by processes other than oxidative stress (Bandmann et al., 2015). Fatal conditions, including mitochondrial disorders, Wilson's disease, Menkes disease and others, can result from genetic mutations in C*c*O. Genetic loss-of-function mutations in systems required for copper transport to C*c*O can also result in mortal diseases (Garza et al., 2023; Martinelli, 2022).

Intracellular concentration of copper is tightly regulated (Hunsaker and Franz, 2019; Metsla et al., 2022) and dyshomeostasis resulting in too little or too much copper (Menkes or Wilson's disease, respectively) is life-threatening (Chen et al., 2022a; Nayeri et al., 2023), with intermittent seizures being a common symptom (Bandmann et al., 2015; Garza et al., 2023). Dysfunctional mitochondria accumulate excess copper ions, which can lead to a copper-dependent, mitochondrially-induced cell death called cuproptosis (Cobine and Brady, 2022). Cuproptosis is a recently discovered regulated cell death pathway that is mediated by copper executed by damaged cells that are heavily reliant on mitochondrial respiration for survival (Kahlson and Dixon, 2022; Tang et al., 2022; Tsvetkov et al., 2022). To be clear, a causative role for cuproptosis in the pathology of Menkes or Wilson's diseases has not yet been firmly established. However, a recently published investigational study (Yang et al., 2023) suggests that cuproptosis may be more directly related to TLE than previously known, and thus it may be a target for seizure control in at least some patients with Menkes or Wilson's diseases. In further support of this notion, in a postmortem analysis of 24 patients with drug-resistant mesial TLE who underwent anterior temporal lobe resection and amygdalohippocampectomy, compared to 17 control hippocampi, copper levels in the subjects with epilepsy were significantly elevated (Ristić et al., 2014).

Similarly, a study reported by Chen et al. (2023b) found that elevated serum copper levels were associated with an increased risk of generalized epilepsy and that cuproptosis may be one of the mechanisms involved. However, a causal relationship between serum copper level and focal epilepsy was not evident (Chen et al., 2023b).

In damaged respiring cells, excess copper ions are attracted to and bind to the lipoyl moiety of tricarboxylic acid (TCA) enzymes (Stacpoole and McCall, 2023). This causes aggregation of lipoylated protein, heat shock protein 70 (HSP70) induction, and decreases in Fe-S cluster-containing proteins, characteristic of proteotoxic acute stress resulting in cell death (cuproptosis) (Tsvetkov et al., 2022). Chelation therapy using dihydrolipoic acid (DHLA) or prodrugs of ALA that *in vivo* are reduced to DHLA in the cellular environment has therapeutic potential (Ajith, 2020; Chen et al., 2023a; Metsla et al., 2022; Smirnova et al., 2018; Zhang et al., 2023; Zheng et al., 2022). DHLA binds strongly to copper (Metsla et al., 2022), with an approximately 10^{-16} M dissociation constant (Smirnova et al., 2018). However, the therapeutic window is likely to be narrow. Too much chelation of copper can result in dysregulation of iron metabolism and inadvertently cause ferroptosis (Jhelum and David, 2022).

2.5. Mitochondrial photobiomodulation and other non-drug therapies — novel, neurotherapeutic strategies for treating epilepsy

Antiepileptic drugs are a significant advance in the treatment and management of epilepsy seizures (Hu et al., 2023). Unfortunately, a sizeable portion of patients (as mentioned earlier, ~30%) is unresponsive to the currently approved drugs. Ketogenic diets are difficult to adhere to (Devi et al., 2023), particularly in the pediatric-adolescent patient group, and a surgery option is invasive and not without risk of death, albeit marginally less risky than the chance of sudden unexpected death with refractory TLE (~0.1%–0.5% vs 0.6%–0.9%) (Edwards et al., 2018). Notwithstanding the risk, surgery remains the standard of treatment for focal mesial temporal or neocortical epilepsy (Torres-Martinez et al., 2023).

Some patients appear to respond well to alternative and/or adjuvant neuromodulation therapies (Asadi-Pooya et al., 2023) (Fig. 6) — which admittedly remain to be fully proven — such as repeated external transcranial magnetic stimulation (TMS) (Anninos et al., 2020; Clemens et al., 2023; Mosilhy et al., 2022; Ning et al., 2022), electrical stimulation of the vagus nerve (Ali et al., 2023; Devinsky et al., 2018; Mayo et al., 2022; Mosilhy et al., 2022; Panebianco et al., 2022), closed-loop neocortical electrical stimulation and deep brain stimulation in select areas of the brain such as the anterior thalamic nuclei, the caudate nucleus, the centromedian nucleus, the cerebellum (Fisher, 2023; Foutz and Wong, 2022; Ilyas et al., 2023; Mosilhy et al., 2022; Vassileva et al., 2018) and the hippocampus (Topalovic et al., 2023). Although stimulation methods can reduce the number of seizures by 40%–65% (Anninos et al., 2020; Torres-Martinez et al., 2023; Vassileva et al., 2018), electrical stimulation is a precarious and invasive technique, obligating careful consideration to be given to patient selection (Jirsa et al., 2023; Zarzycki and Domitrz, 2020) and thus less opted for than drug therapy.

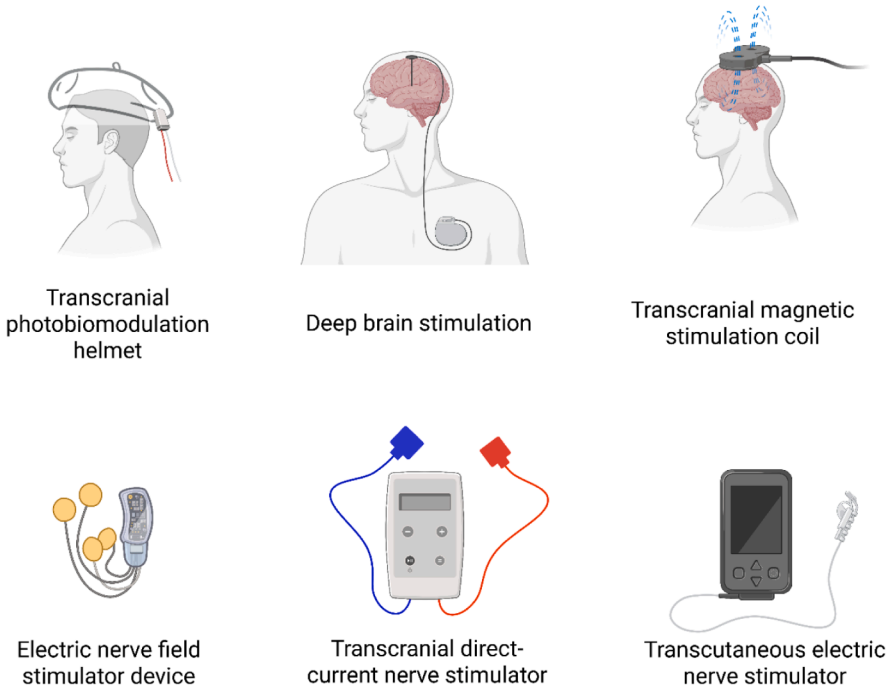

Fig. 6. Examples of neurostimulation devices.

Nonetheless, for many patients with medically intractable epilepsy, brain stimulation may be the only management option available (Foutz and Wong, 2022). Digital therapeutics (Abbadessa et al., 2022) such as software-assisted sensory stimulation (Li et al., 2023b) using light and/or sound (Chan et al., 2022; Larkin, 2023), are emerging non-invasive treatment methods that are being actively researched with an intended goal to supplement and/or possibly replace surgery and drug prescription as an alternative option (Gallagher et al., 2023; Kim et al., 2023; Naddaf, 2023; Wang et al., 2023b). See Table 4 for a partial list of alternative medical approaches to treating epilepsy.

Photobiomodulation (PBM) (Lipko, 2022), a low-level laser/light therapy, is attracting interest as a relatively safe, non-pharmacological and non-invasive procedure with remedial potential in epilepsy treatment (Cardoso et al., 2022; Hong et al., 2023; Mosilhy et al., 2022; Torres-Martinez et al., 2023). PBM therapy, categorized as a medically non-significant risk by the FDA (Beirne et al., 2017), has been used as a therapeutic technique since the 1960s (You et al., 2021) and is indispensably used in several fields of dentistry to regenerate damaged tissues, promote analgesia and reduce tissue inflammation (Kumar et al., 2021; Vochikovski et al., 2022). Its consideration as a method for treating epilepsy, however, is recent (Cardoso et al., 2022; Hamblin, 2023; Mosilhy et al., 2022; Torres-Martinez et al., 2023). While therapeutic proof of concept in humans awaits further study, a greater and deeper understanding of a likely mitochondrial mechanism of action (Cardoso et al., 2022; Mosilhy et al., 2022) has invigorated interest in PBM as a potentially risk-free, non-invasive treatment for epilepsy (Cardoso et al., 2022; Hamblin, 2023; Liebert et al., 2023; Mosilhy et al., 2022; Pan et al., 2023; Torres-Martinez et al., 2023) and other neurological diseases (Hamblin, 2023; Liebert et al., 2023; Pan et al., 2023; Salehpour et al., 2022; Trigo et al., 2023; You et al., 2021).

Table 4
Non-drug medical approaches to treating epilepsy.

Alternative therapies (abbreviation)
Digital therapeutics
Transcranial magnetic stimulation (TMS)
Transcranial photobiomodulation (tPBM)
Vagus nerve stimulation (VNS)

Photons emanating from near infrared light sources used in transcranial PBM (tPBM) can penetrate through the skin and bone of the scalp and reach into the proximal brain tissue where the mitochondrial cuproenzyme CcO in neuronal cells is the intended absorption target (Ayaz et al., 2022; Pan et al., 2023; You et al., 2021). Photochemical stimulation of complex IV (CcO) of the electron transport chain (ETC) — the focal acceptor of red-to-near-infrared photons inside cells - reduces the onset of seizures in animals by inducing a cascade of therapeutic processes that includes increased ATP production and activation of mitochondrial signaling pathways (Collier et al., 2023; Poor and Chandel, 2023) associated with neuroprotection and cell survival (Cardoso et al., 2022; Mosilhy et al., 2022). Indeed, purinergic signaling is a major route for cell–cell communication and is an emerging therapeutic target in treating epilepsy.

2.6. *New pathways of interest in epilepsy*

The metabolic basis of epilepsy, including key factors such as purinergic neurotransmission, has been described well (Rho and Boison, 2022). More specifically, new pathways that have been suggested as targets for drug therapy include metabotropic purinergic P2Y receptors. The signaling of these 7-transmembrane G-protein coupled receptors in the brain is associated with neuronal excitability and neuroinflammation. Changes in P2Y expression have been noted in rodent studies of status epilepticus and in people suffering from intractable epilepsy associated with focal cortical dysplasia (Alves et al., 2018). Mitochondrial dysfunction resulting from inflammation can be traced at least partly to purinergic receptors, specifically the ionotropic purinergic P2X7 receptor, a ligand-gated cation channel (Singh and Singh, 2021). The gap junction family protein, pannexin, is involved in extracellular purinergic receptor signaling, mediating ATP release, and has also been proposed as a therapeutic pathway worth exploring further in epilepsy (Shan et al., 2020). Numerous rodent studies support the involvement of purinergic signaling in epileptogenesis and during partial and generalized seizures, post-traumatic epilepsy and status epilepticus. Other purinergic receptors, including adenosine receptors, also

play a role in the modulation of seizures and epilepsy. Whether purinergic approaches targeting the various primary receptors as well as purine metabolic pathways can provide therapy that reduces the impact of precipitating events, prevents epilepsy, or suppresses seizures in humans remains to be seen, but this line of thinking seems worth exploring further (Beamer et al., 2021). Exploitation of purinergic signaling tools in seizure/epilepsy diagnosis has also been suggested (Wong and Engel, 2023).

3. Concluding remarks

Epilepsy remains a challenging disease to diagnose and treat effectively. In the distant past, diseases like epilepsy were attributed to the spiritual whims of gods who were thought to have control over human health, life and death. Though we have moved well beyond mythology and religious attributes to a more rational, scientific understanding of epilepsy, describing and treating the illness as a dysfunction of the brain, there is still much to be desired in medical practice. Epilepsy has a strong link to mitochondrial function, given that seizures affect approximately one third to more than half of all patients diagnosed with mitochondrial diseases. Indeed, from what we have learned in recent years about mitochondrial diseases writ large, it should come as no surprise that decreased ATP production caused by malfunctioning brain cell mitochondria leads to altered neuronal bioenergetics, metabolism and neurological complications, including seizures. Ferroptosis fits into these mechanistic pathways well, since lipid peroxidation that is iron-dependent initiates this form of cell death, which aligns with the altered mitochondrial bioenergetics, metabolism and morphology found in NDDs. Furthering these connections, studies of seizure phenotypes in murine genetic models targeting the role of the vital selenoprotein GPX4 suggest roles for ferroptosis in epilepsy. This result ties in with GPX4 being pivotal in NDDs, where selenium protects interneurons from ferroptosis, all of this consistent with selenium serving as an essential CNS micronutrient and trace element. Add to this the fact that low serum levels of selenium and other trace elements and minerals including iron are noted in diagnosing childhood epilepsy and the knowledge that selenium supplements alleviate intractable seizures in children with reduced GPX activity. Finally, contributing even more to the story are copper and cuproptosis, which like iron and ferroptosis link significantly to mitochondria and NDDs. Altogether, this mechanistic trail leads to potential new ways to treat seizures, pointing beyond surgery to not only novel small molecule drugs including prodrugs of lipoic acid but also to alternative and/or adjuvant therapies like tPBM.

Declaration of Competing Interest

The following authors make the following disclosures in addition to their academic and nonprofit roles. Walter H. Moos is a co-founder and managing director of Pandect Bioventures. He is also chairman emeritus of ShangPharma Innovation, has been a consultant to Aduro Biotech (Chinook Therapeutics), is an advisor to Azkarra Therapeutics, and serves on the boards of directors of Circle Pharma, Rigel Pharmaceuticals and Valitor. Douglas V. Faller is chief medical officer of Oryzon Genomics, scientific founder and chair of the scientific advisory board of Viracta Therapeutics, co-founder and vice president at Phoenicia Biosciences and serves as a consultant to Briacell Therapeutics. Kosta Steliou is the founder and chief scientific officer of PhenoMatriX. Krishna Kodukula has consulted with and/or served as an executive or on the boards of various biotechnology and pharmaceutical companies from time to time, including PhenoMatriX, and he has been an executive-in-residence at Pandect Bioventures and ShangPharma Innovation. Demetrios G. Vavvas is a co-founder of Drusolv Therapeutics, a member of the scientific and clinical advisory boards of Olix Pharma and Valitor, and a consultant for TwentyTwenty, Sumitomo/Sunovion, and Cambridge Polymer Group.

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References

Abbadessa, G., Brigo, F., Clerico, M., De Mercanti, S., Trojsi, F., Tedeschi, G., Bonavita, S., Lavorgna, L., 2022. Digital therapeutics in neurology. J. Neurol. 269, 1209–1224. https://doi.org/10.1007/s00415-021-10608-4.

Abdelbasir, K.A., Hassan, M.H., Mahmoud, M.H., Bakry, A.H., 2023. Role of minerals in childhood epilepsy. SVU-Int. J. Med. Sci. 6, 337–350. https://doi.org/10.21608/svuijm.2022.156081.1378.

Abraham, C.R., Li, A., 2022. Aging-suppressor Klotho: prospects in diagnostics and therapeutics. Ageing Res. Rev. 82, 101766 https://doi.org/10.1016/j.arr.2022.101766.

Aeby, A., Ceulemans, B., Lagae, L., 2022. Treatment of focal-onset seizures in children: should this be more etiology-driven? Front. Neurol. 13, 842276 https://doi.org/10.3389/fneur.2022.842276.

Ajith, T.A., 2020. Alpha-lipoic acid: a possible pharmacological agent for treating dry eye disease and retinopathy in diabetes. Clin. Exp. Pharmacol. Physiol. 47, 1883–1890. https://doi.org/10.1111/1440-1681.13373.

Ali, R., Connolly, I.D., Feroze, A.H., Awad, A.J., Choudhri, O.A., Grant, G.A., 2016. Epilepsy: a disruptive force in history. World Neurosurg. 90, 685–690. https://doi.org/10.1016/j.wneu.2015.11.060.

Ali, I., Houck, K.M., Sully, K., 2023. Neuromodulation in children with drug-resistant epilepsy. J. Pediatr. Epilepsy 12, 041–049. https://doi.org/10.1055/s-0042-1760293.

Almukainzi, M., 2023. Saliva sampling in therapeutic drug monitoring and physiologically based pharmacokinetic modeling: review. Drug Res. (Stuttg.) 73, 65–69. https://doi.org/10.1055/a-1956-9313.

Alves, M., Beamer, E., Engel, T., 2018. The metabotropic purinergic P2Y receptor family as novel drug target in epilepsy. Front. Pharmacol. 9 https://doi.org/10.3389/fphar.2018.00193.

Anam, S., Hunter, S., Afzal, K., 2016. The effects of antiepileptic drugs on pediatric cognition, mood, and behavior. J. Pediatr. Epilepsy 06, 003–018. https://doi.org/10.1055/s-0036-1584935.

Anitha, A., Thanseem, I., Iype, M., Thomas, S.V., 2023. Mitochondrial dysfunction in cognitive neurodevelopmental disorders: cause or effect? Mitochondrion 69, 18–32. https://doi.org/10.1016/j.mito.2023.01.002.

Anninos, P., Anninou, N., Adamopoulos, A., Kotini, A., Gemousakakis, T., Tsagas, N., 2020. We used a double-blind experiment to investigate weak pT-TMS in epilepsy patients. Maedica (Buchar) 15, 92–95. https://doi.org/10.26574/maedica.2020.15.1.92.

Arena, I.G., Pugliese, A., Volta, S., Toscano, A., Musumeci, O., 2022. Molecular genetics overview of primary mitochondrial myopathies. J. Clin. Med. 11, 632 https://doi.org/10.3390/jcm11030632.

Aro, K., Wei, F., Wong, D.T., Tu, M., 2017. Saliva liquid biopsy for point-of-care applications. Front. Public Health 5, 77. https://doi.org/10.3389/fpubh.2017.00077.

Arulsamy, A., Shaikh, M.F., 2022. Epilepsy-associated comorbidities among adults: a plausible therapeutic role of gut microbiota. Neurobiol. Dis. 165, 105648 https://doi.org/10.1016/j.nbd.2022.105648.

Asadi-Pooya, A.A., Brigo, F., Lattanzi, S., Blumcke, I., 2023. Adult epilepsy. Lancet 402, 412–424. https://doi.org/10.1016/s0140-6736(23)01048-6.

Åsander Frostner, E., Simón Serrano, S., Chamkha, I., Donnelly, E., Elmér, E., Hansson, M., 2022. Towards a treatment for mitochondrial disease: current compounds in clinical development. https://doi.org/10.26124/BEC:2022-0004.

Astaneh, R.K., Bolandnazar, S., Nahandi, F.Z., Oustan, S., 2019. Effects of selenium on enzymatic changes and productivity of garlic under salinity stress. S. Afr. J. Bot. 121, 447–455. https://doi.org/10.1016/j.sajb.2018.10.037.

Avery, J., Hoffmann, P., 2018. Selenium, selenoproteins, and immunity. Nutrients 10, 1203. https://doi.org/10.3390/nu10091203.

Ayaz, H., Baker, W.B., Blaney, G., Boas, D.A., Bortfeld, H., Brady, K., Brake, J., Brigadoi, S., Buckley, E.M., Carp, S.A., Cooper, R.J., Cowdrick, K.R., Culver, J.P., Dan, I., Dehghani, H., Devor, A., Durduran, T., Eggebrecht, A.T., Emberson, L.L., Fang, Q., Fantini, S., Franceschini, M.A., Fischer, J.B., Gervain, J., Hirsch, J., Hong, K.-S., Horstmeyer, R., Kainerstorfer, J.M., Ko, T.S., Licht, D.J., Liebert, A., Luke, R., Lynch, J.M., Mesquida, J., Mesquita, R.C., Naseer, N., Novi, S.L., Orihuela-Espina, F., O’Sullivan, T.D., Peterka, D.S., Pifferi, A., Pollonini, L., Sassaroli, A., Sato, J.R., Scholkmann, F., Spinelli, L., Srinivasan, V.J., St Lawrence, K., Tachtsidis, I., Tong, Y., Torricelli, A., Urner, T., Wabnitz, H., Wolf, M., Wolf, U., Xu, S., Yang, C., Yodh, A.G., Yücel, M.A., Zhou, W., 2022. Optical imaging and spectroscopy for the study of the human brain: status report. Neurophotonics 9, S24001. https://doi.org/10.1117/1.NPh.9.S2.S24001.

Bandmann, O., Weiss, K.H., Kaler, S.G., 2015. Wilson’s disease and other neurological copper disorders. Lancet Neurol. 14, 103–113. https://doi.org/10.1016/S1474-4422(14)70190-5.

Bandopadhyay, R., Singh, T., Ghoneim, M.M., Alshehri, S., Angelopoulou, E., Paudel, Y. N., Piperi, C., Ahmad, J., Alhakamy, N.A., Alfaleh, M.A., Mishra, A., 2021. Recent

developments in diagnosis of epilepsy: scope of MicroRNA and technological advancements. Biology (Basel) 10, 1097. https://doi.org/10.3390/biology10111097.
Barsh, G.R., Wusthoff, C.J., 2023. Can electronic medical records predict neonatal seizures? Lancet Digit. Health 5, e175–e176. https://doi.org/10.1016/S2589-7500(23)00041-9.
Bartlett, C., Gregg, E., Arber, M., Buesch, K., Graziadio, S., 2022. HSD29 costs and healthcare resource use data in mitochondrial diseases associated with seizures: a systematic literature review. Value Health 25, S485. https://doi.org/10.1016/j.jval.2022.04.1031.
Bassani, T.B., Bartolomeo, C.S., Oliveira, R.B., Ureshino, R.P., 2023. Progestogen-mediated neuroprotection in central nervous system disorders. Neuroendocrinology 113, 14–35. https://doi.org/10.1159/000525677.
Bättig, L., Dünner, C., Cserpan, D., Rüegger, A., Hagmann, C., Schmitt, B., Pisani, F., Ramantani, G., 2023. Levetiracetam versus phenobarbital for neonatal seizures: a retrospective cohort study. Pediatr. Neurol. 138, 62–70. https://doi.org/10.1016/j.pediatrneurol.2022.10.004.
Beamer, E., Kuchukulla, M., Boison, D., Engel, T., 2021. ATP and adenosine—Two players in the control of seizures and epilepsy development. Prog. Neurobiol. 204, 102105 https://doi.org/10.1016/j.pneurobio.2021.102105.
Beirne, K., Rozanowska, M., Votruba, M., 2017. Photostimulation of mitochondria as a treatment for retinal neurodegeneration. Mitochondrion 36, 85–95. https://doi.org/10.1016/j.mito.2017.05.002.
Belete, D., Jacobs, B.M., Simonet, C., Bestwick, J.P., Waters, S., Marshall, C.R., Dobson, R., Noyce, A.J., 2023. Association between antiepileptic drugs and incident Parkinson disease. JAMA Neurol. 80, 183–187. https://doi.org/10.1001/jamaneurol.2022.4699.
Ben Mohamed, D., Zouari, R., Ketata, J., Nabli, F., Blel, S., Ben Sassi, S., 2023. Myoclonus status revealing COVID 19 infection. Seizure 104, 12–14. https://doi.org/10.1016/j.seizure.2022.11.010.
Benedetto Tiz, D., Bagnoli, L., Rosati, O., Marini, F., Santi, C., Sancineto, L., 2022. FDA-approved small molecules in 2022: clinical uses and their synthesis. Pharmaceutics 14, 2538. https://doi.org/10.3390/pharmaceutics14112538.
Bindila, L., Eid, T., Mills, J.D., Hildebrand, M.S., Brennan, G.P., Masino, S.A., Whittemore, V., Perucca, P., Reid, C.A., Patel, M., Wang, K.K., van Vliet, E.A., 2022. A companion to the preclinical common data elements for proteomics, lipidomics, and metabolomics data in rodent epilepsy models. A report of the TASK3-WG4 omics working group of the ILAE/AES joint translational TASK force. Epilepsia Open. https://doi.org/10.1002/epi4.12662.
Bindoff, L.A., Engelsen, B.A., 2012. Mitochondrial diseases and epilepsy: Mitochondrial Diseases and Epilepsy. Epilepsia 53, 92–97. https://doi.org/10.1111/j.1528-1167.2012.03618.x.
Birdi, A., Tomo, S., Yadav, D., Sharma, P., Nebhinani, N., Mitra, P., Banerjee, M., Purohit, P., 2023. Role of Klotho protein in neuropsychiatric disorders: a narrative review. Indian J. Clin. Biochem. 38, 13–21. https://doi.org/10.1007/s12291-022-01078-0.
Blank, L.J., Jette, N., 2023. Epilepsy research in 2022: clinical advances. Lancet Neurol. 22, 15–17. https://doi.org/10.1016/S1474-4422(22)00486-0.
Block, E., Batista, V.S., Matsunami, H., Zhuang, H., Ahmed, L., 2017. The role of metals in mammalian olfaction of low molecular weight organosulfur compounds. Nat. Prod. Rep. 34, 529–557. https://doi.org/10.1039/c7np00016b.
Bolea, I., Gella, A., Sanz, E., Prada-Dacasa, P., Menardy, F., Bard, A.M., Machuca-Márquez, P., Eraso-Pichot, A., Mòdol-Caballero, G., Navarro, X., Kalume, F., Quintana, A., 2019. Defined neuronal populations drive fatal phenotype in a mouse model of Leigh syndrome. Elife 8. https://doi.org/10.7554/eLife.47163.
Bornstein, R., James, K., Stokes, J., Park, K.Y., Kayser, E.-B., Snell, J., Bard, A., Chen, Y., Kalume, F., Johnson, S.C., 2022. Differential effects of mTOR inhibition and dietary ketosis in a mouse model of subacute necrotizing encephalomyelopathy. Neurobiol. Dis. 163, 105594 https://doi.org/10.1016/j.nbd.2021.105594.
Bottoni, P., Gionta, G., Scatena, R., 2023. Remarks on mitochondrial myopathies. Int. J. Mol. Sci. 24, 124 https://doi.org/10.3390/ijms24010124.
Bou Nasif, M., Koubeissi, M., Azar, N.J., 2021. Epilepsy - from mysticism to science. Rev. Neurol. (Paris) 177, 1047–1058. https://doi.org/10.1016/j.neurol.2021.01.021.
Bowder, D. (Ed.). 1982. Who was who in the Greek world, 776BC-30BC. Cornell University Press.
Bryson, A., Reid, C., Petrou, S., 2023. Fundamental neurochemistry review: GABAA receptor neurotransmission and epilepsy: principles, disease mechanisms and pharmacotherapy. J. Neurochem. 165, 6–28. https://doi.org/10.1111/jnc.15769.
Burtscher, J., Soltany, A., Visavadiya, N.P., Burtscher, M., Millet, G.P., Khoramipour, K., Khamoui, A.V., 2023. Mitochondrial stress and mitokines in aging. Aging Cell 22, e13770. https://doi.org/10.1111/acel.13770.
Cai, Y., Yang, Z., 2021. Ferroptosis and its role in epilepsy. Front. Cell. Neurosci. 15, 696889 https://doi.org/10.3389/fncel.2021.696889.
Camargo, C.H.F., Teive, H.A.G., 2018. Searching for neurological diseases in the Julio-Claudian dynasty of the Roman Empire. Arq. Neuropsiquiatr. 76, 53–57. https://doi.org/10.1590/0004-282x20170174.
Campos, G., Fortuna, A., Falcão, A., Alves, G., 2018. In vitro and in vivo experimental models employed in the discovery and development of antiepileptic drugs for pharmacoresistant epilepsy. Epilepsy Res. 146, 63–86. https://doi.org/10.1016/j.eplepsyres.2018.07.008.
Cardoso, F.D.S., Gonzalez-Lima, F., Coimbra, N.C., 2022. Mitochondrial photobiomodulation as a neurotherapeutic strategy for epilepsy. Front. Neurol. 13, 873496 https://doi.org/10.3389/fneur.2022.873496.
Castelli, M.A., Whiteley, S.L., Georges, A., Holleley, C.E., 2020. Cellular calcium and redox regulation: the mediator of vertebrate environmental sex determination? Biol. Rev. Camb. Philos. Soc. 95, 680–695. https://doi.org/10.1111/brv.12582.
Chakraborty, P., Dey, A., Gopalakrishnan, A.V., Swati, K., Ojha, S., Prakash, A., Kumar, D., Ambasta, R.K., Jha, N.K., Jha, S.K., Dewanjee, S., 2023. Glutamatergic neurotransmission: a potential pharmacotherapeutic target for the treatment of cognitive disorders. Ageing Res. Rev. 85, 101838 https://doi.org/10.1016/j.arr.2022.101838.
Chakraborty, S., Parayil, R., Mishra, S., Nongthomba, U., Clement, J.P., 2022. Epilepsy characteristics in neurodevelopmental disorders: Research from patient cohorts and animal models focusing on autism spectrum disorder. Int. J. Mol. Sci. 23 https://doi.org/10.3390/ijms231810807.
Chalia, M., Hartmann, H., Pressler, R., 2022. Practical approaches to the treatment of neonatal seizures. Curr. Treat. Options. Neurol. 24, 111–127. https://doi.org/10.1007/s11940-022-00711-w.
Chan, D., Suk, H.-J., Jackson, B.L., Milman, N.P., Stark, D., Klerman, E.B., Kitchener, E., Fernandez Avalos, V.S., de Weck, G., Banerjee, A., Beach, S.D., Blanchard, J., Stearns, C., Boes, A.D., Uitermarkt, B., Gander, P., Howard 3rd, M., Sternberg, E.J., Nieto-Castanon, A., Anteraper, S., Whitfield-Gabrieli, S., Brown, E.N., Boyden, E.S., Dickerson, B.C., Tsai, L.-H., 2022. Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients: Results of feasibility and pilot studies. PLoS ONE 17, e0278412. https://doi.org/10.1371/journal.pone.0278412.
Chen, Z., Brodie, M.J., Kwan, P., 2020b. What has been the impact of new drug treatments on epilepsy? Curr. Opin. Neurol. 33, 185–190. https://doi.org/10.1097/WCO.0000000000000803.
Chen, S., Chen, Y., Zhang, Y., Kuang, X., Liu, Y., Guo, M., Ma, L., Zhang, D., Li, Q., 2020a. Iron metabolism and ferroptosis in epilepsy. Front. Neurosci. 14, 601193 https://doi.org/10.3389/fnins.2020.601193.
Chen, L.-L., Fan, Y.-G., Zhao, L.-X., Zhang, Q., Wang, Z.-Y., 2023a. The metal ion hypothesis of Alzheimer's disease and the anti-neuroinflammatory effect of metal chelators. Bioorg. Chem. 131, 106301 https://doi.org/10.1016/j.bioorg.2022.106301.
Chen, S., Huang, W., Xu, Q., He, T., Zhang, M., Xu, H., 2023b. The impact of serum copper on the risk of epilepsy: a Mendelian randomization study. Acta Epileptologica 5. https://doi.org/10.1186/s42494-023-00126-3.
Chen, L., Min, J., Wang, F., 2022a. Copper homeostasis and cuproptosis in health and disease. Signal Transduct. Target. Ther. 7, 378. https://doi.org/10.1038/s41392-022-01229-y.
Chen, Y.-X., Zuliyaer, T., Liu, B., Guo, S., Yang, D.-G., Gao, F., Yu, Y., Yang, M.-L., Du, L.-J., Li, J.-J., 2022b. Sodium selenite promotes neurological function recovery after spinal cord injury by inhibiting ferroptosis. Neural Regen. Res. 17, 2702–2709. https://doi.org/10.4103/1673-5374.339491.
Cheng, R., Dhorajia, V.V., Kim, J., Kim, Y., 2022. Mitochondrial iron metabolism and neurodegenerative diseases. Neurotoxicology 88, 88–101. https://doi.org/10.1016/j.neuro.2021.11.003.
Cheng, Y., Luo, F., Zhang, Q., Sang, Y., Chen, X., Zhang, L., Liu, Y., Li, X., Li, J., Ding, H., Mei, Y., 2018. α-Lipoic acid alleviates pentetrazol-induced neurological deficits and behavioral dysfunction in rats with seizures via an Nrf2 pathway. RSC Adv. 8, 4084–4092. https://doi.org/10.1039/c7ra11491e.
Chinnery, P.F., 2023. Precision mitochondrial medicine. Camb. Prisms Precis. Med. 1, 1–23. https://doi.org/10.1017/pcm.2022.8.
Chung, C., Yang, X., Bae, T., Vong, K.I., Mittal, S., Donkels, C., Westley Phillips, H., Li, Z., Marsh, A.P.L., Breuss, M.W., Ball, L.L., Garcia, C.A.B., George, R.D., Gu, J., Xu, M., Barrows, C., James, K.N., Stanley, V., Nidhiry, A.S., Khoury, S., Howe, G., Riley, E., Xu, X., Copeland, B., Wang, Y., Kim, S.H., Kang, H.-C., Schulze-Bonhage, A., Haas, C. A., Urbach, H., Prinz, M., Limbrick, D.D., Jr, Gurnett, C.A., Smyth, M.D., Sattar, S., Nespeca, M., Gonda, D.D., Imai, K., Takahashi, Y., Chen, H.-H., Tsai, J.-W., Conti, V., Guerrini, R., Devinsky, O., Silva, W.A., Jr, Machado, H.R., Mathern, G.W., Abyzov, A., Baldassari, S., Baulac, S., Focal Cortical Dysplasia Neurogenetics Consortium, Brain Somatic Mosaicism Network, Gleeson, J.G., 2023. Comprehensive multi-omic profiling of somatic mutations in malformations of cortical development. Nat. Genet. 55, 209–220. https://doi.org/10.1038/s41588-022-01276-9.
Clemens, B., Emri, M., Fekete, I., Fekete, K., 2023. Epileptic diathesis: An EEG-LORETA study. Clin. Neurophysiol. 145, 54–61. https://doi.org/10.1016/j.clinph.2022.11.004.
Cobine, P.A., Brady, D.C., 2022. Cuproptosis: Cellular and molecular mechanisms underlying copper-induced cell death. Mol. Cell 82, 1786–1787. https://doi.org/10.1016/j.molcel.2022.05.001.
Collier, J.J., Oláhová, M., McWilliams, T.G., Taylor, R.W., 2023. Mitochondrial signalling and homeostasis: from cell biology to neurological disease. Trends Neurosci. 46, 137–152. https://doi.org/10.1016/j.tins.2022.12.001.
Corona, L., Tamilia, E., Perry, M.S., Madsen, J.R., Bolton, J., Stone, S.S.D., Stufflebeam, S.M., Pearl, P.L., Papadelis, C., 2023. Non-invasive mapping of epileptogenic networks predicts surgical outcome. Brain 146, 1916–1931. https://doi.org/10.1093/brain/awac477.
David, S., Jhelum, P., Ryan, F., Jeong, S.Y., Kroner, A., 2022. Dysregulation of iron homeostasis in the central nervous system and the role of ferroptosis in neurodegenerative disorders. Antioxid. Redox Signal. 37, 150–170. https://doi.org/10.1089/ars.2021.0218.
Davis, O., 2023. Abnormal chromatin folding in the molecular pathogenesis of epilepsy and autism spectrum disorder: a meta-synthesis with systematic searching. Mol. Neurobiol. 60, 768–779. https://doi.org/10.1007/s12035-022-03106-9.
Davis, H.E., McCorkell, L., Vogel, J.M., Topol, E.J., 2023. Long COVID: major findings, mechanisms and recommendations. Nat. Rev. Microbiol. 21, 133–146. https://doi.org/10.1038/s41579-022-00846-2.
De Bartolo, M.I., Vivacqua, G., Belvisi, D., Mancinelli, R., Fabbrini, A., Manzo, N., Costanzo, M., Leodori, G., Conte, A., Fabbrini, G., Morini, S., Berardelli, A., 2023. A combined panel of salivary biomarkers in de novo Parkinson's disease. Ann. Neurol. 93, 446–459. https://doi.org/10.1002/ana.26550.

De Costa, A.E.M., da Silva, B.M., Thomazin, I.M., Porto, I.O., Pereira, C.U., Rabelo, N.N., Furtado, M.S., 2023. Epilepsy in childhood: an update on management. Arch. Pediat. Neurosurg. 5, e1582023 https://doi.org/10.46900/apn.v5i1.158.

Del Pozo, A., Lehmann, L., Knox, K.M., Barker-Haliski, M., 2022. Can old animals reveal new targets? The aging and degenerating brain as a new precision medicine opportunity for epilepsy. Front. Neurol. 13, 833624 https://doi.org/10.3389/fneur.2022.833624.

Devi, N., Madaan, P., Kandoth, N., Bansal, D., Sahu, J.K., 2023. Efficacy and safety of dietary therapies for childhood drug-resistant epilepsy: a systematic review and network meta-analysis: a systematic review and network meta-analysis. JAMA Pediatr. 177, 258–266. https://doi.org/10.1001/jamapediatrics.2022.5648.

Devinsky, O., Vezzani, A., O'Brien, T.J., Jette, N., Scheffer, I.E., de Curtis, M., Perucca, P., 2018. Epilepsy. Nat. Rev. Dis. Primers 4, 18024. https://doi.org/10.1038/nrdp.2018.24.

Diskin, C.J., 2002. Does abnormal trace element metabolism contribute to dialysis patient morbidity?: Trace element metabolism and morbidity. Semin. Dial. 12, 18–20. https://doi.org/10.1046/j.1525-139x.1999.12103.x.

Do, M., Shin, B., Lioudis, E., Munn, E., 2022. Novel drugs approved in 2021–2022. Transform. Med. 1, 72–77. https://doi.org/10.54299/tmed/zcno1399.

Domínguez-Álvarez, E., Rácz, B., Marć, M.A., Nasim, M.J., Szemerédi, N., Viktorová, J., Jacob, C., Spengler, G., 2022. Selenium and tellurium in the development of novel small molecules and nanoparticles as cancer multidrug resistance reversal agents. Drug Resist. Updat. 63, 100844 https://doi.org/10.1016/j.drup.2022.100844.

dos Santos, S.M., Romeiro, C.F.R., Rodrigues, C.A., Cerqueira, A.R.L., Monteiro, M.C., 2019. Mitochondrial dysfunction and alpha-lipoic acid: beneficial or harmful in Alzheimer's disease? Oxid. Med. Cell. Longev. 2019, 1–14. https://doi.org/10.1155/2019/8409329.

Du, K., He, M., Zhao, D., Wang, Y., Ma, C., Liang, H., Wang, W., Min, D., Xue, L., Guo, F., 2022. Mechanism of cell death pathways in status epilepticus and related therapeutic agents. Biomed. Pharmacother. 149, 112875 https://doi.org/10.1016/j.biopha.2022.112875.

Duncan, J.S., 2022. Epilepsy in the 21st century. Lancet Neurol. 21, 501–503. https://doi.org/10.1016/S1474-4422(22)00175-2.

Duncan, J.S., Taylor, P.N., 2023. Optimising epilepsy surgery. Lancet Neurol. 22, 373–374. https://doi.org/10.1016/S1474-4422(23)00082-0.

Dunn, E., Ibrahim, F., Neme-Mercante, S., Nair, D., Morris, S., Wang, I., Punia, V., 2023. Possible post-COVID epilepsy: a review of epilepsy monitoring unit admissions during the two years of COVID-19 pandemic. Epilepsy Behav. Rep. 21, 100584 https://doi.org/10.1016/j.ebr.2023.100584.

Dusek, P., Hofer, T., Alexander, J., Roos, P.M., Aaseth, J.O., 2022. Cerebral iron deposition in neurodegeneration. Biomolecules 12, 714. https://doi.org/10.3390/biom12050714.

Dyńka, D., Kowalcze, K., Paziewska, A., 2022. The role of ketogenic diet in the treatment of neurological diseases. Nutrients 14, 5003. https://doi.org/10.3390/nu14235003.

Edwards, J.C., Sobel, R.S., Bonilha, L., 2018. Marginal decision-making in the treatment of refractory epilepsy. J. Med. Econ. 21, 438–442. https://doi.org/10.1080/13696998.2017.1412975.

Egawa, K., Nakakubo, S., Kimura, S., Goto, T., Manabe, A., Shiraishi, H., 2021. Flurothyl-induced seizure paradigm revealed higher seizure susceptibility in middle-aged Angelman syndrome mouse model. Brain Dev. 43, 515–520. https://doi.org/10.1016/j.braindev.2020.12.011.

Eloge, J.C., Ross, D.A., Cooper, J.J., 2020. Afflicted by the gods: the shared history and neurobiology of psychosis and epilepsy. Biol. Psychiatry 87, e35–e36. https://doi.org/10.1016/j.biopsych.2020.04.018.

Emmanuele, V., Ganesh, J., Vladutiu, G., Haas, R., Kerr, D., Saneto, R.P., Cohen, B.H., Van Hove, J.L.K., Scaglia, F., Hoppel, C., Rosales, X.Q., Barca, E., Buchsbaum, R., Thompson, J.L., DiMauro, S., Hirano, M., North American Mitochondrial Disease Consortium (NAMDC), 2022. Time to harmonize mitochondrial syndrome nomenclature and classification: A consensus from the North American Mitochondrial Disease Consortium (NAMDC). Mol. Genet. Metab. 136, 125–131. https://doi.org/10.1016/j.ymgme.2022.05.001.

Falsaperla, R., Sciuto, L., La Spina, L., Sciuto, S., Praticò, A.D., Ruggieri, M., 2021. Neonatal seizures as onset of Inborn Errors of Metabolism (IEMs): from diagnosis to treatment. A systematic review. Metab. Brain Dis. 36, 2195–2203. https://doi.org/10.1007/s11011-021-00798-1.

Fisher, R.S., 2023. Deep brain stimulation of thalamus for epilepsy. Neurobiol. Dis. 179, 106045 https://doi.org/10.1016/j.nbd.2023.106045.

Fisher, R.S., Cross, J.H., D'Souza, C., French, J.A., Haut, S.R., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E., Scheffer, I.E., Schulze-Bonhage, A., Somerville, E., Sperling, M., Yacubian, E.M., Zuberi, S.M., 2017. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 58, 531–542. https://doi.org/10.1111/epi.13671.

Foutz, T.J., Wong, M., 2022. Brain stimulation treatments in epilepsy: basic mechanisms and clinical advances. Biomed. J. 45, 27–37. https://doi.org/10.1016/j.bj.2021.08.010.

Fricker, M., Tolkovsky, A.M., Borutaite, V., Coleman, M., Brown, G.C., 2018. Neuronal cell death. Physiol. Rev. 98, 813–880. https://doi.org/10.1152/physrev.00011.2017.

Friedmann Angeli, J.P., Conrad, M., 2018. Selenium and GPX4, a vital symbiosis. Free Radic. Biol. Med. 127, 153–159. https://doi.org/10.1016/j.freeradbiomed.2018.03.001.

Gallagher, A., Wallois, F., Obrig, H., 2023. Functional near-infrared spectroscopy in pediatric clinical research: different pathophysiologies and promising clinical applications. Neurophotonics 10, 023517. https://doi.org/10.1117/1.NPh.10.2.023517.

Garza, N.M., Swaminathan, A.B., Maremanda, K.P., Zulkifli, M., Gohil, V.M., 2023. Mitochondrial copper in human genetic disorders. Trends Endocrinol. Metab. 34, 21–33. https://doi.org/10.1016/j.tem.2022.11.001.

Golomb, M.R., Illner, A., Christensen, C.K., Walsh, L.E., 2005. A child with Friedreich's ataxia and epilepsy. J. Child Neurol. 20, 248–250. https://doi.org/10.1177/08830738050200031201.

Gorman, G.S., Chinnery, P.F., DiMauro, S., Hirano, M., Koga, Y., McFarland, R., Suomalainen, A., Thorburn, D.R., Zeviani, M., Turnbull, D.M., 2016. Mitochondrial diseases. Nat. Rev. Dis. Primers 2, 16080. https://doi.org/10.1038/nrdp.2016.80.

Graifman, J.L., Lippa, N.C., Mulhern, M.S., Bergner, A.L., Sands, T.T., 2023. Clinical utility of exome sequencing in a pediatric epilepsy cohort. Epilepsia 64, 986–997. https://doi.org/10.1111/epi.17534.

Grammatikopoulou, M.G., Tousinas, G., Balodimou, C., Anastasilakis, D.A., Gkiouras, K., Dardiotis, E., Evangeliou, A.E., Bogdanos, D.P., Goulis, D.G., 2022. Ketogenic therapy for Parkinson's disease: a systematic review and synthesis without meta-analysis of animal and human trials. Maturitas 163, 46–61. https://doi.org/10.1016/j.maturitas.2022.06.001.

Gribkoff, V.K., Winquist, R.J., 2023. Potassium channelopathies associated with epilepsy-related syndromes and directions for therapeutic intervention. Biochem. Pharmacol. 208, 115413 https://doi.org/10.1016/j.bcp.2023.115413.

Grimal, P., 1986. The dictionary of classical mythology (A. R. Maxwell-Hyslop, Trans.). Blackwell.

Guo, Y., Zhang, H., Yan, C., Shen, B., Zhang, Y., Guo, X., Sun, S., Yu, F., Yan, J., Liu, R., Zhang, Q., Zhang, D., Liu, H., Liu, Y., Zhang, Y., Li, W., Qin, J., Lv, H., Wang, Z., Yuan, Y., Yang, J.-F., Zhong, Y.-T., Gao, S., Zhou, B., Liu, L., Kong, D., Hao, X., Hu, J., Chen, Q., 2023. Small molecule agonist of mitochondrial fusion repairs mitochondrial dysfunction. Nat. Chem. Biol. 19, 468–477. https://doi.org/10.1038/s41589-022-01224-y.

Guo, J., Zhou, Y., Liu, D., Wang, M., Wu, Y., Tang, D., Liu, X., 2022. Mitochondria as multifaceted regulators of ferroptosis. Life Metab. 1, 134–148. https://doi.org/10.1093/lifemeta/loac035.

Hakami, T., 2021. Efficacy and tolerability of antiseizure drugs. Ther. Adv. Neurol. Disord. 14 https://doi.org/10.1177/17562864211037430.

Hakeem, H., Feng, W., Chen, Z., Choong, J., Brodie, M.J., Fong, S.-L., Lim, K.-S., Wu, J., Wang, X., Lawn, N., Ni, G., Gao, X., Luo, M., Chen, Z., Ge, Z., Kwan, P., 2022. Development and validation of a deep learning model for predicting treatment response in patients with newly diagnosed epilepsy. JAMA Neurol. 79, 986–996. https://doi.org/10.1001/jamaneurol.2022.2514.

Hamblin, M.R., 2023. Could photobiomodulation therapy be helpful in epilepsy? Photobiomodul. Photomed. Laser Surg. 41, 35–36. https://doi.org/10.1089/photob.2023.0003.

Hamdy, R.M., Abdel-Tawab, H., Abd Elaziz, O.H., Sobhy El Attar, R., Kotb, F.M., 2022a. Evaluation of heart rate variability parameters during awake and sleep in refractory and controlled epileptic patients. Int. J. Gen. Med. 15, 3865–3877. https://doi.org/10.2147/IJGM.S354895.

Hamdy, R.M., Elaziz, O.H.A., El Attar, R.S., Abdel-Tawab, H., Kotb, F.M., 2022b. Evaluation of QT dispersion in epileptic patients and its association with SUDEP risk. Epilepsy Res. 180, 106860 https://doi.org/10.1016/j.eplepsyres.2022.106860.

Hamed, R., Eyal, A.D., Berman, E., Eyal, S., 2023. In silico screening for clinical efficacy of antiseizure medications: not all central nervous system drugs are alike. Epilepsia 64, 311–319. https://doi.org/10.1111/epi.17479.

Hanjani, K., Fatehi, M., Schmidt, N., Aghakhani, Y., Redekop, G.J., 2021. A history of diagnostic investigations in epilepsy surgery. Can. J. Neurol. Sci. 48, 845–851. https://doi.org/10.1017/cjn.2021.16.

Hikmat, O., Eichele, T., Tzoulis, C., Bindoff, L.A., 2017. Understanding the epilepsy in POLG related disease. Int. J. Mol. Sci. 18 https://doi.org/10.3390/ijms18091845.

Hilal, A.M., Albraikan, A.A., Dhahbi, S., Nour, M.K., Mohamed, A., Motwakel, A., Zamani, A.S., Rizwanullah, M., 2022. Intelligent epileptic seizure detection and classification model using optimal deep canonical sparse autoencoder. Biology (Basel) 11, 1220. https://doi.org/10.3390/biology11081220.

Hirota, T., King, B.H., 2023. Autism spectrum disorder: a review. J. Am. Med. Assoc. 329, 157–168. https://doi.org/10.1001/jama.2022.23661.

Hong, N., Kim, H.J., Kang, K., Park, J.O., Mun, S., Kim, H.-G., Kang, B.H., Chung, P.-S., Lee, M.Y., Ahn, J.-C., 2023. Photobiomodulation improves the synapses and cognitive function and ameliorates epileptic seizure by inhibiting downregulation of Nlgn3. Cell Biosci. 13, 8. https://doi.org/10.1186/s13578-022-00949-6.

Hoppe, C., Beeres, K., Witt, J.-A., Sassen, R., Helmstaedter, C., 2023. Clinical adult outcome 11–30 years after pediatric epilepsy surgery: Complications and other surgical adverse events, seizure control, and cure of epilepsy. Epilepsia 64, 335–347. https://doi.org/10.1111/epi.17477.

Hosseinian, S., Ali Pour, P., Kheradvar, A., 2022. Prospects of mitochondrial transplantation in clinical medicine: aspirations and challenges. Mitochondrion 65, 33–44. https://doi.org/10.1016/j.mito.2022.04.006.

Hsieh, J.K., Pucci, F.G., Sundar, S.J., Kondylis, E., Sharma, A., Sheikh, S.R., Vegh, D., Moosa, A.N., Gupta, A., Najm, I., Rammo, R., Bingaman, W., Jehi, L., 2023. Beyond seizure freedom: dissecting long-term seizure control after surgical resection for drug-resistant epilepsy. Epilepsia 64, 103–113. https://doi.org/10.1111/epi.17445.

Hu, T., Zhang, J., Wang, J., Sha, L., Xia, Y., Ortyl, T.C., Tian, X., Chen, L., 2023. Advances in epilepsy: Mechanisms, clinical trials, and drug therapies. J. Med. Chem. 66, 4434–4467. https://doi.org/10.1021/acs.jmedchem.2c01975.

Huang, L., Li, H., Zhong, J., Yang, L., Chen, G., Wang, D., Zheng, G., Han, H., Han, X., Long, Y., Wang, X., Liang, J., Yu, M., Shen, X., Fan, M., Fang, F., Liao, J., Sun, D., 2022. Efficacy and safety of the ketogenic diet for mitochondrial disease with epilepsy: a prospective, open-labeled, controlled study. Front. Neurol. 13, 880944 https://doi.org/10.3389/fneur.2022.880944.

Huang, Z., Yang, X., Huang, Y., Tang, Z., Chen, Y., Liu, H., Huang, M., Qing, L., Li, L., Wang, Q., Jie, Z., Jin, X., Jia, B., 2023. Saliva - a new opportunity for fluid biopsy. Clin. Chem. Lab. Med. 61, 4–32. https://doi.org/10.1515/cclm-2022-0793.
Huisman, T.A.G.M., Kralik, S.F., Desai, N.K., Serrallach, B.L., Orman, G., 2022. Neuroimaging of primary mitochondrial disorders in children: a review. J. Neuroimaging 32, 191–200. https://doi.org/10.1111/jon.12976.
Hunsaker, E.W., Franz, K.J., 2019. Emerging opportunities to manipulate metal trafficking for therapeutic benefit. Inorg. Chem. 58, 13528–13545. https://doi.org/10.1021/acs.inorgchem.9b01029.
Ilyas, A., Alamoudi, O.A., Riley, K.O., Pati, S., 2023. Pro-ictal state in human temporal lobe epilepsy. NEJM Evid. 2 https://doi.org/10.1056/evidoa2200187.
Ingold, I., Berndt, C., Schmitt, S., Doll, S., Poschmann, G., Buday, K., Roveri, A., Peng, X., Porto Freitas, F., Seibt, T., Mehr, L., Aichler, M., Walch, A., Lamp, D., Jastroch, M., Miyamoto, S., Wurst, W., Ursini, F., Arnér, E.S.J., Fradejas-Villar, N., Schweizer, U., Zischka, H., Friedmann Angeli, J.P., Conrad, M., 2018. Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis. Cell 172, 409–422. https://doi.org/10.1016/j.cell.2017.11.048.
Ingold, I., Conrad, M., 2018. Selenium and iron, two elemental rivals in the ferroptotic death process. Oncotarget 9, 22241–22242. https://doi.org/10.18632/oncotarget.25295.
Ingraham, C.A., Burwell, L.S., Skalska, J., Brookes, P.S., Howell, R.L., Sheu, S.-S., Pinkert, C.A., 2009. NDUFS4: creation of a mouse model mimicking a Complex I disorder. Mitochondrion 9, 204–210. https://doi.org/10.1016/j.mito.2009.02.001.
Ismail, F.S., Spatola, M., Woermann, F.G., Popkirov, S., Jungilligens, J., Bien, C.G., Wellmer, J., Schlegel, U., 2022. Diagnostic challenges in patients with temporal lobe seizures and features of autoimmune limbic encephalitis. Eur. J. Neurol. 29, 1303–1310. https://doi.org/10.1111/ene.15026.
Izumi, Y., Ishikawa, M., Nakazawa, T., Kunikata, H., Sato, K., Covey, D.F., Zorumski, C. F., 2023. Neurosteroids as stress modulators and neurotherapeutics: lessons from the retina. Neural Regen. Res. 18, 1004–1008. https://doi.org/10.4103/1673-5374.355752.
Javaid, M.S., Antonic-Baker, A., Pitsillou, E., Liang, J., French, C., Hung, A., O'Brien, T. J., Kwan, P., Karagiannis, T.C., Anderson, A., 2022. Alpha-lipoic acid analogues in the regulation of redox balance in epilepsy: A molecular docking and simulation study. J. Mol. Graph. Model. 112, 108116 https://doi.org/10.1016/j.jmgm.2021.108116.
Jhelum, P., David, S., 2022. Ferroptosis: copper-iron connection in cuprizone-induced demyelination. Neural Regen. Res. 17, 89–90. https://doi.org/10.4103/1673-5374.314300.
Jia, M.-Q., Guan, C.-X., Tao, J.-H., Zhou, Y., 2022a. Research progress of fibroblast growth factor 21 in fibrotic diseases. Oxid. Med. Cell. Longev. 2022, 5042762 https://doi.org/10.1155/2022/5042762.
Jia, X., Zhang, S., Tan, S., Du, B., He, M., Qin, H., Chen, J., Duan, X., Luo, J., Chen, F., Ouyang, L., Wang, J., Chen, G., Yu, B., Zhang, G., Zhang, Z., Lyu, Y., Huang, Y., Jiao, J., Chen, J.Y.H., Swoboda, K.J., Agolini, E., Novelli, A., Leoni, C., Zampino, G., Cappuccio, G., Brunetti-Pierri, N., Gerard, B., Ginglinger, E., Richer, J., McMillan, H., White-Brown, A., Hoekzema, K., Bernier, R.A., Kurtz-Nelson, E.C., Earl, R.K., Meddens, C., Alders, M., Fuchs, M., Caumes, R., Brunelle, P., Smol, T., Kuehl, R., Day-Salvatore, D.-L., Monaghan, K.G., Morrow, M.M., Eichler, E.E., Hu, Z., Yuan, L., Tan, J., Xia, K., Shen, Y., Guo, H., 2022. De novo variants in genes regulating stress granule assembly associate with neurodevelopmental disorders. Sci. Adv. 8, eabo7112. https://doi.org/10.1126/sciadv.abo7112.
Jiang, X., Stockwell, B.R., Conrad, M., 2021. Ferroptosis: mechanisms, biology and role in disease. Nat. Rev. Mol. Cell Biol. 22, 266–282. https://doi.org/10.1038/s41580-020-00324-8.
Jin, Y., Ren, L., Jing, X., Wang, H., 2023. Targeting ferroptosis as novel therapeutic approaches for epilepsy. Front. Pharmacol. 14 https://doi.org/10.3389/fphar.2023.1185071.
Jirsa, V., Wang, H., Triebkorn, P., Hashemi, M., Jha, J., Gonzalez-Martinez, J., Guye, M., Makhalova, J., Bartolomei, F., 2023. Personalised virtual brain models in epilepsy. Lancet Neurol. 22, 443–454. https://doi.org/10.1016/S1474-4422(23)00008-X.
Johannesen, K.M., 2023. From precision diagnosis to precision treatment in epilepsy. Nat. Rev. Neurol. 19, 69–70. https://doi.org/10.1038/s41582-022-00756-0.
Jomova, K., Makova, M., Alomar, S.Y., Alwasel, S.H., Nepovimova, E., Kuca, K., Rhodes, C.J., Valko, M., 2022. Essential metals in health and disease. Chem. Biol. Interact. 367, 110173 https://doi.org/10.1016/j.cbi.2022.110173.
Kaculini, C.M., Tate-Looney, A.J., Seifi, A., 2021. The history of epilepsy: from ancient mystery to modern misconception. Cureus. https://doi.org/10.7759/cureus.13953.
Kahlson, M.A., Dixon, S.J., 2022. Copper-induced cell death. Science 375, 1231–1232. https://doi.org/10.1126/science.abo3959.
Kahn-Kirby, A.H., Amagata, A., Maeder, C.I., Mei, J.J., Sideris, S., Kosaka, Y., Hinman, A., Malone, S.A., Bruegger, J.J., Wang, L., Kim, V., Shrader, W.D., Hoff, K. G., Latham, J.C., Ashley, E.A., Wheeler, M.T., Bertini, E., Carrozzo, R., Martinelli, D., Dionisi-Vici, C., Chapman, K.A., Enns, G.M., Gahl, W., Wolfe, L., Saneto, R.P., Johnson, S.C., Trimmer, J.K., Klein, M.B., Holst, C.R., 2019. Targeting ferroptosis: A novel therapeutic strategy for the treatment of mitochondrial disease-related epilepsy. PLoS ONE 14, e0214250. https://doi.org/10.1371/journal.pone.0214250.
Kalra, J., 2023. Crosslink between mutations in mitochondrial genes and brain disorders: implications for mitochondrial-targeted therapeutic interventions. Neural Regen. Res. 18, 94. https://doi.org/10.4103/1673-5374.343884.
Kang, H.-C., Lee, Y.-M., Kim, H.D., 2013. Mitochondrial disease and epilepsy. Brain Dev. 35, 757–761. https://doi.org/10.1016/j.braindev.2013.01.006.
Kang, Y., Zhu, R., Li, S., Qin, K.-P., Tang, H., Shan, W.-S., Yin, Z.-S., 2023. Erythropoietin inhibits ferroptosis and ameliorates neurological function after spinal cord injury. Neural Regen. Res. 18, 881–888. https://doi.org/10.4103/1673-5374.353496.
Kanmounye, U.S., Abu-Bonsrah, N., Shlobin, N.A., Djoutsop, O.M., 2022. Letter: The world health organization's intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Neurosurgery 90, e201–e203. https://doi.org/10.1227/neu.0000000000001976.
Kanner, A.M., Bicchi, M.M., 2022. Antiseizure medications for adults with epilepsy: a review: a review. J. Am. Med. Assoc. 327, 1269–1281. https://doi.org/10.1001/jama.2022.3880.
Kanner, A.M., Saporta, A.S., Kim, D.H., Barry, J.J., Altalib, H., Omotola, H., Jette, N., O'Brien, T.J., Nadkarni, S., Winawer, M.R., Sperling, M., French, J.A., Abou-Khalil, B., Alldredge, B., Bebin, M., Cascino, G.D., Cole, A.J., Cook, M.J., Detyniecki, K., Devinsky, O., Dlugos, D., Faught, E., Ficker, D., Fields, M., Gidal, B., Gelfand, M., Glynn, S., Halford, J.J., Haut, S., Hegde, M., Holmes, M.G., Kalviainen, R., Kang, J., Klein, P., Knowlton, R.C., Krishnamurthy, K., Kuzniecky, R., Kwan, P., Lowenstein, D.H., Marcuse, L., Meador, K.J., Mintzer, S., Pardoe, H.R., Park, K., Penovich, P., Singh, R.K., Somerville, E., Szabo, C.A., Szaflarski, J.P., Lin Thio, K.L., Trinka, E., Burneo, J.G., Human Epilepsy Project, 2023. Mood and anxiety disorders and suicidality in patients with newly diagnosed focal epilepsy: an analysis of a complex comorbidity: an analysis of a complex comorbidity. Neurology 100, e1123–e1134. https://doi.org/10.1212/WNL.0000000000201671.
Karoly, P.J., Rao, V.R., Gregg, N.M., Worrell, G.A., Bernard, C., Cook, M.J., Baud, M.O., 2021. Cycles in epilepsy. Nat. Rev. Neurol. 17, 267–284. https://doi.org/10.1038/s41582-021-00464-1.
Kasteleijn-Nolst Trenite, D., Reed, R.C., 2023. Brivaracetam or levetiracetam in status epilepticus?: Lessons from the photosensitivity model. Epilepsy Behav. 138, 109018 https://doi.org/10.1016/j.yebeh.2022.109018.
Keating, C.T., Hickman, L., Leung, J., Monk, R., Montgomery, A., Heath, H., Sowden, S., 2023. Autism-related language preferences of English-speaking individuals across the globe: a mixed methods investigation. Autism Res. 16, 406–428. https://doi.org/10.1002/aur.2864.
Kerezoudis, P., Singh, R., Parisi, V., Worrell, G.A., Miller, K.J., Marsh, W.R., Van Gompel, J.J., 2021. Outcomes of epilepsy surgery in the older population: not too old, not too late. J. Neurosurg. 136, 1–10. https://doi.org/10.3171/2021.5.JNS204211.
Khalil, N., Benbadis, S., Robertson, D., 2020. Ceasing antiquated conceptions: a telling of the early and evolving history of epilepsy. Eur. Neurol. 83, 341–344. https://doi.org/10.1159/000509496.
Khamis, S., Mitakidou, M.R., Champion, M., Goyal, S., Jones, R.L., Siddiqui, A., Sabanathan, S., Hedderly, T., Lin, J.-P., Jungbluth, H., Papandreou, A., 2023. Clinical reasoning: a teenage girl with progressive hyperkinetic movements, seizures, and encephalopathy. Neurology 100, 30–37. https://doi.org/10.1212/WNL.0000000000201385.
Khan, H., Singh, T.G., Dahiya, R.S., Abdel-Daim, M.M., 2022. α-Lipoic acid, an organosulfur biomolecule a novel therapeutic agent for neurodegenerative disorders: an mechanistic perspective. Neurochem. Res. 47, 1853–1864. https://doi.org/10.1007/s11064-022-03598-w.
Khurana, D.S., Valencia, I., Goldenthal, M.J., Legido, A., 2013. Mitochondrial dysfunction in epilepsy. Semin. Pediatr. Neurol. 20, 176–187. https://doi.org/10.1016/j.spen.2013.10.001.
Kieliszek, M., Bano, I., 2022. Selenium as an important factor in various disease states - a review. EXCLI J. 21, 948–966. https://doi.org/10.17179/excli2022-5137.
Kim, S., Park, S., Choi, T.G., Kim, S.S., 2022. Role of short chain fatty acids in epilepsy and potential benefits of probiotics and prebiotics: targeting "health" of epileptic patients. Nutrients 14, 2982. https://doi.org/10.3390/nu14142982.
Kim, T.H., Petrou, S., Reid, C.A., 2014. Low glycaemic index diet reduces seizure susceptibility in a syndrome-specific mouse model of generalized epilepsy. Epilepsy Res. 108, 139–143. https://doi.org/10.1016/j.eplepsyres.2013.10.014.
Kim, D., Woo, J., Jeong, J., Kim, S., 2023. The sound stimulation method and EEG change analysis for development of digital therapeutics that can stimulate the nervous system: cortical activation and drug substitution potential. CNS Neurosci. Ther. 29, 402–411. https://doi.org/10.1111/cns.14014.
Kizilkilic, E.K., Unkun, R., Uygunoglu, U., Delil, S., Ozkara, C., 2022. Treatment of COVID-19-induced refractory status epilepticus by tocilizumab. Eur. J. Neurol. 29, 2861–2863. https://doi.org/10.1111/ene.15440.
Kleen, J.K., Guterman, E.L., 2023. The New Era of automated electroencephalogram interpretation. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2023.1082.
Knight, E.M.P., Amin, S., Bahi-Buisson, N., Benke, T.A., Cross, J.H., Demarest, S.T., Olson, H.E., Specchio, N., Fleming, T.R., Aimetti, A.A., Gasior, M., Devinsky, O., Marigold Trial Group, 2022. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol 21, 417–427. https://doi.org/10.1016/S1474-4422(22)00077-1.
Kocaaga, A., Yimenicioglu, S., 2023. Identification of novel gene variants in children with drug-resistant epilepsy: expanding the genetic spectrum. Pediatr. Neurol. 139, 7–12. https://doi.org/10.1016/j.pediatrneurol.2022.11.005.
Kocatürk, R.R., Nutrition, Dietetics, Faculty of Health Sciences, Üsküdar University, Istanbul, Turkey, 2022. Use of ketogenic diet therapy in epilepsy with mitochondrial dysfunction: A systematic and critical review. Biotechnol. Acta 15, 15 – 36. https://doi.org/10.15407/biotech15.02.015.
Kodukula, K., Faller, D.V., Harpp, D.N., Kanara, I., Pernokas, J., Pernokas, M., Powers, W.R., Soukos, N.S., Steliou, K., Moos, W.H., 2017. Gut Microbiota and salivary diagnostics: the mouth is salivating to tell us something. Biores. Open Access 6, 123–132. https://doi.org/10.1089/biores.2017.0020.
Kolb, B., 2021. Brenda Milner: pioneer of the study of the human frontal lobes. Front. Hum. Neurosci. 15, 786167 https://doi.org/10.3389/fnhum.2021.786167.
Kong, D., Saqer, A.A., Carpinelli de Jesus, M., Khan, N., Jones, A., Blanchfield, J.T., Smith, M.T., Williams, C.M., 2022. Design, synthesis and evaluation of alpha lipoic

acid derivatives to treat multiple sclerosis-associated central neuropathic pain. Bioorg. Med. Chem. 69, 116889 https://doi.org/10.1016/j.bmc.2022.116889.
Kośmider, K., Kamieniak, M., Czuczwar, S.J., Miziak, B., 2023. Second generation of antiepileptic drugs and oxidative stress. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24043873.
Kostev, K., Doege, C., Jacob, L., Smith, L., Koyanagi, A., Gollop, C., Schrag, A., 2023. Association between antiepileptic drugs and incident Parkinson's disease among patients followed in German primary care practices. Brain Sci. 13 https://doi.org/10.3390/brainsci13030450.
Kumar, A.N., Jadhav, V., Jawalekar, R., Akhare, P., Atram, H., Jaiswal, E., Khan, A., Gosavi, S., 2021. Light emitting diode mediated photobiomodulation therapy in orthodontics–a review of contemporary literature. J. Evol. Med. Dent. Sci. 10, 2672. https://go.gale.com/ps/i.do?p=HRCA&sw=w&issn=22784748&v=2.1&it=r&id=GALE %7CA673736913&sid=googleScholar&linkaccess=abs.
Kumari, R.S., Dhiman, P., Singh, D., Saneja, A., 2022. *R*-α-Lipoic acid conjugated to d-α-tocopherol polyethylene glycol 1000 succinate: synthesis, characterization, and effect on antiseizure activity. J. Agric. Food Chem. 70, 7674–7682. https://doi.org/10.1021/acs.jafc.2c01685.
Kurokawa, M., Kurokawa, R., Lin, A.Y., Capizzano, A.A., Baba, A., Kim, J., Johnson, T.D., Srinivasan, A., Moritani, T., 2023. Neurological and neuroradiological manifestations in neonates born to mothers with Coronavirus disease 2019. Pediatr. Neurol. 141, 9–17. https://doi.org/10.1016/j.pediatrneurol.2022.12.003.
La Rosa, P., Petrillo, S., Fiorenza, M.T., Bertini, E.S., Piemonte, F., 2020. Ferroptosis in Friedreich's Ataxia: a metal-induced neurodegenerative disease. Biomolecules 10, 1551. https://doi.org/10.3390/biom10111551.
Larkin, H., 2023. Noninvasive sensory stimulation with light and sound tested in Alzheimer disease. J. Am. Med. Assoc. 329, 114. https://doi.org/10.1001/jama.2022.23513.
Leblanc, R., 2021. Penfield, focal microgyria, and epilepsy. J. Neurosurg. 1–7. https://doi.org/10.3171/2020.9.JNS202900.
Leblanc, R., 2022a. Prelude-neurology and neurosurgery at McGill University 1894–1928. Can. J. Neurol. Sci. 49, 406–413. https://doi.org/10.1017/cjn.2021.132.
Leblanc, R., 2022b. The birth of experimental neurosurgery: Wilder Penfield at Montreal's Royal Victoria Hospital, 1928–1934. J. Neurosurg. 136, 553–560. https://doi.org/10.3171/2021.1.jns203929.
Leblanc, R., 2023. Wilder Penfield and academic neurosurgery in North America: 1934–1945. Can. J. Neurol. Sci. 50, 99–108. https://doi.org/10.1017/cjn.2021.498.
Leung, A.K., Hon, K.L., Leung, T.N., 2018. Febrile seizures: an overview. Drugs Context 7, 212536. https://doi.org/10.7573/dic.212536.
Li, Z., Chen, L., Xu, C., Chen, Z., Wang, Y., 2023b. Non-invasive sensory neuromodulation in epilepsy: updates and future perspectives. Neurobiol. Dis. 179, 106049 https://doi.org/10.1016/j.nbd.2023.106049.
Li, X.-H., Hou, X.-Y., Chen, R., 2015. The roles of vitamin B_{12} and vitamin D in children with intractable epilepsy. Int. J. Clin. Exp. Med. 8, 764–769. PMID: 25785055.
Li, J., Jia, B., Cheng, Y., Song, Y., Li, Q., Luo, C., 2022b. Targeting molecular mediators of ferroptosis and oxidative stress for neurological disorders. Oxid. Med. Cell. Longev. 2022, 3999083 https://doi.org/10.1155/2022/3999083.
Li, Q.-S., Jia, Y.-J., 2023. Ferroptosis: a critical player and potential therapeutic target in traumatic brain injury and spinal cord injury. Neural Regen. Res. 18, 506–512. https://doi.org/10.4103/1673-5374.350187.
Li, Y., Jin, M., Yin, X., Zhou, B., Ni, H., 2023a. Effects of leptin treatment immediately after neonatal seizures on serum clusterin and VEGF levels and brain oxidative stress-related proteins and neurobehavioral phenotypes. Epilepsy Behav. 138, 109016 https://doi.org/10.1016/j.yebeh.2022.109016.
Li, J., Leverton, L.K., Naganatanahalli, L.M., Christian-Hinman, C.A., 2020. Seizure burden fluctuates with the female reproductive cycle in a mouse model of chronic temporal lobe epilepsy. Exp. Neurol. 334, 113492 https://doi.org/10.1016/j.expneurol.2020.113492.
Li, D., Pi, W., Sun, Z., Liu, X., Jiang, J., 2022a. Ferroptosis and its role in cardiomyopathy. Biomed. Pharmacother. 153, 113279 https://doi.org/10.1016/j.biopha.2022.113279.
Li, J., Zhang, W., Cui, Z., Li, Z., Jiang, T., Meng, H., 2021. Epilepsy associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Front. Neurol. 12, 675816 https://doi.org/10.3389/fneur.2021.675816.
Liebert, A., Capon, W., Pang, V., Vila, D., Bicknell, B., McLachlan, C., Kiat, H., 2023. Photophysical mechanisms of photobiomodulation therapy as precision medicine. Biomedicines 11, 237. https://doi.org/10.3390/biomedicines11020237.
Lipko, N.B., 2022. Photobiomodulation: evolution and adaptation. Photobiomodul. Photomed. Laser Surg. 40, 213–233. https://doi.org/10.1089/photob.2021.0145.
Liu, C., Hu, Y., Zhou, J., Guan, Y., Wang, M., Qi, X., Wang, X., Zhang, H., Adilijiang, A., Li, T., Luan, G., 2022a. Retrospective clinical analysis of epilepsy treatment for children with drug-resistant epilepsy (A single-center experience). Brain Sci. 13, 14. https://doi.org/10.3390/brainsci13010014.
Liu, X., Sun, X., Sun, C., Zou, M., Chen, Y., Huang, J., Wu, L., Chen, W.-X., 2022b. Prevalence of epilepsy in autism spectrum disorders: a systematic review and meta-analysis. Autism 26, 33–50. https://doi.org/10.1177/13623613211045029.
Liu, L., Yang, S., Wang, H., 2021. α-Lipoic acid alleviates ferroptosis in the MPP+-induced PC12 cells via activating the PI3K/Akt/Nrf2 pathway. Cell Biol. Int. 45, 422–431. https://doi.org/10.1002/cbin.11505.
Lobo, F., Haase, J., Brandhorst, S., 2022. The effects of dietary interventions on brain aging and neurological diseases. Nutrients 14, 5086. https://doi.org/10.3390/nu14235086.
Lopriore, P., Gomes, F., Montano, V., Siciliano, G., Mancuso, M., 2022a. Mitochondrial epilepsy, a challenge for neurologists. Int. J. Mol. Sci. 23, 13216 https://doi.org/10.3390/ijms232113216.
Lopriore, P., Ricciarini, V., Siciliano, G., Mancuso, M., Montano, V., 2022b. Mitochondrial ataxias: molecular classification and clinical heterogeneity. Neurol. Int. 14, 337–356. https://doi.org/10.3390/neurolint14020028.
Löscher, W., 2017. Animal models of seizures and epilepsy: past, present, and future role for the discovery of antiseizure drugs. Neurochem. Res. 42, 1873–1888. https://doi.org/10.1007/s11064-017-2222-z.
Löscher, W., Klein, P., 2021. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. CNS Drugs 35, 935–963. https://doi.org/10.1007/s40263-021-00827-8.
Löscher, W., Stafstrom, C.E., 2023. Epilepsy and its neurobehavioral comorbidities: insights gained from animal models. Epilepsia 64, 54–91. https://doi.org/10.1111/epi.17433.
Löscher, W., 2021. Models of seizures and epilepsy: important tools in the discovery and evaluation of novel epilepsy therapies. Springer US, New York, NY, pp. 3–7. https://doi.org/10.1007/978-1-0716-1254-5_1.
Łukasiuk, K., Lasoń, W., 2023. Emerging molecular targets for anti-epileptogenic and epilepsy modifying drugs. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24032928.
Lv, S.-Y., He, S., Ling, X.-L., Wang, Y.-Q., Huang, C., Long, J.-R., Wang, J.-Q., Qin, Y., Wei, H., Yu, C.-Y., 2022. Review of lipoic acid: from a clinical therapeutic agent to various emerging biomaterials. Int. J. Pharm. 627, 122201 https://doi.org/10.1016/j.ijpharm.2022.122201.
Ma, Z.-X., Liu, Z., Xiong, H.-H., Zhou, Z.-P., Ouyang, L.-S., Xie, F.-K., Tang, Y.-M., Wu, Z.-D., Feng, Y., 2023. MicroRNAs: protective regulators for neuron growth and development. Neural Regen. Res. 18, 734–745. https://doi.org/10.4103/1673-5374.353481.
Maenner, M.J., Warren, Z., Williams, A.R., Amoakohene, E., Bakian, A.V., Bilder, D.A., Durkin, M.S., Fitzgerald, R.T., Furnier, S.M., Hughes, M.M., Ladd-Acosta, C.M., McArthur, D., Pas, E.T., Salinas, A., Vehorn, A., Williams, S., Esler, A., Grzybowski, A., Hall-Lande, J., Nguyen, R.H.N., Pierce, K., Zahorodny, W., Hudson, A., Hallas, L., Mancilla, K.C., Patrick, M., Shenouda, J., Sidwell, K., DiRienzo, M., Gutierrez, J., Spivey, M.H., Lopez, M., Pettygrove, S., Schwenk, Y.D., Washington, A., Shaw, K.A., 2023. Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2020. Morb. Mortal. Wkly. Rep. Surveill. Summ. 72, 1–14. https://doi.org/10.15585/mmwr.ss7202a1.
Magiorkinis, E., Sidiropoulou, K., Diamantis, A., 2010. Hallmarks in the history of epilepsy: epilepsy in antiquity. Epilepsy Behav. 17, 103–108. https://doi.org/10.1016/j.yebeh.2009.10.023.
Mameniškienė, R., Wolf, P., 2017. Epilepsia partialis continua: a review. Seizure 44, 74–80. https://doi.org/10.1016/j.seizure.2016.10.010.
Manea, M.M., Mincă, A., Dragoş, D., Tuţă, S., Popa, C., 2015. Friedreich's ataxia with epileptic seizures [WWW Document]. Acad.ro. URL https://acad.ro/sectii2002/proceedingsChemistry/doc2015-3s/art31_116.pdf (accessed 7.20.23).
Martinelli, D., 2022. Disorders of copper, zinc, and selenium metabolism. In: Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases. Springer International Publishing, pp. 607–623. https://doi.org/10.1007/978-3-030-67727-5_36.
Martinez, B., Peplow, P.V., 2023. MicroRNAs as potential biomarkers in temporal lobe epilepsy and mesial temporal lobe epilepsy. Neural Regen. Res. 18, 716–726. https://doi.org/10.4103/1673-5374.354510.
Matias, M., Santos, A.O., Silvestre, S., Alves, G., 2023. Fighting epilepsy with nanomedicines-is this the right weapon? Pharmaceutics 15, 306. https://doi.org/10.3390/pharmaceutics15020306.
Matricardi, S., Canafoglia, L., Ardissone, A., Moroni, I., Ragona, F., Ghezzi, D., Lamantea, E., Nardocci, N., Franceschetti, S., Granata, T., 2019. Epileptic phenotypes in children with early-onset mitochondrial diseases. Acta Neurol. Scand. 140, 184–193. https://doi.org/10.1111/ane.13130.
Mattson, M.P., Moehl, K., Ghena, N., Schmaedick, M., Cheng, A., 2018. Intermittent metabolic switching, neuroplasticity and brain health. Nat. Rev. Neurosci. 19, 81–94. https://doi.org/10.1038/nrn.2017.156.
Maurya, S.K., Gupta, S., Bakshi, A., Kaur, H., Jain, A., Senapati, S., Baghel, M.S., 2022. Targeting mitochondria in the regulation of neurodegenerative diseases: a comprehensive review. J. Neurosci. Res. 100, 1845–1861. https://doi.org/10.1002/jnr.25110.
Mavrogenis, A.F., Saranteas, T., Markatos, K., Kotsiou, A., Tesseromatis, C., 2019. Pharmacies for pain and trauma in ancient Greece. Int. Orthop. 43, 1529–1536. https://doi.org/10.1007/s00264-018-4219-x.
Mayo, J., Panahi, S., Roghani, A., Van Cott, A.C., Pugh, M.J., 2022. Treatment of epilepsy in the setting of cognitive decline in older adults. Curr. Treat. Options. Neurol. 24, 619–630. https://doi.org/10.1007/s11940-022-00740-5.
McElroy, T., Zeidan, R.S., Rathor, L., Han, S.M., Xiao, R., 2023. The role of mitochondria in the recovery of neurons after injury. Neural Regen. Res. 18, 317–318. https://doi.org/10.4103/1673-5374.343907.
McKee, J.L., Kaufman, M.C., Gonzalez, A.K., Fitzgerald, M.P., Massey, S.L., Fung, F., Kessler, S.K., Witzman, S., Abend, N.S., Helbig, I., 2023. Leveraging electronic medical record-embedded standardised electroencephalogram reporting to develop neonatal seizure prediction models: a retrospective cohort study. Lancet Digit. Health 5, e217–e226. https://doi.org/10.1016/S2589-7500(23)00004-3.
McKnight, D., Morales, A., Hatchell, K.E., Bristow, S.L., Bonkowsky, J.L., Perry, M.S., Berg, A.T., Borlot, F., Esplin, E.D., Moretz, C., Angione, K., Ríos-Pohl, L., Nussbaum, R.L., Aradhya, S., ELEVIATE Consortium, Haldeman-Englert, C.R., Levy, R.J., Parachuri, V.G., Lay-Son, G., de Montellano, D.J.D.-O., Ramirez-Garcia, M.A., Benítez Alonso, E.O., Ziobro, J., Chirita-Emandi, A., Felix, T.M., Kulasa-Luke, D., Megarbane, A., Karkare, S., Chagnon, S.L., Humberson, J.B., Assaf, M.J., Silva, S., Zarroli, K., Boyarchuk, O., Nelson, G.R., Palmquist, R., Hammond, K.C., Hwang, S.T.,

Boutlier, S.B., Nolan, M., Batley, K.Y., Chavda, D., Reyes-Silva, C.A., Miroshnikov, O., Zuccarelli, B., Amlie-Wolf, L., Wheless, J.W., Seinfeld, S., Kanhangad, M., Freeman, J.L., Monroy-Santoyo, S., Rodriguez-Vazquez, N., Ryan, M.M., Machie, M., Guerra, P., Hassan, M.J., Candee, M.S., Bupp, C.P., Park, K.L., Muller, E., 2nd, Lupo, P., Pedersen, R.C., Arain, A.M., Murphy, A., Schatz, K., Mu, W., Kalika, P.M., Plaza, L., Kellogg, M.A., Lora, E.G., Carson, R.P., Svystilnyk, V., Venegas, V., Luke, R.R., Jiang, H., Stetsenko, T., Dueñas-Roque, M.M., Trasmonte, J., Burke, R.J., Hurst, A.C. E., Smith, D.M., Massingham, L.J., Pisani, L., Costin, C.E., Ostrander, B., Filloux, F. M., Ananth, A.L., Mohamed, I.S., Nechai, A., Dao, J.M., Fahey, M.C., Aliu, E., Falchek, S., Press, C.A., Treat, L., Eschbach, K., Starks, A., Kammeyer, R., Bear, J.J., Jacobson, M., Chernuha, V., Meibos, B., Wong, K., Sweney, M.T., Espinoza, A.C., Van Orman, C.B., Weinstock, A., Kumar, A., Soler-Alfonso, C., Nolan, D.A., Raza, M., Rojas Carrion, M.D., Chari, G., Marsh, E.D., Shiloh-Malawsky, Y., Parikh, S., Gonzalez-Giraldo, E., Fulton, S., Sogawa, Y., Burns, K., Malets, M., Montiel Blanco, J. D., Habela, C.W., Wilson, C.A., Guzmán, G.G., Pavliuk, M., 2022. Genetic testing to inform epilepsy treatment management from an international study of clinical practice. JAMA Neurol. 79, 1267–1276. https://doi.org/10.1001/jamaneurol.2022.3651.

Metsla, K., Kirss, S., Laks, K., Sildnik, G., Palgi, M., Palumaa, T., Tõugu, V., Palumaa, P., 2022. α-Lipoic acid has the potential to normalize copper metabolism, which is dysregulated in Alzheimer's disease. J. Alzheimers Dis. 85, 715–728. https://doi.org/10.3233/JAD-215026.

Migdady, I., Rosenthal, E.S., Cock, H.R., 2022. Management of status epilepticus: a narrative review. Anaesthesia 77 (Suppl. 1), 78–91. https://doi.org/10.1111/anae.15606.

Minich, W.B., 2022. Selenium metabolism and biosynthesis of selenoproteins in the human body. Biochemistry (Mosc.) 87, S168–S177. https://doi.org/10.1134/s0006297922140139.

Monzel, A.S., Enríquez, J.A., Picard, M., 2023. Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. Nat. Metab. 5, 546–562. https://doi.org/10.1038/s42255-023-00783-1.

Moos, W.H., Faller, D.V., Glavas, I.P., Harpp, D.N., Irwin, M.H., Kanara, I., Pinkert, C.A., Powers, W.R., Steliou, K., Vavvas, D.G., Kodukula, K., 2017. Epigenetic treatment of neurodegenerative ophthalmic disorders: an eye toward the future. Biores. Open Access 6, 169–181. https://doi.org/10.1089/biores.2017.0036.

Moos, W.H., Faller, D.V., Glavas, I.P., Harpp, D.N., Irwin, M.H., Kanara, I., Pinkert, C.A., Powers, W.R., Steliou, K., Vavvas, D.G., Kodukula, K., 2018. A new approach to treating neurodegenerative otologic disorders. Biores. Open Access 7, 107–115. https://doi.org/10.1089/biores.2018.0017.

Moos, W.H., Faller, D.V., Glavas, I.P., Harpp, D.N., Kanara, I., Mavrakis, A.N., Pernokas, J., Pernokas, M., Pinkert, C.A., Powers, W.R., Sampani, K., Steliou, K., Vavvas, D.G., Zamboni, R.J., Kodukula, K., Chen, X., 2020. Klotho pathways, myelination disorders, neurodegenerative diseases, and epigenetic drugs. Biores. Open Access 9, 94–105. https://doi.org/10.1089/biores.2020.0004.

Moos, W.H., Faller, D.V., Glavas, I.P., Harpp, D.N., Kamperi, N., Kanara, I., Kodukula, K., Mavrakis, A.N., Pernokas, J., Pernokas, M., Pinkert, C.A., Powers, W.R., Steliou, K., Tamvakopoulos, C., Vavvas, D.G., Zamboni, R.J., Sampani, K., 2021. Pathogenic mitochondrial dysfunction and metabolic abnormalities. Biochem. Pharmacol. 193, 114809 https://doi.org/10.1016/j.bcp.2021.114809.

Moos, W.H., Faller, D.V., Glavas, I.P., Harpp, D.N., Kamperi, N., Kanara, I., Kodukula, K., Mavrakis, A.N., Pernokas, J., Pernokas, M., Pinkert, C.A., Powers, W.R., Sampani, K., Steliou, K., Tamvakopoulos, C., Vavvas, D.G., Zamboni, R.J., Chen, X., 2022. Treatment and prevention of pathological mitochondrial dysfunction in retinal degeneration and in photoreceptor injury. Biochem. Pharmacol. 203, 115168 https://doi.org/10.1016/j.bcp.2022.115168.

Mosilhy, E.A., Alshial, E.E., Eltaras, M.M., Rahman, M.M.A., Helmy, H.I., Elazoul, A.H., Hamdy, O., Mohammed, H.S., 2022. Non-invasive transcranial brain modulation for neurological disorders treatment: a narrative review. Life Sci. 307, 120869 https://doi.org/10.1016/j.lfs.2022.120869.

Mu, C., Tompkins, T.A., Rho, J.M., Scantlebury, M.H., Shearer, J., 2022. Gut-based manipulations spur hippocampal mitochondrial bioenergetics in a model of pediatric epilepsy. Biochim. Biophys. Acta Mol. basis Dis. 1868, 166446 https://doi.org/10.1016/j.bbadis.2022.166446.

Mula, M., 2022. Suicidality and antiepileptic drugs in people with epilepsy: an update. Expert Rev. Neurother. 22, 405–410. https://doi.org/10.1080/14737175.2022.2064744.

Muramoto, O., 2018. Solving the Socratic problem—a contribution from medicine. Mous. J. Class. Assoc. Can. 15, 445–473. https://doi.org/10.3138/mous.15.3.

Myers, K.A., Scheffer, I.E., 2022. Precision medicine approaches for infantile-onset developmental and epileptic encephalopathies. Annu. Rev. Pharmacol. Toxicol. 62, 641–662. https://doi.org/10.1146/annurev-pharmtox-052120-084449.

Naddaf, M., 2023. How virtual models of the brain could transform epilepsy surgery. Nature 616, 227–228. https://doi.org/10.1038/d41586-023-00990-6.

Naderi, M., Puar, P., Zonouzi-Marand, M., Chivers, D.P., Niyogi, S., Kwong, R.W.M., 2021. A comprehensive review on the neuropathophysiology of selenium. Sci. Total Environ. 767, 144329 https://doi.org/10.1016/j.scitotenv.2020.144329.

Nayeri, N., Li, P., Górecki, K., Lindkvist-Petersson, K., Gourdon, P., 2023. Principles to recover copper-conducting CTR proteins for the purpose of structural and functional studies. Protein Expr. Purif. 203, 106213 https://doi.org/10.1016/j.pep.2022.106213.

Nevitt, S.J., Sudell, M., Cividini, S., Marson, A.G., Tudur Smith, C., 2022. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst. Rev. 4, CD011412 https://doi.org/10.1002/14651858.CD011412.pub4.

Nicholson, J.L., Toh, P., Alfulaij, N., Berry, M.J., Torres, D.J., 2022. New insights on selenoproteins and neuronal function. Free Radic. Biol. Med. 190, 55–61. https://doi.org/10.1016/j.freeradbiomed.2022.07.021.

Nickels, K.C., Wong-Kisiel, L.C., Moseley, B.D., Wirrell, E.C., 2012. Temporal lobe epilepsy in children. Epilepsy Res. Treat. 2012, 1–16. https://doi.org/10.1155/2012/849540.

Niesvizky-Kogan, I., Bass, M., Goldenholz, S.R., Goldenholz, D.M., 2022. Focal cooling for drug-resistant epilepsy: a review. JAMA Neurol. 79, 937–944. https://doi.org/10.1001/jamaneurol.2022.1936.

NINDS, 2023. PANAChE current screening [WWW Document], n.d. Nih.gov. URL https://panache.ninds.nih.gov/Home/CurrentModels (accessed 7.25.23).

Ning, S., Jorfi, M., Patel, S.R., Kim, D.Y., Tanzi, R.E., 2022. Neurotechnological approaches to the diagnosis and treatment of Alzheimer's disease. Front. Neurosci. 16, 854992 https://doi.org/10.3389/fnins.2022.854992.

Nunes, L.G.A., Pitts, M.W., Hoffmann, P.R., 2022. Selenoprotein I (selenoi) as a critical enzyme in the central nervous system. Arch. Biochem. Biophys. 729, 109376 https://doi.org/10.1016/j.abb.2022.109376.

O'Neal, T.B., Shrestha, S., Singh, H., Osagie, I., Ben-Okafor, K., Cornett, E.M., Kaye, A.D., 2022. Sudden unexpected death in epilepsy. Neurol. Int. 14, 600–613. https://doi.org/10.3390/neurolint14030048.

Okun, M.S., Mayberg, H.S., DeLong, M.R., 2023. Muhammad Ali and young-onset idiopathic Parkinson disease-the missing evidence. JAMA Neurol. 80, 5–6. https://doi.org/10.1001/jamaneurol.2022.3584.

Olson, H.E., Daniels, C.I., Haviland, I., Swanson, L.C., Greene, C.A., Denny, A.M.M., Demarest, S.T., Pestana-Knight, E., Zhang, X., Moosa, A.N., Fidell, A., Weisenberg, J. L., Suter, B., Fu, C., Neul, J.L., Percy, A.K., Marsh, E.D., Benke, T.A., Poduri, A., 2021. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J. Neurodev. Disord. 13, 40. https://doi.org/10.1186/s11689-021-09384-z.

Ou, M., Jiang, Y., Ji, Y., Zhou, Q., Du, Z., Zhu, H., Zhou, Z., 2022. Role and mechanism of ferroptosis in neurological diseases. Mol. Metab. 61, 101502 https://doi.org/10.1016/j.molmet.2022.101502.

OUPblog, 2015. The history of epilepsy: an interactive timeline [WWW Document]. OUPblog. URL https://blog.oup.com/2015/03/purple-day-history-epilepsy-timeline/ (accessed 7.17.23).

Pacheu-Grau, D., Rucktäschel, R., Deckers, M., 2018. Mitochondrial dysfunction and its role in tissue-specific cellular stress. Cell Stress 2, 184–199. https://doi.org/10.15698/cst2018.07.147.

Padamsey, Z., Rochefort, N.L., 2023. Paying the brain's energy bill. Curr. Opin. Neurobiol. 78, 102668 https://doi.org/10.1016/j.conb.2022.102668.

Pallardó, F.V., Pagano, G., Rodríguez, L.R., Gonzalez-Cabo, P., Lyakhovich, A., Trifuoggi, M., 2021. Friedreich Ataxia: current state-of-the-art, and future prospects for mitochondrial-focused therapies. Transl. Res. 229, 135–141. https://doi.org/10.1016/j.trsl.2020.08.009.

Pan, W.-T., Liu, P.-M., Ma, D., Yang, J.-J., 2023. Advances in photobiomodulation for cognitive improvement by near-infrared derived multiple strategies. J. Transl. Med. 21, 135. https://doi.org/10.1186/s12967-023-03988-w.

Panebianco, M., Rigby, A., Marson, A.G., 2022. Vagus nerve stimulation for focal seizures. Cochrane Database Syst. Rev. 7, CD002896 https://doi.org/10.1002/14651858.CD002896.pub3.

Panteliadis, C.P., 2021. Historical overview of electroencephalography: from antiquity to the beginning of the 21st century. J. Brain Neurol. Disord. 3, 1–10. https://doi.org/10.5281/ZENODO.5359323.

Panteliadis, C.P., Vassilyadi, P., Fehlert, J., Hagel, C., 2017. Historical documents on epilepsy: From antiquity through the 20th century. Brain Dev. 39, 457–463. https://doi.org/10.1016/j.braindev.2017.02.002.

Parissis, D., Dimitriou, M., Ioannidis, P., 2022. Genetic causes of acute encephalopathy in adults: beyond inherited metabolic and epileptic disorders. Neurol. Sci. 43, 1617–1626. https://doi.org/10.1007/s10072-022-05899-y.

Patel, P., Moshé, S.L., 2020. The evolution of the concepts of seizures and epilepsy: What's in a name? Epilepsia Open 5, 22–35. https://doi.org/10.1002/epi4.12375.

Patel, T., Patel, K., 2022. The annual epilepsy review. InnovAiT 15, 286–293. https://doi.org/10.1177/17557380221078041.

Patergnani, S., Morciano, G., Carinci, M., Leo, S., Pinton, P., Rimessi, A., 2022. The "mitochondrial stress responses": the "Dr. Jekyll and Mr. Hyde" of neuronal disorders. Neural Regen. Res. 17, 2563–2575. https://doi.org/10.4103/1673-5374.339473.

Patrikelis, P., Messinis, L., Folia, V., Nasios, G., Alexoudi, A., Verentzioti, A., Korfias, S., Kimiskidis, V., Gatzonis, S., 2023. Epilepsy and the "dark" literature of the Greek novelist Demosthenes Voutyras: an outstanding epileptic personality. Arq. Neuropsiquiatr. 81, 384–391. https://doi.org/10.1055/s-0042-1758443.

Peng, J., Ramatchandirin, B., Pearah, A., Maheshwari, A., He, L., 2022. Development and functions of mitochondria in early life. Newborn (Clarksville) 1, 131–141. https://doi.org/10.5005/jp-journals-11002-0013.

Pepi, C., De Benedictis, A., Rossi-Espagnet, M.C., Cappelletti, S., Da Rold, M., Falcicchio, G., Vigevano, F., Marras, C.E., Specchio, N., De Palma, L., 2022. Hemispherotomy in infants with hemimegalencephaly: Long-term seizure and developmental outcome in early treated patients. Brain Sci. 13 https://doi.org/10.3390/brainsci13010073.

Perucca, E., 2021. The pharmacological treatment of epilepsy: recent advances and future perspectives. Acta Epileptologica 3. https://doi.org/10.1186/s42494-021-00055-z.

Perucca, P., Gotman, J., 2022. Delineating the epileptogenic zone: spikes versus oscillations. Lancet Neurol. 21, 949–951. https://doi.org/10.1016/S1474-4422(22)00396-9.

Perucca, E., Perucca, P., White, H.S., Wirrell, E.C., 2023. Drug resistance in epilepsy. Lancet Neurol. 22, 723–734. https://doi.org/10.1016/s1474-4422(23)00151-5.
Pickrell, W.O., Fry, A.E., 2023. Epilepsy genetics: a practical guide for adult neurologists. Pract. Neurol. 23, 111–119. https://doi.org/10.1136/pn-2022-003623.
Pinkert, C.A., 2014. Transgenic Animal Technology: A Laboratory Handbook, 3rd ed. Elsevier Science Publishing. https://doi.org/10.1016/C2012-0-07277-8.
Pinto, L.F., de Oliveira, J.P.S., Midon, A.M., 2022. Status epilepticus: review on diagnosis, monitoring and treatment. Arq. Neuropsiquiatr. 80, 193–203. https://doi.org/10.1590/0004-282X-ANP-2022-S113.
Pitkänen, A., Löscher, W., Vezzani, A., Becker, A.J., Simonato, M., Lukasiuk, K., Gröhn, O., Bankstahl, J.P., Friedman, A., Aronica, E., Gorter, J.A., Ravizza, T., Sisodiya, S.M., Kokaia, M., Beck, H., 2016. Advances in the development of biomarkers for epilepsy. Lancet Neurol. 15, 843–856. https://doi.org/10.1016/S1474-4422(16)00112-5.
Poor, T.A., Chandel, N.S., 2023. SnapShot: mitochondrial signaling. Mol. Cell 83, 1012–1012.e1. https://doi.org/10.1016/j.molcel.2023.01.008.
Prentice, R.N., Rizwan, S.B., 2023. Translational considerations in the development of intranasal treatments for epilepsy. Pharmaceutics 15. https://doi.org/10.3390/pharmaceutics15010233.
Pressler, R.M., Lagae, L., 2020. Why we urgently need improved seizure and epilepsy therapies for children and neonates. Neuropharmacology 170, 107854. https://doi.org/10.1016/j.neuropharm.2019.107854.
Prud'homme, G.J., Kurt, M., Wang, Q., 2022. Pathobiology of the Klotho antiaging protein and therapeutic considerations. Front. Aging 3, 931331. https://doi.org/10.3389/fragi.2022.931331.
Qi, Y.-L., Wang, H.-R., Chen, L.-L., Duan, Y.-T., Yang, S.-Y., Zhu, H.-L., 2022. Recent advances in small-molecule fluorescent probes for studying ferroptosis. Chem. Soc. Rev. 51, 7752–7778. https://doi.org/10.1039/d1cs01167g.
Rakshit, D., Nayak, S., Kundu, S., Angelopoulou, E., Pyrgelis, E.-S., Piperi, C., Mishra, A., 2023. The pharmacological activity of garlic (*Allium sativum*) in Parkinson's disease: from molecular mechanisms to the therapeutic potential. ACS Chem. Nerosci. 14, 1033–1044. https://doi.org/10.1021/acschemneuro.2c00789.
Ralston, N.V.C., 2023. Concomitant selenoenzyme inhibitor exposures as etiologic contributors to disease: implications for preventative medicine. Arch. Biochem. Biophys. 733, 109469 https://doi.org/10.1016/j.abb.2022.109469.
Rektor, I., Schachter, S.C., Arzy, S., Baloyannis, S.J., Bazil, C., Brázdil, M., Engel Jr, J., Helmstaedter, G., Hesdorffer, D.C., Jones-Gotman, M., Kesner, L., Komárek, V., Krämer, G., Leppik, I.E., Mann, M.W., Mula, M., Risse, G.L., Stoker, G.W., Kasteleijn-Nolst Trenité, D.G.A., Trimble, M., Tyrliková, I., Korczyn, A.D., 2013. Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1). Epilepsy Behav. 28, 261–282. https://doi.org/10.1016/j.yebeh.2013.03.011.
Ren, J.-X., Sun, X., Yan, X.-L., Guo, Z.-N., Yang, Y., 2020. Ferroptosis in neurological diseases. Front. Cell. Neurosci. 14, 218. https://doi.org/10.3389/fncel.2020.00218.
Reynolds, E.H., 2020. Epilepsy and neuroscience: evolution and interaction. Front. Neuroanat. 14, 25 https://doi.org/10.3389/fnana.2020.00025.
Rho, J.M., Boison, D., 2022. The metabolic basis of epilepsy. Nat. Rev. Neurol. 18, 333–347. https://doi.org/10.1038/s41582-022-00651-8.
Riikonen, R., 2023. Biochemical mechanisms in pathogenesis of infantile epileptic spasm syndrome. Seizure 105, 1–9. https://doi.org/10.1016/j.seizure.2023.01.004.
Ríos, C., Aguirre-Aranda, I., Avendaño-Estrada, A., Ángel Ávila-Rodríguez, M., Manjarrez-Marmolejo, J., Franco-Pérez, J., Islas-Cortez, M., Ruiz-Diaz, A., Méndez-Armenta, M., Diaz-Ruiz, A., 2023. Characterization of the anticonvulsant effect of dapsone on metabolic activity assessed by [^{18}F]FDG -PET after kainic acid-induced status epilepticus in rats. Brain Res. 1803, 148227 https://doi.org/10.1016/j.brainres.2022.148227.
Ristić, A.J., Sokić, D., Baščarević, V., Spasić, S., Vojvodić, N., Savić, S., Raičević, S., Kovačević, M., Savić, D., Spasojević, I., 2014. Metals and electrolytes in sclerotic hippocampi in patients with drug-resistant mesial temporal lobe epilepsy. Epilepsia 55. https://doi.org/10.1111/epi.12593.
Rizwan, G., Sabetghadam, A., Wu, C., Liu, J., Zhang, L., Reid, A.Y., 2019. Increased seizure susceptibility in a mouse model of neurofibromatosis type 1. Epilepsy Res. 156, 106190 https://doi.org/10.1016/j.eplepsyres.2019.106190.
Rogawski, M.A., 2021. Antiseizure drugs. Basic & Clinical Pharmacology. McGrawHill, Duluth, MN.
Ruan, L., Li, H., Zhang, J., Zhou, M., Huang, H., Dong, J., Li, J., Zhao, F., Wu, Z., Chen, J., Chai, Z., Hu, Y., 2023. Chemical transformation and cytotoxicity of iron oxide nanoparticles (IONPs) accumulated in mitochondria. Talanta 251, 123770. https://doi.org/10.1016/j.talanta.2022.123770.
Salehi, B., Berkay Yılmaz, Y., Antika, G., Boyunegmez Tumer, T., Fawzi Mahomoodally, M., Lobine, D., Akram, M., Riaz, M., Capanoglu, E., Sharopov, F., Martins, N., Cho, W.C., Sharifi-Rad, J., 2019. Insights on the use of α-lipoic acid for therapeutic purposes. Biomolecules 9, 356. https://doi.org/10.3390/biom9080356.
Salehpour, F., Khademi, M., Bragin, D.E., DiDuro, J.O., 2022. Photobiomodulation therapy and the glymphatic system: promising applications for augmenting the brain lymphatic drainage system. Int. J. Mol. Sci. 23 https://doi.org/10.3390/ijms23062975.
Saneto, R.P., 2017. Epilepsy and mitochondrial dysfunction: a single center's experience. J. Inborn Errors Metab. Screen. 5, 232640981773301 https://doi.org/10.1177/2326409817733012.
Saris, C.G.J., Timmers, S., 2022. Ketogenic diets and Ketone suplementation: a strategy for therapeutic intervention. Front. Nutr. 9, 947567 https://doi.org/10.3389/fnut.2022.947567.
Schiller, K., Berrahmoune, S., Dassi, C., Corriveau, I., Ayash, T.A., Osterman, B., Poulin, C., Shevell, M.I., Simard-Tremblay, E., Sébire, G., Myers, K.A., 2023. Randomized placebo-controlled crossover trial of memantine in children with epileptic encephalopathy. Brain 146, 873–879. https://doi.org/10.1093/brain/awac380.
Schomburg, L., 2022. Selenoprotein P - Selenium transport protein, enzyme and biomarker of selenium status. Free Radic. Biol. Med. 191, 150–163. https://doi.org/10.1016/j.freeradbiomed.2022.08.022.
Sebastian, A., 2018. A Dictionary of the History of Medicine, 1st ed. Routledge, London, England. https://www.perlego.com/book/1580121/a-dictionary-of-the-history-of-medicine-pdf.
Servick, K., 2022. Window of opportunity. Science 375, 256–259. https://doi.org/10.1126/science.ada0099.
Sethi, N., Kaura, S., Dilbaghi, N., Parle, M., Pal, M., 2014. Garlic: a pungent wonder from nature. Int. Res. J. Pharm. 5, 523–529. https://doi.org/10.7897/2230-8407.0507106.
Sewell, E.K., Hamrick, S.E.G., Patel, R.M., Bennett, M., Tolia, V.N., Ahmad, K.A., 2022. Association between anti-seizure medication and outcomes in infants. J. Perinatol. 42, 359–364. https://doi.org/10.1038/s41372-021-01240-1.
Shahar, E., Attias, U., Savulescu, D., Genizin, J., Gavish, M., Nagler, R., 2014. Oxidative stress, metalloproteinase and LDH in children with intractable and non-intractable epilepsy as reflected in salivary analysis. Epilepsy Res. 108, 117–124. https://doi.org/10.1016/j.eplepsyres.2013.10.003.
Shan, Y., Ni, Y., Gao, Z., 2020. Pannexin-1 channel regulates ATP release in epilepsy. Neurochem. Res. 45, 965–971. https://doi.org/10.1007/s11064-020-02981-9.
Shao, E., Chang, C.-W., Li, Z., Yu, X., Ho, K., Zhang, M., Wang, X., Simms, J., Lo, I., Speckart, J., Holtzman, J., Yu, G.-Q., Roberson, E.D., Mucke, L., 2022b. TAU ablation in excitatory neurons and postnatal TAU knockdown reduce epilepsy, SUDEP, and autism behaviors in a Dravet syndrome model. Sci. Transl. Med. 14, eabm5527 https://doi.org/10.1126/scitranslmed.abm5527.
Shao, C., Liu, Y., Chen, Z., Qin, Y., Wang, X., Wang, X., Yan, C., Zhu, H.-L., Zhao, J., Qian, Y., 2022a. 3D two-photon brain imaging reveals dihydroartemisinin exerts antiepileptic effects by modulating iron homeostasis. Cell Chem. Biol. 29, 43–56. https://doi.org/10.1016/j.chembiol.2021.12.006.
Sharifi-Rad, J., Mnayer, D., Tabanelli, G., Stojanović-Radić, Z.Z., Sharifi-Rad, M., Yousaf, Z., Vallone, L., Setzer, W.N., Iriti, M., 2016. Plants of the genus *Allium* as antibacterial agents: from tradition to pharmacy. Cell. Mol. Biol. (Noisy-le-Grand) 62, 57–68. https://doi.org/10.14715/cmb/2016.62.9.10.
Shlobin, N.A., Sander, J.W., 2022. The need for a pragmatic seizure classification in clinical trials. Epilepsia 63, 1279–1280. https://doi.org/10.1111/epi.17218.
Shnayder, N.A., Grechkina, V.V., Khasanova, A.K., Bochanova, E.N., Dontceva, E.A., Petrova, M.M., Asadullin, A.R., Shipulin, G.A., Altynbekov, K.S., Al-Zamil, M., Nasyrova, R.F., 2023. Therapeutic and toxic effects of valproic acid metabolites. Metabolites 13, 134. https://doi.org/10.3390/metabo13010134.
Singewald, N., Sartori, S.B., Reif, A., Holmes, A., 2023. Alleviating anxiety and taming trauma: novel pharmacotherapeutics for anxiety disorders and posttraumatic stress disorder. Neuropharmacology 226, 109418. https://doi.org/10.1016/j.neuropharm.2023.109418.
Singh, S., Singh, T.G., 2021. Emerging perspectives on mitochondrial dysfunctioning and inflammation in epileptogenesis. Inflamm. Res. 70, 1027–1042. https://doi.org/10.1007/s00011-021-01511-9.
Singh, S., Singh, T.G., Rehni, A.K., Sharma, V., Singh, M., Kaur, R., 2021. Reviving mitochondrial bioenergetics: a relevant approach in epilepsy. Mitochondrion 58, 213–226. https://doi.org/10.1016/j.mito.2021.03.009.
Sivcev, S., Kudova, E., Zemkova, H., 2023. Neurosteroids as positive and negative allosteric modulators of ligand-gated ion channels: P2X receptor perspective. Neuropharmacology 234, 109542. https://doi.org/10.1016/j.neuropharm.2023.109542.
Smirnova, J., Kabin, E., Järving, I., Bragina, O., Tõugu, V., Plitz, T., Palumaa, P., 2018. Copper(I)-binding properties of de-coppering drugs for the treatment of Wilson disease. α-Lipoic acid as a potential anti-copper agent. Sci. Rep. 8, 1463. https://doi.org/10.1038/s41598-018-19873-2.
Smith, L.A., Erskine, D., Blain, A., Taylor, R.W., McFarland, R., Lax, N.Z., 2022. Delineating selective vulnerability of inhibitory interneurons in Alpers' syndrome. Neuropathol. Appl. Neurobiol. 48, e12833 https://doi.org/10.1111/nan.12833.
Song, Y., Wu, Z., Xue, H., Zhao, P., 2022. Ferroptosis is involved in regulating perioperative neurocognitive disorders: emerging perspectives. J. Neuroinflammation 19, 219. https://doi.org/10.1186/s12974-022-02570-3.
Sourbron, J., Auvin, S., Arzimanoglou, A., Cross, J.H., Hartmann, H., Pressler, R., Riney, K., Sugai, K., Wilmshurst, J.M., Yozawitz, E., Lagae, L., 2023. Medical treatment in infants and young children with epilepsy: Off-label use of antiseizure medications. Survey Report of ILAE Task Force Medical Therapies in Children. Epilepsia Open 8, 77–89. https://doi.org/10.1002/epi4.12666.
Stacpoole, P.W., McCall, C.E., 2023. The pyruvate dehydrogenase complex: Life's essential, vulnerable and druggable energy homeostat. Mitochondrion 70, 59–102. https://doi.org/10.1016/j.mito.2023.02.007.
Steliou, K., Faller, D.V., Pinkert, C.A., Irwin, M.H., Moos, W.H., 2015. Bioprotective carnitinoids: lipoic acid, butyrate, and mitochondria-targeting to treat radiation injury: mitochondrial drugs come of age: Bioprotective carnitinoids. Drug Dev. Res. 76, 167–175. https://doi.org/10.1002/ddr.21258.
Stepanić, V., Kučerová-Chlupáčová, M., 2023. Review and chemoinformatic analysis of ferroptosis modulators with a focus on natural plant products. Molecules 28, 475. https://doi.org/10.3390/molecules28020475.
Steriade, C., Sperling, M.R., DiVentura, B., Lozano, M., Shellhaas, R.A., Kessler, S.K., Dlugos, D., French, J., 2022. Proposal for an updated seizure classification framework in clinical trials. Epilepsia 63, 565–572. https://doi.org/10.1111/epi.17120.

Stockwell, B.R., 2022. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 185, 2401–2421. https://doi.org/10.1016/j.cell.2022.06.003.

Stokes, J.C., Bornstein, R.L., James, K., Park, K.Y., Spencer, K.A., Vo, K., Snell, J.C., Johnson, B.M., Morgan, P.G., Sedensky, M.M., Baertsch, N.A., Johnson, S.C., 2022. Leukocytes mediate disease pathogenesis in the *Ndufs4*(KO) mouse model of Leigh syndrome. JCI Insight 7. https://doi.org/10.1172/jci.insight.156522.

Stowe, R.C., Sun, Q., Elsea, S.H., Scaglia, F., 2018. LIPT1 deficiency presenting as early infantile epileptic encephalopathy, Leigh disease, and secondary pyruvate dehydrogenase complex deficiency. Am. J. Med. Genet. A 176, 1184–1189. https://doi.org/10.1002/ajmg.a.38654.

Sun, H., Li, X., Guo, Q., Liu, S., 2022. Research progress on oxidative stress regulating different types of neuronal death caused by epileptic seizures. Neurol. Sci. 43, 6279–6298. https://doi.org/10.1007/s10072-022-06302-6.

Szczurowska, E., Szánti-Pintér, E., Chetverikov, N., Randáková, A., Kudová, E., Jakubík, J., 2022. Modulation of muscarinic signalling in the central nervous system by steroid hormones and neurosteroids. Int. J. Mol. Sci. 24, 507 https://doi.org/10.3390/ijms24010507.

Tan, Q.Y., Kundap, U.P., Kumari, Y., Shaikh, M.F., 2015. A review on natural therapy for seizure disorders. Pharm. Pharmacol. Int. J. 3, 255–259. https://doi.org/10.15406/ppij.2015.03.00051.

Tang, D., Chen, X., Kroemer, G., 2022. Cuproptosis: a copper-triggered modality of mitochondrial cell death. Cell Res. 32, 417–418. https://doi.org/10.1038/s41422-022-00653-7.

Taquet, M., Devinsky, O., Cross, J.H., Harrison, P.J., Sen, A., 2023. Incidence of epilepsy and seizures over the first 6 months after a COVID-19 diagnosis: a retrospective cohort study. Neurology 100, e790–e799. https://doi.org/10.1212/WNL.0000000000201595.

The Lancet Neurology, 2022. Epilepsy syndromes: an essential piece of the puzzle. Lancet Neurol. 21, 577. https://doi.org/10.1016/S1474-4422(22)00226-5.

Tiberi, J., Segatto, M., Fiorenza, M.T., La Rosa, P., 2023. Apparent opportunities and hidden pitfalls: The conflicting results of restoring NRF2-regulated redox metabolism in friedreich's ataxia pre-clinical models and clinical trials. Biomedicines 11, 1293. https://doi.org/10.3390/biomedicines11051293.

Timoshnikov, V.A., Selyutina, O.Y., Polyakov, N.E., Didichenko, V., Kontoghiorghes, G. J., 2022. Mechanistic insights of Chelator complexes with essential transition metals: antioxidant/pro-oxidant activity and applications in medicine. Int. J. Mol. Sci. 23, 1247 https://doi.org/10.3390/ijms23031247.

Toncheva, D., Karachanak-Yankova, S., Marinova, M., Borovska, P., Serbezov, D., 2023. Susceptibility to neurodegenerative disorders: Insights from paleogenomic data 93. Hum. Biol. Open Access Pre-Prints 202. https://digitalcommons.wayne.edu/humbiol_preprints/202.

Topalovic, U., Barclay, S., Ling, C., Alzuhair, A., Yu, W., Hokhikyan, V., Chandrakumar, H., Rozgic, D., Jiang, W., Basir-Kazeruni, S., Maoz, S.L., Inman, C.S., Stangl, M., Gill, J., Bari, A., Fallah, A., Eliashiv, D., Pouratian, N., Fried, I., Suthana, N., Markovic, D., 2023. A wearable platform for closed-loop stimulation and recording of single-neuron and local field potential activity in freely moving humans. Nat. Neurosci. 26, 517–527. https://doi.org/10.1038/s41593-023-01260-4.

Torres-Martinez, N., Chabardes, S., Mitrofanis, J., 2023. Lights for epilepsy: can photobiomodulation reduce seizures and offer neuroprotection? Neural Regen. Philos. Phenomenol. Res. 18, 1423–1426. https://doi.org/10.4103/1673-5374.360288.

Treadwell, J.R., Kessler, S.K., Wu, M., Abend, N.S., Massey, S.L., Tsou, A.Y., 2023. Pharmacologic and dietary treatments for epilepsies in children aged 1–36 months: a systematic review. Neurology 100, e16–e27. https://doi.org/10.1212/WNL.0000000000201026.

Trigo, D., Vitória, J.J., da Cruz, E., Silva, O.A.B., 2023. Novel therapeutic strategies targeting mitochondria as a gateway in neurodegeneration. Neural Regen. Res. 18, 991–995. https://doi.org/10.4103/1673-5374.355750.

Trinka, E., 2023. Phenobarbital in Status epilepticus - rediscovery of an effective drug. Epilepsy Behav. 141, 109104 https://doi.org/10.1016/j.yebeh.2023.109104.

Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A.O., Scheffer, I.E., Shinnar, S., Shorvon, S., Lowenstein, D.H., 2015. A definition and classification of status epilepticus - report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 56, 1515–1523. https://doi.org/10.1111/epi.13121.

Tsang, T., Davis, C.I., Brady, D.C., 2021. Copper biology. Curr. Biol. 31, R421–R427. https://doi.org/10.1016/j.cub.2021.03.054.

Tsvetkov, P., Coy, S., Petrova, B., Dreishpoon, M., Verma, A., Abdusamad, M., Rossen, J., Joesch-Cohen, L., Humeidi, R., Spangler, R.D., Eaton, J.K., Frenkel, E., Kocak, M., Corsello, S.M., Lutsenko, S., Kanarek, N., Santagata, S., Golub, T.R., 2022. Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375, 1254–1261. https://doi.org/10.1126/science.abf0529.

Turovsky, E.A., Mal'tseva, V.N., Sarimov, R.M., Simakin, A.V., Gudkov, S.V., Plotnikov, E.Y., 2022. Features of the cytoprotective effect of selenium nanoparticles on primary cortical neurons and astrocytes during oxygen-glucose deprivation and reoxygenation. Sci. Rep. 12, 1710. https://doi.org/10.1038/s41598-022-05674-1.

Tveit, J., Aurlien, H., Plis, S., Calhoun, V.D., Tatum, W.O., Schomer, D.L., Arntsen, V., Cox, F., Fahoum, F., Gallentine, W.B., Gardella, E., Hahn, C.D., Husain, A.M., Kessler, S., Kural, M.A., Nascimento, F.A., Tankisi, H., Ulvin, L.B., Wennberg, R., Beniczky, S., 2023. Automated interpretation of clinical electroencephalograms using Artificial Intelligence. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2023.1645.

Urbizu, A., Arnaldo, L., Beyer, K., 2023. Obtaining miRNA from saliva-comparison of sampling and purification methods. Int. J. Mol. Sci. 24, 2386 https://doi.org/10.3390/ijms24032386.

Urquhart, L., 2022. FDA new drug approvals in Q1 2022. Nat. Rev. Drug Discov. 21, 329. https://doi.org/10.1038/d41573-022-00063-9.

Urzì Brancati, V., Pinto Vraca, T., Minutoli, L., Pallio, G., 2023. Polymorphisms affecting the response to novel antiepileptic drugs. Int. J. Mol. Sci. 24, 2535 https://doi.org/10.3390/ijms24032535.

Usacheva, A.M., Chernikov, A.V., Karmanova, E.E., Bruskov, V.I., 2022. Pharmacological aspects of the use of lipoic acid (review). Pharm. Chem. J. 55, 1138–1146. https://doi.org/10.1007/s11094-022-02549-7.

Valiente-Pallejà, A., Tortajada, J., Bulduk, B.K., Vilella, E., Garrabou, G., Muntané, G., Martorell, L., 2022. Comprehensive summary of mitochondrial DNA alterations in the postmortem human brain: a systematic review. EBioMedicine 76, 103815. https://doi.org/10.1016/j.ebiom.2022.103815.

van Erum, J., Valkenburg, F., Van Dam, D., De Deyn, P.P., 2020. Pentylenetetrazole-induced seizure susceptibility in the Tau58/4 transgenic mouse model of tauopathy. Neuroscience 425, 112–122. https://doi.org/10.1016/j.neuroscience.2019.11.007.

van Vliet, E.A., Marchi, N., 2022. Neurovascular unit dysfunction as a mechanism of seizures and epilepsy during aging. Epilepsia 63, 1297–1313. https://doi.org/10.1111/epi.17210.

Vassileva, A., van Blooijs, D., Leijten, F., Huiskamp, G., 2018. Neocortical electrical stimulation for epilepsy: closed-loop versus open-loop. Epilepsy Res. 141, 95–101. https://doi.org/10.1016/j.eplepsyres.2018.02.010.

Vawter-Lee, M., Natarajan, N., Rang, K., Horn, P.S., Pardo, A.C., Thomas, C.W., 2022. Topiramate is safe for refractory neonatal seizures: A multicenter retrospective cohort study of necrotizing enterocolitis risk. Pediatr. Neurol. 129, 7–13. https://doi.org/10.1016/j.pediatrneurol.2021.12.003.

Vishwakarma, S., Singh, S., Singh, T.G., 2022. Pharmacological modulation of cytokines correlating neuroinflammatory cascades in epileptogenesis. Mol. Biol. Rep. 49, 1437–1452. https://doi.org/10.1007/s11033-021-06896-8.

Vochikovski, L., Favoreto, M.W., Rezende, M., Terra, R.M.O., Gumy, F.N., Loguercio, A. D., Reis, A., 2022. Use of infrared photobiomodulation with low-level laser therapy for reduction of bleaching-induced tooth sensitivity after in-office bleaching: a double-blind, randomized controlled trial. Lasers Med. Sci. 38, 18. https://doi.org/10.1007/s10103-022-03682-1.

Wandt, V.K., Winkelbeiner, N., Bornhorst, J., Witt, B., Raschke, S., Simon, L., Ebert, F., Kipp, A.P., Schwerdtle, T., 2021. A matter of concern - trace element dyshomeostasis and genomic stability in neurons. Redox Biol. 41, 101877 https://doi.org/10.1016/j.redox.2021.101877.

Wang, J.Y., Li, J.Q., Xiao, Y.M., Fu, B., Qin, Z.H., 2020. Triphenylphosphonium (TPP)-based antioxidants: a new perspective on antioxidant design. ChemMedChem 15, 404–410. https://doi.org/10.1002/cmdc.201900695.

Wang, H.E., Woodman, M., Triebkorn, P., Lemarechal, J.-D., Jha, J., Dollomaja, B., Vattikonda, A.N., Sip, V., Medina Villalon, S., Hashemi, M., Guye, M., Makhalova, J., Bartolomei, F., Jirsa, V., 2023b. Delineating epileptogenic networks using brain imaging data and personalized modeling in drug-resistant epilepsy. Sci. Transl. Med. 15, eabp8982 https://doi.org/10.1126/scitranslmed.abp8982.

Wang, F., Zhang, Q., Wang, Y.u., Chen, J., Wang, Y.i., 2023a. Insight into drug resistance in status epilepticus: evidence from animal models. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24032039.

Warui, D.M., Sil, D., Lee, K.-H., Neti, S.S., Esakova, O.A., Knox, H.L., Krebs, C., Booker, S. J., 2022. In vitro demonstration of human lipoyl synthase catalytic activity in the presence of NFU1. ACS Bio Med Chem Au 2, 456–468. https://doi.org/10.1021/acsbiomedchemau.2c00020.

Watkins, L.V., O'Dwyer, M., Shankar, R., 2022. A review of the pharmacotherapeutic considerations for managing epilepsy in people with autism. Expert Opin. Pharmacother. 23, 841–851. https://doi.org/10.1080/14656566.2022.2055461.

Wei, Y., Huang, Y., Yang, Y., Qian, M., 2021. MELAS/LS overlap syndrome associated with mitochondrial DNA mutations: clinical, genetic, and radiological studies. Front. Neurol. 12, 648740 https://doi.org/10.3389/fneur.2021.648740.

Wesół-Kucharska, D., Rokicki, D., Jezela-Stanek, A., 2021. Epilepsy in mitochondrial diseases-current state of knowledge on aetiology and treatment. Children (Basel) 8, 532. https://doi.org/10.3390/children8070532.

Wheless, J.W., 2004. History and origin of the ketogenic diet. In: Epilepsy and the Ketogenic Diet. Humana Press, pp. 31–50. https://doi.org/10.1007/978-1-59259-808-3_2.

Wheless, J.W., 2008. History of the ketogenic diet. Epilepsia 49 (Suppl. 8), 3–5. https://doi.org/10.1111/j.1528-1167.2008.01821.x.

Whitlock, J.H., Soelter, T.M., Williams, A.S., Hardigan, A.A., Lasseigne, B.N., 2022. Liquid biopsies in epilepsy: biomarkers for etiology, diagnosis, prognosis, and therapeutics. Hum. Cell 35, 15–22. https://doi.org/10.1007/s13577-021-00624-x.

Wikström, M., Gennis, R.B., Rich, P.R., 2023. Structures of the intermediates in the catalytic cycle of mitochondrial cytochrome c oxidase. Biochim. Biophys. Acta Bioenerg. 1864, 148933 https://doi.org/10.1016/j.bbabio.2022.148933.

Wilson, J.V., Reynolds, E.H., 1990. Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. Med. Hist. 34, 185–198. https://doi.org/10.1017/s0025727300050651.

Wolf, P., 2023. The idea of epilepsy. A medical and social history of epilepsy in the modern era (1860-2020) By Simon Shorvon, Cambridge University Press. 2023. ISBN Nr: 9781 108829519. Epilepsia Open. https://doi.org/10.1002/epi4.12759.

Wolgin, M., Zobernig, M., Dvornyk, V., Braun, R.J., Kielbassa, A.M., 2022. Systematic review on saliva biomarkers in patients diagnosed with morbus Alzheimer and morbus Parkinson. Biomedicines 10. https://doi.org/10.3390/biomedicines10071702.

Wong, Z.W., Engel, T., 2023. More than a drug target: purinergic signalling as a source for diagnostic tools in epilepsy. Neuropharmacology 222, 109303. https://doi.org/10.1016/j.neuropharm.2022.109303.

Wu, H., Liu, Y., Li, H., Du, C., Li, K., Dong, S., Meng, Q., Zhang, H., 2021. TRAK1-mediated abnormality of mitochondrial fission increases seizure susceptibility in temporal lobe epilepsy. Mol. Neurobiol. 58, 1237–1247. https://doi.org/10.1007/s12035-020-02175-y.

Xiang, T., Luo, X., Zeng, C., Li, S., Ma, M., Wu, Y., 2021. Klotho ameliorated cognitive deficits in a temporal lobe epilepsy rat model by inhibiting ferroptosis. Brain Res. 1772, 147668 https://doi.org/10.1016/j.brainres.2021.147668.

Xiang, T., Luo, X., Ye, L., Huang, H., Wu, Y., 2022. Klotho alleviates NLRP3 inflammasome-mediated neuroinflammation in a temporal lobe epilepsy rat model by activating the Nrf2 signaling pathway. Epilepsy Behav. 128, 108509 https://doi.org/10.1016/j.yebeh.2021.108509.

Xie, Y., Hou, W., Song, X., Yu, Y., Huang, J., Sun, X., Kang, R., Tang, D., 2016. Ferroptosis: process and function. Cell Death Differ. 23, 369–379. https://doi.org/10.1038/cdd.2015.158.

Xu, Z.-E., Li, W.-B., Qiao, M.-Y., Cui, H.-T., Zhao, L.-Z., Chen, Q.-X., Miao, J.-K., 2021. Comparative efficacy of anti-epileptic drugs for neonatal seizures: a network meta-analysis. Pediatr. Neonatol. 62, 598–605. https://doi.org/10.1016/j.pedneo.2021.06.005.

Xu, L., Liu, Y., Chen, X., Zhong, H., Wang, Y., 2023. Ferroptosis in life: to be or not to be. Biomed. Pharmacother. 159, 114241 https://doi.org/10.1016/j.biopha.2023.114241.

Yang, X., Zhang, X., Shen, K., Wang, Z., Liu, G., Huang, K., He, Z., Li, Y., Hou, Z., Lv, S., Zhang, C., Yang, H., Liu, S., Ke, Y., 2023. Cuproptosis-related genes signature and validation of differential expression and the potential targeting drugs in temporal lobe epilepsy. Front. Pharmacol. 14 https://doi.org/10.3389/fphar.2023.1033859.

Yao, M.-Y., Liu, T., Zhang, L., Wang, M.-J., Yang, Y., Gao, J., 2021. Role of ferroptosis in neurological diseases. Neurosci. Lett. 747, 135614 https://doi.org/10.1016/j.neulet.2020.135614.

Yasmen, N., Sluter, M.N., Yu, Y., Jiang, J., 2023. Ganaxolone for management of seizures associated with CDKL5 deficiency disorder. Trends Pharmacol. Sci. 44, 128–129. https://doi.org/10.1016/j.tips.2022.11.007.

Yawno, T., Miller, S.L., Bennet, L., Wong, F., Hirst, J.J., Fahey, M., Walker, D.W., 2017. Ganaxolone: a new treatment for neonatal seizures. Front. Cell. Neurosci. 11, 246 https://doi.org/10.3389/fncel.2017.00246.

Ye, R., Huang, J., Wang, Z., Chen, Y., Dong, Y., 2022. The role and mechanism of essential selenoproteins for homeostasis. Antioxidants (Basel) 11, 973. https://doi.org/10.3390/antiox11050973.

Yea, C., Barton, M., Bitnun, A., Morris, S.K., El Tal, T., Ulloa-Gutierrez, R., Brenes-Chacon, H., Yock-Corrales, A., Ivankovich-Escoto, G., Soriano-Fallas, A., Hernandez-de Mezerville, M., Gill, P., Nateghian, A., Aski, B.H., Manafi, A.A., Dwilow, R., Bullard, J., Papenburg, J., Scuccimarri, R., Lefebvre, M.-A., Cooke, S., Dewan, T., Restivo, L., Lopez, A., Sadarangani, M., Roberts, A., Wong, J., Saux, N.L., Bowes, J., Purewal, R., Lautermilch, J., Foo, C., Merckx, J., Robinson, J., Yeh, E.A., P.I.C. Network on Infections in Canada (PICNIC), 2023. Neurological involvement in hospitalized children with SARS-CoV-2 infection: a multinational study. Can. J. Neurol. Sci. 1–10. https://doi.org/10.1017/cjn.2022.347.

You, J., Bragin, A., Liu, H., Li, L., 2021. Preclinical studies of transcranial photobiomodulation in the neurological diseases. Transl. Biophotonics 3. https://doi.org/10.1002/tbio.202000024.

Zamzow, R., 2023. Disorder or difference? Autism researchers face off over field's terminology (February 7, 2023). In: AAAS Articles DO Group. Science 379, 523–524. https://doi.org/10.1126/science.adh0585.

Zanotti, S., Velardo, D., Sciacco, M., 2022. Traumatic brain injury triggers neurodegeneration in a mildly symptomatic MELAS patient: Implications on the detrimental role of damaged mitochondria in determining head trauma sequalae in the general population. Metabolites 13. https://doi.org/10.3390/metabo13010046.

Zarzycki, M.Z., Domitrz, I., 2020. Stimulation-induced side effects after deep brain stimulation - a systematic review. Acta Neuropsychiatr. 32, 57–64. https://doi.org/10.1017/neu.2019.35.

Zeviani, M., Viscomi, C., 2022. Mitochondrial neurodegeneration. Cells 11, 637. https://doi.org/10.3390/cells11040637.

Zhang, Y., Gao, H., Zheng, W., Xu, H., 2022b. Current understanding of the interactions between metal ions and Apolipoprotein E in Alzheimer's disease. Neurobiol. Dis. 172, 105824 https://doi.org/10.1016/j.nbd.2022.105824.

Zhang, X., Yang, L., Xu, X., Tang, F., Yi, P., Qiu, B., Hao, Y., 2019. A review of fibroblast growth factor 21 in diabetic cardiomyopathy. Heart Fail. Rev. 24, 1005–1017. https://doi.org/10.1007/s10741-019-09809-x.

Zhang, X., Wu, S., Guo, C., Guo, K., Hu, Z., Peng, J., Zhang, Z., Li, J., 2022a. Vitamin E exerts neuroprotective effects in pentylenetetrazole kindling epilepsy via suppression of ferroptosis. Neurochem. Res. 47, 739–747. https://doi.org/10.1007/s11064-021-03483-y.

Zhang, R.-F., Zeng, M., Lv, N., Wang, L.-M., Yang, Q.-Y., Gan, J.-L., Li, H.-H., Yu, B., Jiang, X.-J., Yang, L., 2023. Ferroptosis in neurodegenerative diseases: inhibitors as promising candidate mitigators. Eur. Rev. Med. Pharmacol. Sci. 27, 46–65. https://doi.org/10.26355/eurrev_202301_30852.

Zheng, Z.-W., Dong, Y., Wu, Z.-Y., 2022. Latest innovations in the treatment of Wilson's disease. iLIVER 1, 181–186. https://doi.org/10.1016/j.iliver.2022.09.002.

Zhou, Y., Lin, W., Rao, T., Zheng, J., Zhang, T., Zhang, M., Lin, Z., 2022. Ferroptosis and its potential role in the nervous system diseases. J. Inflamm. Res. 15, 1555–1574. https://doi.org/10.2147/JIR.S351799.

Zhou, Y., Sun, L., Wang, H., 2023. Ketogenic diet for neonatal hypoxic-ischemic encephalopathy. ACS Chem. Nerosci. 14, 1–8. https://doi.org/10.1021/acschemneuro.2c00609.

Zhu, H., Bi, D., Zhang, Y., Kong, C., Du, J., Wu, X., Wei, Q., Qin, H., 2022. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. Signal Transduct. Target. Ther. 7, 11. https://doi.org/10.1038/s41392-021-00831-w.

Zielonka, J., Joseph, J., Sikora, A., Hardy, M., Ouari, O., Vasquez-Vivar, J., Cheng, G., Lopez, M., Kalyanaraman, B., 2017. Mitochondria-targeted triphenylphosphonium-based compounds: Syntheses, mechanisms of action, and therapeutic and diagnostic applications. Chem. Rev. 117, 10043–10120. https://doi.org/10.1021/acs.chemrev.7b00042.

Zilberter, Y., Popova, I., Zilberter, M., 2022. Unifying mechanism behind the onset of acquired epilepsy. Trends Pharmacol. Sci. 43, 87–96. https://doi.org/10.1016/j.tips.2021.11.009.

Zsurka, G., Kunz, W.S., 2015. Mitochondrial dysfunction and seizures: the neuronal energy crisis. Lancet Neurol. 14, 956–966. https://doi.org/10.1016/S1474-4422(15)00148-9.

Zuberi, S.M., Wirrell, E., Yozawitz, E., Wilmshurst, J.M., Specchio, N., Riney, K., Pressler, R., Auvin, S., Samia, P., Hirsch, E., Galicchio, S., Triki, C., Snead, O.C., Wiebe, S., Cross, J.H., Tinuper, P., Scheffer, I.E., Perucca, E., Moshé, S.L., Nabbout, R., 2022. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia 63, 1349–1397. https://doi.org/10.1111/epi.17239.

Zweiphenning, W., Klooster, M.A. van 't, van Klink, N.E.C., Leijten, F.S.S., Ferrier, C.H., Gebbink, T., Huiskamp, G., van Zandvoort, M.J.E., van Schooneveld, M.M.J., Bourez, M., Goemans, S., Straumann, S., van Rijen, P.C., Gosselaar, P.H., van Eijsden, P., Otte, W.M., van Diessen, E., Braun, K.P.J., Zijlmans, M., HFO study group, 2022. Intraoperative electrocorticography using high-frequency oscillations or spikes to tailor epilepsy surgery in the Netherlands (the HFO trial): a randomised, single-blind, adaptive non-inferiority trial. Lancet Neurol. 21, 982–993. https://doi.org/10.1016/S1474-4422(22)00311-8.