Scientific Research Publishing

Voice of the Publisher, 2025, 11(2), 242-250
https://www.scirp.org/journal/vp
ISSN Online: 2380-7598
ISSN Print: 2380-7571

An Overview of the Neurological Mechanisms of Juvenile Myoclonic Epilepsy and Antiepileptic Drugs

Hannah K. Markopoulos

Department of Natural Sciences, Life University, Marietta, USA
Email: hannah.markopoulos@gmail.com

How to cite this paper: Markopoulos, H. K. (2025). An Overview of the Neurological Mechanisms of Juvenile Myoclonic Epilepsy and Antiepileptic Drugs. *Voice of the Publisher, 11,* 242-250.
https://doi.org/10.4236/vp.2025.112017

Received: March 26, 2025
Accepted: April 21, 2025
Published: April 24, 2025

Abstract

Juvenile Myoclonic Epilepsy (JME) is a prevalent form of generalized epilepsy, predominantly affecting adolescents and young adults. It is characterized by myoclonic seizures, grand mal seizures, and abnormal electroencephalogram (EEG) findings. Though the exact etiology remains unclear, genetic factors, particularly mutations in ion channels and neurotransmitter receptors, play a crucial role in its pathogenesis. The condition is marked by an imbalance between excitatory and inhibitory signaling in the brain, involving neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA). This imbalance leads to neuronal hyperexcitability, with excessive synchronization of neuronal firing resulting in seizures. Additionally, mutations in genes like GABRA1, CACNB4, and EFHC1 are associated with altered synaptic transmission and calcium signaling, further contributing to the pathophysiology of JME. The primary treatment for JME involves antiepileptic drugs (AEDs), which aim to restore the excitatory-inhibitory balance. These drugs function by modulating ion channels, enhancing GABAergic inhibition, and blocking glutamate receptors. By stabilizing neuronal activity, AEDs reduce the occurrence of seizures and improve the quality of life for patients. This paper provides a brief overview of the neurological mechanisms underlying JME and the role of AEDs in its management.

Keywords

Epilepsy, Myoclonic, Antiepileptics, Voltage-Gated, Inhibitory, Excitatory, GABRA1, CACNB4, EFHC1, CLCN2, Glutamatergic, Synchronization

1. Introduction

Juvenile myoclonic epilepsy (JME), accounting for 5% - 10% of all epileptic cases,

presents significant difficulties due to its complicated neurophysiological mechanisms. Its other titles include Janz syndrome or impulsive petit mal. It is idiopathic but studies suggest that family history significantly influences the onset with 50% of cases, showing a genetic predisposition. Most commonly, it initially presents between ages 12 to 18 (Amrutkar & Riel-Romero, 2023). It is a complex disorder rooted in abnormal brain function, specifically related to the neurological mechanisms that govern neurotransmission synaptic activity, and neural circuit function. It is the most prevalent form of generalized epilepsy.

2. Background and Epidemiology

JME is recognized as one of the most common forms of generalized epilepsy (Epilepsy Foundation, n.d.) among adolescents and young adults, with some studies suggesting a slightly higher incidence in males than females (Giuliano et al., 2021). Although the exact cause of the disorder remains unclear, it is understood to be primarily genetic with specific gene mutations in ion channels and neurotransmitter receptors playing a role. Studies reveal that 50% of people with JME reported having seizures in first- or second-degree relatives (Delgado-Escueta et al., 2016; Delgado-Escueta et al., 1989). Despite its prevalence, JME often goes underdiagnosed or misdiagnosed due to the complexity of its symptoms, which overlap with other neurological conditions or forms of epilepsy.

It is clinically identified by myoclonic seizures as the individual wakes up (Cvetkovska et al., 2016), grand mal seizures (in certain cases), and an electroencephalogram (EEG) that displays generalized spike-wave or polyspike-wave activity. "The main neurophysiological finding of JME is the EEG feature of short discharges of generalized spike-wave (SW) or poly-spike wave (PSW) complexes associated with epileptic myoclonus" (Wolf et al., 2017). JME can also be diagnosed through the process of exclusion, where alternative causes are systematically ruled out, and it remains the only viable explanation for myoclonic seizures. In cases where no other underlying condition can account for the observed symptoms, JME is the most likely cause. This diagnostic method can leave room for error, often leading to misdiagnosis.

To understand how JME works on a neurophysiological level, we need to explore the specific details of how neuronal firing, neurotransmitter imbalances, and synaptic signaling contribute to seizures and how antiepileptic drugs (AEDs) modulate these processes.

3. Neuropathophysiology of JME

At the core of JME, as with other forms of epilepsy, is a disequilibrium between excitatory and inhibitory signaling within the brain. A properly functioning brain needs a balance of excitatory and inhibitory inputs that are carefully regulated. Disruptions in this balance are seen in many neurological disorders, including epilepsy (Sears & Hewett, 2021). Under normal conditions, neurons communicate through a highly regulated system that involves excitatory neurotransmit-

ters like glutamate, and inhibitory neurotransmitters like gamma-aminobutyric acid (GABA). This dynamic balance ensures that neurons fire appropriately and in a controlled manner. However, in JME, the excitatory drive is overly excessive, and the inhibitory control becomes insufficient, which leads to hyperexcitability of neurons. This is where the development of seizures arises (Wang et al., 2021). "Glutamate and gamma-aminobutyric acid (GABA) are the main neurotransmitters playing a critical role in the pathophysiology of this balance, and irreversible neuronal damage may occur as a result of abnormal changes in these molecules. Acetylcholine (ACh), the main stimulant of the autonomic nervous system, mediates signal transmission through cholinergic and nicotinic receptors. Accumulating evidence indicates that dysfunction of nicotinic ACh receptors, which are widely expressed in hippocampal and cortical neurons, may be significantly implicated in the pathogenesis of epilepsy" (Akyuz et al., 2021).

The myoclonic jerks present in JME are thought to result from the excessive synchronization of neuronal firing, specifically in the motor cortex and other regions that are involved in muscle coordination (Strigaro et al., 2012). The brain's electrical activity becomes too synchronized in particular regions, creating a high-frequency discharge of action potentials. This inappropriate release of action potentials causes a rapid, jerking contraction of muscles. This abnormal electrical activity is often seen in the frontal lobe and motor cortex, as well as in the thalamocortical circuits. To be specific, thalamic neurons, which relay sensory and motor information, play an important role in the generalized seizure characteristic of JME.

In some cases, in addition to myoclonic seizures, grand mal seizures can occur in individuals with JME. These are more modernly known as tonic-clonic seizures. It is highly unusual to see a patient with JME also suffer from grand mal seizures. Grand mal seizures are characterized by a loss of consciousness, followed by a tonic phase, where the muscles stiffen, and a clonic phase, which involves rhythmic jerking movement of the limbs. In JME, these seizures typically arise in the early morning or after the individual wakes up, which is consistent with the pattern of myoclonic jerks that often occur shortly after waking.

The pathophysiology of grand mal seizures in JME is more than likely due to the same mechanisms that underlie myoclonic seizures—excessive synchronization of neuronal firing in the motor cortex and thalamocortical circuits. The difference lies in the widespread involvement of brain regions in grand mal seizures, which results in the loss of consciousness and the tonic-clonic motor manifestations. While myoclonic jerks are usually brief and isolated, grand mal seizures are more prolonged and can involve a complete disruption of normal brain activity. These seizures are often triggered by factors like sleep deprivation, stress, and flashing lights, which highlight the delicate balance of neuronal activity in JME.

4. Imbalance in Excitation and Inhibition

The imbalance between excitatory glutamatergic signaling and inhibitory GA-

BAergic signaling underpins the pathophysiology of JME. Neurons in the brain rely on precise, supervised control over their excitation and inhibition to avoid excessive firing. In JME, excitatory synaptic transmission involving glutamate, an amino acid, becomes dysregulated, with N-methyl-D-aspartate receptors (NMDA receptors) (Sivakumar et al., 2022), AMPA receptors, and metabotropic glutamate receptors (mGluRs) being implicated in promoting the excitatory drive. Glutamate is the principal excitatory neurotransmitter in the brain, and its receptors, especially NMDA and AMPA receptors, are involved in fast synaptic transmission (Hanada, 2020). In JME, these receptors become *hyper*sensitive, leading to increased neuronal firing and synaptic plasticity that supports seizure generation.

Simultaneously, inhibitory neurotransmission via GABA is compromised in this condition. GABA is the main inhibitory neurotransmitter in the brain, and its effects are mediated primarily through GABA-A receptors, which are ligand-gated chloride ion channels. When GABA binds to these receptors, chloride ions flow into the neuron, causing hyperpolarization and making the neuron less likely to fire. In JME, however, there is often a reduction in GABAergic inhibition—either due to defective GABA-A receptors or a decrease in GABA synthesis. This leads to decreased inhibitory control. This reduction in GABAergic signaling can result in the hyperexcitability that drives seizure activity, as the neurons are more easily depolarized by excitatory signals (Ngomba et al., 2011).

In addition to GABA and glutamate imbalances, calcium signaling also plays a vital role in the pathophysiology of JME. The calcium ions (Ca^{2+}) are vitally important for neurotransmitter release, synaptic plasticity, and neuron firing. Calcium channels, especially those encoded by the CACNA1A gene (Fox et al., 2024), can contribute to hyperexcitability when mutated. This disrupts the influx of calcium ions and alters neuronal firing patterns. This abnormal calcium regulation contributes to the synchronization of neuronal activity, which underlies generalized seizures in JME.

5. Genetics and Biochemical Pathways

JME has a strong genetic aspect, with multiple genes contributing to its pathology. Several of the mutations associated with JME implicate genes that encode ion channels and neurotransmitter receptors, which are both necessary to maintain the excitatory-inhibitory balance in the brain.

The first gene is GABRA1 (Gamma-Aminobutyric Acid Type A Receptor Subunit Alpha 1). Mutations in this gene severely affect the GABA-A receptor, which is responsible for inhibitory neurotransmission (Fu et al., 2022). A defective GABA-A receptor reduces inhibitory signaling. This leads to increased neuronal excitability and seizure susceptibility.

The second gene involved in the genetic pathology of JME is CACNB4 (Calcium Channel, Voltage-Dependent, Beta 4 Subunit). This gene encodes a subunit of voltage-gated calcium channels, which regulate calcium influx into neurons. Mutations in CACNB4 can result in altered calcium homeostasis, which contrib-

utes to neuronal hyperexcitability and seizure generation. These voltage-gated sodium channels are abundant at the neuromuscular junctions throughout the body, and dysfunction leads to abnormal muscle contraction (George, 2005).

The third gene involved is EFHC1 (EF-Hand Domain Containing 1). EFHC1 mutations have been commonly found in JME patients, and these mutations are thought to affect neuronal pathway development as well as calcium signaling, which are both important in regulating synaptic transmission and excitability control (de Nijs et al., 2012).

The last major gene is CLCN2 (Chloride Channel 2). The function of this gene is to encode a chloride channel that helps maintain neuronal membrane potential. Mutations in CLCN2 can impair inhibitory control, making neurons significantly more prone to excessive firing (Niemeyer et al., 2004).

At the chemical level, JME is characterized by altered synaptic transmission, specifically in glutamatergic and GABAergic pathways (Kang, 2017). Hyperactivation of glutamate receptors (like NMDA and AMPA receptors) leads to excessive excitatory signaling, while compromised GABAergic inhibition results in a failure to regulate this excitatory drive (Sarola & Holton, 2021). Additionally, dysfunction in voltage-gated calcium and chloride channels disrupts ion homeostasis, further promoting neuronal hyperexcitability.

6. Mechanisms of Antiepileptic Medications

There are various holistic remedies to epileptic seizures, but the primary treatment needs to be antiepileptic drugs (AEDs). AEDs aim to normalize the excitatory and inhibitory balance in the brain and suppress the abnormal neuronal firing associated with seizures. AEDs function by modulating the function of ion channels, neurotransmitter systems, and synaptic receptors, which aids in reducing the likelihood of electrical misfiring (Macdonald & Kelly, 1995).

One of the primary mechanisms of action of AEDs is through the modulation of ion channels, or more specifically, voltage-gated sodium and calcium channels (Kwan et al., 2001). By stabilizing the function of these channels, AEDs reduce the process of rapid neuron depolarization, and prevent them from excessive firing. This stabilization helps prevent the propagation of abnormal electrical activity that leads to seizures. Sodium channel blockers, like phenytoin and lamotrigine, help maintain a steady membrane potential by preventing the rapid influx of sodium ions, which is important during the depolarization phase of neuronal firing. Similarly, calcium channel blockers, such as ethosuximide, work by reducing the influx of calcium ions into neurons, further limiting neuronal excitability and preventing synchronization of electrical activity in the brain (Armijo et al., 2005).

Voltage-gated Na+ channels are crucial for generating action potentials, and mutations in these channels contribute to generalized epilepsy with febrile seizures plus and benign familial neonatal infantile seizures. Inhibition of Na^+ channels is the primary action of drugs like carbamazepine, phenytoin, and lamotrigine, and likely plays a role in many other traditional and newer AEDs. Voltage-

gated K^+ channels are vital for repolarization and hyperpolarization following paroxysmal depolarization shifts (PDSs), with mutations in these channels linked to benign neonatal epilepsy and episodic ataxia type 1. These channels are also new targets for AEDs, such as retigabine. Voltage-gated Ca^{2+} channels participate in neurotransmitter release, the sustained depolarization phase of PDSs, and the initiation of absence seizures. Mutations in these channels contribute to juvenile myoclonic epilepsy and an absence-like pattern in some mice. The anti-absence effects of ethosuximide are due to its inhibition of thalamic T-type Ca^{2+} channels. Voltage-gated Cl^- channels are involved in GABA(A) transmission, with mutations in these channels found in some families with juvenile myoclonic epilepsy, epilepsy with grand mal seizures upon awakening, or juvenile absence epilepsy (Meldrum & Rogawski, 2007).

Another critical mechanism of AEDs is the enhancement of GABAergic inhibition. GABA is the brain's primary inhibitory neurotransmitter, and AEDs that enhance its function can reduce neuronal excitability. Drugs like valproate and benzodiazepines increase the binding affinity of GABA to its receptors, facilitating the influx of chloride ions into neurons. This hyperpolarizes the neurons and makes them less likely to fire, reducing the likelihood of seizure generation. The potentiation of GABAergic activity is particularly important in conditions like JME, where GABA inhibition is often insufficient to counteract excessive excitation.

In addition to modulating ion channels and enhancing GABAergic signaling, some AEDs also block glutamate receptors (Huang et al., 2023). Glutamate is the primary excitatory neurotransmitter in the brain, as we previously discussed, and its overactivation is implicated in seizures in JME. AEDs such as topiramate and lamotrigine block glutamate receptors (NMDA and AMPA) (Lyseng-Williamson & Yang, 2007; Choi & Morrell, 2003), reducing the excitatory drive that leads to neuronal hyperexcitability. By inhibiting glutamate activity, these drugs help prevent the excessive synaptic activity that can trigger seizures.

Finally, AEDs like levetiracetam work by modulating synaptic vesicle proteins involved in neurotransmitter release (Abou-Khalil, 2008). By altering the release of neurotransmitters, levetiracetam helps reduce the synchronization of neuronal firing and prevents the propagation of seizure activity.

7. Complications and Quality of Life

While AEDs are effective in many cases of JME, several complications can arise that significantly impact the patient's quality of life. These complications include insomnia, drug-resistant epilepsy, and the psychological strain of living with a chronic condition that cannot be easily controlled. The threat of a seizure is constantly looming, and can be overwhelming, leading to decreased social engagement and poor mental health. Many individuals with JME have difficulty maintaining a social life or pursuing career opportunities due to the fear of having a seizure in public or while performing everyday tasks. This social isolation, along

with the unpredictable nature of seizures, can contribute to depression, anxiety, and emotional health issues. Their mental health is often deeply affected, as the stigma of epilepsy and the lack of control over their own bodies can create a profound sense of hopelessness and depression. Despite advancements in treatments, there are still too many individuals who cannot live a life free of seizures, and the emotional toll is far-reaching.

Moreover, insomnia is a common complication due to the hyperactivity of neurons, as the nervous system remains in a state of heightened excitability, alertness, and the sympathetic division is chronically overactive (Krishnan et al., 2012; Greenlund & Carter, 2022). The inability to obtain proper rest only worsens the condition, contributing to the frequency and severity of seizures. A lack of sleep and stress are both well-known seizure triggers for people with JME.

A critical complication is drug-resistant epilepsy, where patients do not respond to common AED treatments. Approximately 15% - 30% of people with JME have drug-resistant epilepsy (Martin et al., 2019), and this requires alternative approaches like polytherapy, where multiple AEDs are used in conjunction, or surgical intervention.

8. Conclusion

The pathophysiology of Juvenile Myoclonic Epilepsy (JME) is rooted in a complex interplay between excitatory and inhibitory neurotransmission, with genetic mutations affecting extremely vital neuronal processes like GABAergic inhibition, glutamatergic excitation, and calcium signaling. The abnormal firing of neurons in the motor cortex leads to the characteristic myoclonic jerks and, in rare situations, grand mal seizures. New genetic discoveries and further studies on synaptic mechanisms continue to shed light on potential treatments that may better regulate neuronal excitability. Although current treatments such as valproate and levetiracetam offer relief for many patients, further research into newer, more targeted therapies and medications is needed to address the underlying causes and improve outcomes.

JME has been known for its high rate of genetic inheritance, yet it remains poorly understood. As more advanced research and genetic studies are conducted, a better understanding of the underlying causes and mechanisms of JME will allow for more effective treatments. Further studies and clinical trials will be pivotal in advancing our understanding of JME's neurological mechanisms.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

Abou-Khalil, B. (2008). Levetiracetam in the Treatment of Epilepsy. *Neuropsychiatric Disease and Treatment, 4,* 507-523. https://doi.org/10.2147/ndt.s2937

Akyuz, E., Polat, A. K., Eroglu, E., Kullu, I., Angelopoulou, E., & Paudel, Y. N. (2021). Re-

visiting the Role of Neurotransmitters in Epilepsy: An Updated Review. *Life Sciences, 265,* Article ID: 118826. https://doi.org/10.1016/j.lfs.2020.118826

Amrutkar, C. V., & Riel-Romero, R. M. (2023). *Juvenile Myoclonic Epilepsy.* StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK537109/

Armijo, J., Shushtarian, M., Valdizan, E., Cuadrado, A., Cuevas, I., & Adin, J. (2005). Ion Channels and Epilepsy. *Current Pharmaceutical Design, 11,* 1975-2003. https://doi.org/10.2174/1381612054021006

Choi, H., & Morrell, M. J. (2003). Review of Lamotrigine and Its Clinical Applications in Epilepsy. *Expert Opinion on Pharmacotherapy, 4,* 243-251. https://doi.org/10.1517/14656566.4.2.243

Cvetkovska, E., Kuzmanovski, I., Sazdova-Burneska, S., & Aleksovska-Stanojkovska, L. (2016). Clinical Genetic Study in Juvenile Myoclonic Epilepsy. *Seizure, 23,* 903-905.

de Nijs, L., Wolkoff, N., Coumans, B., Delgado-Escueta, A. V., Grisar, T., & Lakaye, B. (2012). Mutations of EFHC1, Linked to Juvenile Myoclonic Epilepsy, Disrupt Radial and Tangential Migrations during Brain Development. *Human Molecular Genetics, 21,* 5106-5117. https://doi.org/10.1093/hmg/dds356

Delgado-Escueta, A. V. et al. (2016). The Quest for Juvenile Myoclonic Epilepsy Genes. *Epilepsy & Behavior, 28,* S52-S57.

Delgado-Escueta, A. V., Greenberg, D. A., Treiman, L., Liu, A., Sparkes, R. S., Barbetti, A. et al. (1989). Mapping the Gene for Juvenile Myoclonic Epilepsy. *Epilepsia, 30,* S8-S18. https://doi.org/10.1111/j.1528-1157.1989.tb05835.x

Epilepsy Foundation (n.d.). *Juvenile Myoclonic Epilepsy.* https://www.epilepsy.com/what-is-epilepsy/syndromes/juvenile-myoclonic-epilepsy

Fox, P. M., Malepati, S., Manaster, L., Rossignol, E., & Noebels, J. L. (2024). Developing a Pathway to Clinical Trials for *CACNA1A*-Related Epilepsies: A Patient Organization Perspective. *Therapeutic Advances in Rare Disease, 5,* 26330040241245725. https://doi.org/10.1177/26330040241245725

Fu, X., Wang, Y. J., Kang, J. Q., & Czuczwar, S. J. (2022). Chap. 7. $GABA_A$ Receptor Variants in Epilepsy. In S. J. Czuczwar (Ed.), *Epilepsy*. Exon Publications. https://www.ncbi.nlm.nih.gov/books/NBK580621/

George, A. L. (2005). Inherited Disorders of Voltage-Gated Sodium Channels. *Journal of Clinical Investigation, 115,* 1990-1999. https://doi.org/10.1172/jci25505

Giuliano, L., Mainieri, G., Aguglia, U., Bilo, L., Durante, V., Ermio, C. et al. (2021). Long-term Prognosis of Juvenile Myoclonic Epilepsy: A Systematic Review Searching for Sex Differences. *Seizure, 86,* 41-48. https://doi.org/10.1016/j.seizure.2021.01.005

Greenlund, I. M., & Carter, J. R. (2022). Sympathetic Neural Responses to Sleep Disorders and Insufficiencies. *American Journal of Physiology-Heart and Circulatory Physiology, 322,* H337-H349. https://doi.org/10.1152/ajpheart.00590.2021

Hanada, T. (2020). Ionotropic Glutamate Receptors in Epilepsy: A Review Focusing on AMPA and NMDA Receptors. *Biomolecules, 10,* Article 464. https://doi.org/10.3390/biom10030464

Huang, T., Lai, M., Chen, Y., & Huang, C. (2023). The Roles of Glutamate Receptors and Their Antagonists in Status Epilepticus, Refractory Status Epilepticus, and Super-Refractory Status Epilepticus. *Biomedicines, 11,* Article 686. https://doi.org/10.3390/biomedicines11030686

Kang, J. (2017). Defects at the Crossroads of Gabaergic Signaling in Generalized Genetic Epilepsies. *Epilepsy Research, 137,* 9-18. https://doi.org/10.1016/j.eplepsyres.2017.08.013

Krishnan, P., Sinha, S., Taly, A. B., Ramachandraiah, C. T., Rao, S., & Satishchandra, P. (2012). Sleep Disturbances in Juvenile Myoclonic Epilepsy: A Sleep Questionnaire-Based Study. *Epilepsy & Behavior, 23,* 305-309. https://doi.org/10.1016/j.yebeh.2011.12.018

Kwan, P., Sills, G. J., & Brodie, M. J. (2001). The Mechanisms of Action of Commonly Used Antiepileptic Drugs. *Pharmacology & Therapeutics, 90,* 21-34. https://doi.org/10.1016/s0163-7258(01)00122-x

Lyseng-Williamson, K. A., & Yang, L. P. H. (2007). Topiramate: A Review of Its Use in the Treatment of Epilepsy. *Drugs, 67,* 2231-2256. https://doi.org/10.2165/00003495-200767150-00008

Macdonald, R. L., & Kelly, K. M. (1995). Antiepileptic Drug Mechanisms of Action. *Epilepsia, 36,* S2-S12. https://doi.org/10.1111/j.1528-1157.1995.tb05996.x

Martin, S., Strzelczyk, A., Lindlar, S., Krause, K., Reif, P. S., Menzler, K. et al. (2019). Drug-resistant Juvenile Myoclonic Epilepsy: Misdiagnosis of Progressive Myoclonus Epilepsy. *Frontiers in Neurology, 10,* Article 946. https://doi.org/10.3389/fneur.2019.00946

Meldrum, B. S., & Rogawski, M. A. (2007). Molecular Targets for Antiepileptic Drug Development. *Neurotherapeutics, 4,* 18-61. https://www.sciencedirect.com/science/article/pii/S1878747923006876 https://doi.org/10.1016/j.nurt.2006.11.010

Ngomba, R. T., Santolini, I., Salt, T. E., Ferraguti, F., Battaglia, G., Nicoletti, F. et al. (2011). Metabotropic Glutamate Receptors in the Thalamocortical Network: Strategic Targets for the Treatment of Absence Epilepsy. *Epilepsia, 52,* 1211-1222. https://doi.org/10.1111/j.1528-1167.2011.03082.x

Niemeyer, M. I., Yusef, Y. R., Cornejo, I., Flores, C. A., Sepúlveda, F. V., & Cid, L. P. (2004). Functional Evaluation of Human CLC-2 Chloride Channel Mutations Associated with Idiopathic Generalized Epilepsies. *Physiological Genomics, 19,* 74-83. https://doi.org/10.1152/physiolgenomics.00070.2004

Sarola, G. L., & Holton, K. F. (2021). Brain Concentrations of Glutamate and GABA in Human Epilepsy: A Review. *Seizure, 91,* 213-227. https://doi.org/10.1016/j.seizure.2021.06.028

Sears, S. M., & Hewett, S. J. (2021). Influence of Glutamate and GABA Transport on Brain Excitatory/Inhibitory Balance. *Experimental Biology and Medicine, 246,* 1069-1083. https://doi.org/10.1177/1535370221989263

Sivakumar, S., Ghasemi, M., & Schachter, S. C. (2022). Targeting NMDA Receptor Complex in Management of Epilepsy. *Pharmaceuticals, 15,* Article 1297. https://doi.org/10.3390/ph15101297

Strigaro, G., Cantello, R., & Comi, C. (2012). Abnormal Motor Cortex Plasticity in Juvenile Myoclonic Epilepsy. *Seizure, 21,* 537-540.

Wang, Y., Tan, B., Wang, Y., & Chen, Z. (2021). Cholinergic Signaling, Neural Excitability, and Epilepsy. *Molecules, 26,* Article 2258. https://doi.org/10.3390/molecules26082258

Wolf, P., Yacubian, E. M. T., Avanzini, G., Sander, T., Schmitz, B., Wandschneider, B., & Koepp, M. (2017). Juvenile Myoclonic Epilepsy: A System Disorder of the Brain. *Epilepsy Research, 114,* 2-12.