JPPT | Review

Nontraditional Antiseizure Medications to Consider When Traditional Options Have Failed: Medications for Refractory Seizures and Epilepsies

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In the field of epilepsy, the advent of precision medicine and the repurposing of medications for new applications have fortuitously allowed more accurate diagnosing and individually targeted therapeutics. Despite these advances, there remain patients who do not respond sufficiently—or at all—to traditionally prescribed treatments. Clinicians often need to be creative, using clinical experience and rigorous research to intuit the next step when most, if not all, anti-seizure treatments have not produced sufficient results. Herein we describe 5 medications with emerging reports of efficacy for seizure control identified by coauthor clinical experience and prescribers in clinical practice for drug information purposes (e.g., ketamine, memantine, quinidine, riluzole, trazodone). Additionally, we summarize pertinent pharmacokinetics, adverse effects, and known and potential interactions with neurologically focused medications to further guide clinical application. Ketamine and memantine appear to be promising options to apply to patients presently, while quinidine, riluzole, and trazodone have data that could contribute to future applications in specific patient populations.

ABBREVIATIONS ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy; DS, Dravet Syndrome; EEG, electroencephalogram; EIMFS, epilepsy with migrating focal seizures; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; ICU, intensive care unit; IM, intramuscular; IN, intranasal; IV, intravenous; LGS, Lennox Gastaut Syndrome; NMDA, N-methyl-D-aspartate; RSE, refractory status epilepticus; SE, status epilepticus;

KEYWORDS epilepsy; ketamine; memantine; quinidine; riluzole; seizure; trazodone

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Introduction and Background

The practice of medicine is ever-changing. In the field of epilepsy, the advent of precision medicine and the repurposing of medications for new applications have fortuitously allowed more accurate diagnosing and individually targeted therapeutics. Despite these advances, there remain patients who do not respond sufficiently—or at all—to traditionally prescribed treatments. Twenty to forty percent of newly diagnosed patients with epilepsy will not achieve seizure remission for many years.[1–3] Patients with medication-resistant seizures are at further risk with mortality rates 4 to 7 times higher compared with pharmacoresponsive patients.[4–6] Clinicians often need to be creative, using clinical experience and rigorous research to intuit the next step when most, if not all, anti-seizure treatments have not produced sufficient results. Expanding on a previously published review of nontraditional anti-seizure medication treatments,[7] herein we describe 5 medications with emerging reports of efficacy for seizure control identified by coauthor clinical experience and prescribers in clinical practice for drug information purposes (e.g., ketamine, memantine, riluzole, quinidine, trazodone). Literature searches were performed via PubMed database by using search terms "[medication name]," "seizure," "epilepsy," "status epilepticus," and/or known or potential associated genetic mutations. Additionally, we summarize pertinent pharmacokinetics, adverse effects, and known and potential interactions with neurologically focused medications to further guide clinical application.

Ketamine. Ketamine exerts its action via noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism, resulting in the blockade of glutamate—the major excitatory neurotransmitter in the central nervous system. [see Table 1] The blockade of glutamate ultimately results in analgesia, modulation of central sensitization, and reduction of polysynaptic spinal reflexes.[8,9] Ketamine's US Food and Drug Administration (FDA) approved indications are limited to anesthetic purposes (sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation;

Table 1. Ketamine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[8,9]

Labeled/Reported Dosing	IM	5–13 mg/kg (Indications: induction of anesthesia; procedural sedation/analgesia)
	IN	0.5–6 mg/kg/dose (Indications: acute pain; preanesthetic sedation; procedural sedation/analgesia)
	IV	Loading dose: 0.5–2 mg/kg Maintenance: 0.3–15 mg/kg/hr (Indications: induction of anesthesia; procedural sedation/analgesia; sedation/analgesia in critically ill patients; status epilepticus)
	PO	5–8 mg/kg/dose (Indications: preanesthetic sedation; procedural sedation/analgesia)
	PR	8–10 mg/kg/dose (Indications: preanesthetic sedation; procedural sedation/analgesia)
Pharmacokinetics	Onset	~30 sec (IV); 3–15 min (IM); 5–10 min (IN); 9.5–30 min (PO)
	Peak	5–30 min (IM); 10–20 min (IN); ~30 min (PO); ~45 min (PR)
	Bioavailability	93% (IM); 20%–30% (PO); 35%–50% (IN); 25% (PR)
	Distribution	2.1–3.1 L/kg
	Protein binding	27%
	Metabolism	Hepatic; active metabolite norketamine 33% as potent as parent compound (higher norketamine concentrations with PO due to extensive 1st pass metabolism)
	Half-life	4–6 hr; ~7 hr (CrCl < 30 mL/min); 9.7 hr (ESRD)
	Excretion	Urine (91%); feces (3%)
Interactions	Increased CNS depression	Barbiturates; benzodiazepines; cannabinoid containing products; dexmedetomidine; ethosuximide; felbamate; fenfluramine; gabapentin; lacosamide; lamotrigine; levetiracetam; methsuximide; perampanel; propofol; stiripentol; tiagabine; topiramate; vigabatrin; VPA; zonisamide
	Decreased ketamine serum concentration	CYP2B6 inducers (moderate, strong); CYP3A4 inducers (moderate, strong)
	Increased ketamine serum concentration	CYP3A4 inhibitors (strong)
Commercially Available Formulations	Solution, injection	10 mg/mL; 50 mg/mL; 100 mg/mL

CrCl, creatinine clearance; ESRD, end-stage renal disease; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; PO, oral; VPA, valproic acid and derivatives

induction of anesthesia before the administration of other general anesthetic agents; and as a supplement to other anesthetic agents).[8,9] However, ketamine's usefulness in the treatment of posttraumatic stress disorder, depression, migraines, pain, and seizures has emerged.[10–17] For seizures, it is reasonable to deduce some anti-seizure activity may stem from NMDA receptor antagonism. In fact, ketamine may be especially useful in prolonged seizures where seizures become more difficult to treat, in part due to loss of sensitivity to gamma-aminobutyric acid (GABA) agonists[18,19] but do not appear to have the same sensitivity loss to NMDA antagonists.[19–22]

Gaspard et al[23] reported experience with intravenous (IV) ketamine in the treatment of refractory status epilepticus (RSE) via a retrospective, multicenter study in 2013. Sixty episodes in patients with RSE were included for analysis (age 7 months to 74 years); 12 (20%) were less than 18 years old. The authors defined response as *likely response* being permanent control of status epilepticus (SE) within 24 hours of ketamine initiation and *possible response* being permanent

control of SE within 24 hours when ketamine was not the last medication added. Furthermore, permanent control of SE was defined as no SE recurrence during the same intensive care unit stay. Sixty-three percent (n = 38/60) had a seizure semiology of focal nonconvulsive SE, 23% (n = 14/60) were classified as generalized convulsive seizures, and the remaining seizure types varied. Only 9 patients (15%) had a prior history of epilepsy. Overall ketamine regimens included a median loading dose of 1.5 mg/kg (maximum of 5 mg/kg) followed by a median continuous infusion rate of 2.75 mg/kg/hr (maximum rate of 10 mg/kg/hr). Seven episodes were categorized as *likely response*; of *likely response* patients with available data, 6 of 6 (100%) received a loading dose of ketamine and had a maximum median rate of 7 mg/kg/hr (0.9–10 mg/kg/hr). Twelve episodes were categorized as *possible response*; of *possible response* patients with available data, 5 of 8 (63%) received a ketamine loading dose and had a maximum median rate of 1.8 mg/kg/hr (0.6–7 mg/kg/hr). Based on a stepwise, multivariable logistic regression analysis, the authors noted younger age and positive response to ketamine were associated with lower mortality. It was also noted that improved response was observed with "early" ketamine initiation (e.g., third- or fourth-line agent in contrast to agent introduced > 8 days into a course or as a seventh-line agent or later).[23]

In one of the largest studies examining ketamine in the management of pediatric and neonatal RSE, Jacobwitz et al[24] reported positive outcomes. Sixty-nine patients in the intensive care unit (median age = 0.7 [0.15–7.2] years) underwent continuous electroencephalogram (EEG) and were treated with ketamine. At baseline, 17 of 69 patients (25%) had preexisting epilepsy; the majority were classified as focal (9 of 17 [53%]), while 2 of 17 (12%) were classified as generalized. The remaining 6 of 17 (35%) were classified as having both focal and generalized seizure types. Sixty-five patients (94%) received a ketamine bolus (specific dosing not defined); continuous ketamine infusions ranged from 1 to 7 mg/kg/hr. After ketamine initiation, seizure termination on continuous EEG was seen in 32 of 69 patients (46%), seizure reduction in 19 of 69 patients (28%), and no change in 18 of 69 patients (26%). Of the 51 of 69 patients (74%) with complete or some reduction in seizures, 37 (73%) saw effects within 6 hours of ketamine initiation. Of note, seizure termination was more likely to be seen when ketamine was administered as the first anesthetic antiseizure medication (ASM) compared with ketamine administered after midazolam (23/38, 61% vs 9/31, 29% [$p < 0.01$]).[24] While one of the largest studies in this population, generalizability is limited as it was performed at a single institution. Interpretations for neonates may also be limited due to the small neonatal sample size. Additionally, clinician variation in clinical data interpretation may be present as multiple practitioners were involved in the interpretation, classification, and documentation.

In a case series of 3 pediatric patients with RSE and super-refractory SE, DeVine et al[25] reported some success with adjunctive continuous ketamine infusions. All 3 patients (aged 29–79 days) were refractory to an average of 6 ASMs at optimized doses before ketamine initiation. Ketamine infusions were initiated at 1 mg/kg/hr and titrated up, with 1 patient requiring a maximum of 6 mg/kg/hr. After ketamine initiation, patients were maintained on an average of 3 ASMs; additionally, 1 patient was able to taper a benzodiazepine continuous infusion to a lower rate. However, 1 patient, in whom ketamine was initiated on day 7, did not have a response to ketamine after 5 days and was tapered off over 24 hours. The second patient initiated ketamine on hospital day 52 (24 hours after the patient's first seizure), and seizures ceased within 1 hour of ketamine initiation. Over the course of admission and readmissions, ketamine was tapered, and seizures recurred. Once ketamine resumed, most clinical seizures resolved, and some subclinical seizures remained. In the last patient, ketamine was initiated on day 7 of admission after the patient was placed on continuous renal replacement therapy due to propylene glycol toxicity from pentobarbital. Unfortunately, no significant changes were seen on the EEG by day 8, and the family opted for limitation of life-sustaining therapy. The patient passed away shortly thereafter. The authors stated it was unclear if seizures were controlled on continuous ketamine in this patient.[25]

In a 2022 single-center, retrospective review, Machado et al[26] presented data that could further delineate effective SE seizure termination with ketamine. Twenty-four adult patients with RSE were included; all patients' video EEGs were examined for any changes after ketamine administration. Patients were classified as responders (complete seizure cessation of electrographic seizures and no recurrence of SE during admission) and nonresponders (cessation of electrographic seizures with recurrence of SE during the same admission or no cessation of SE). Ketamine doses were not significantly different between responders and nonresponders; patients were administered a loading dose (101–105 mg) and started on a ketamine infusion (0.69–6 mg/kg/hr). Ultimately, 12 of 24 patients (50%) were classified as responders. All 12 responding patients' EEGs showed significantly more beta activity superimposed to the background 1 hour after ketamine was initiated compared with only 4 of 12 (33.3%) in the nonresponder group ($p = 0.001$). Further statistically significant differences were seen between the responder and nonresponder groups' EEG backgrounds at the ketamine peak dose. Theta with superimposed beta activity was seen in 11 of 12 (91.6%) responders and only 4 (33.3%) nonresponders ($p = 0.003$); sustained beta activity was statistically significantly observed in 11 of

12 (91.6% responders) and 1 of 12 (8.3%) nonresponders (p = 0.005). In contrast to Jacobwitz et al[24] and Gaspard et al,[23] time to ketamine initiation was not found to be significantly different between responders and nonresponders.[26] Like Jacobwitz et al,[24] however, varying clinicians documented, interpreted, and analyzed a myriad of data points—thus limiting consistency and increasing the potential for bias.[26] Machado et al[26] did not report any side effects in their subjects throughout the duration of the study. The authors concluded background superimposed beta activity induced by ketamine could be an early, reliable EEG finding indicating the success of SE termination.[26]

Perlmutter et al[27] reported promising results in a 6-patient case series using IV and IM ketamine as a prehospital, second-line ASM for pediatric seizures refractory to benzodiazepines. All 6 patients (aged 18 months to 10 years) received ketamine after multiple doses of benzodiazepines (diazepam PR/IV, midazolam IN/IM/IV) and/or levetiracetam IV; 5 patients (83%) received ketamine IV at doses ranging from 1.6 to 2.5 mg/kg and 1 patient (17%) received IM ketamine at a dose of 4.1 mg/kg. All 6 patients were noted to have seizure resolution after ketamine, and only 1 patient experienced further seizures after presentation to the emergency department. Only 1 patient was noted to have any side effects; this ventilator-dependent patient was noted to have a decreased oxygen saturation of 70% after ketamine administration. Baseline oxygen saturation was not recorded. It is unclear if the desaturation was related to the patient's underlying respiratory condition, prolonged seizures, or ketamine administration. Perlmutter et al[27] acknowledged the small sample size and retrospective review of emergency medical services records as limitations but concluded that, despite these limitations, ketamine might appear to be a safe and useful medication in the prehospital setting for seizures unresponsive to benzodiazepines.[27] This report is unique in that it provides evidence of safe and efficacious applications in a prehospital setting as most literature examines ketamine administration in-hospital and as a later-line option. While this case review alone is not compelling enough to warrant protocol changes, it could perhaps spur the design and implementation of more robust trials. This could further elucidate optimal ketamine implementation in pre- and in-hospital seizure emergencies.

Pin et al[28] described their experience with ketamine in a patient with neonatal seizures. The authors additionally systematically reviewed 7 other cases of ketamine application in neonatal seizures. In the single case report from their institution, a term male with an uneventful gestational period and birth presented with apneic spells and bilateral clonic jerks at 18 hours of life. An EEG subsequently revealed multifocal seizures, and magnetic resonance imaging showed abnormal diffusion restriction in fronto-temporal-parietal cortical/subcortical regions and thalamus bilaterally. The patient's seizures worsened and soon developed into RSE (unresponsive to phenobarbital, levetiracetam, phenytoin, midazolam, lidocaine, and pyridoxine). Thiopental reduced clinical seizures, but electrical seizures persisted. Ketamine 10 mcg/kg/min was initiated and titrated up to 100 mcg/kg/min. Electroclinical seizures ceased, and all other ASMs and sedative medications were able to be tapered to discontinuation. Unfortunately, imaging showed diffuse white matter edema and bilateral necrotic lesions; the patient had severe neurologic impairment, extensive brain damage, and the absence of spontaneous respiratory activity and ultimately passed at day 23 of life. In the subsequent review of 7 other cases, 6 of 7 patients had seizure cessation, and 1 had seizure reduction in the acute phase with the addition of ketamine (1.5–100 mcg/kg/hr). Most patients received phenobarbital as the first line, followed by phenytoin, midazolam, levetiracetam, lacosamide, and/or propofol; ketamine was the third or later line ASM in 6 of 7 patients. Two patients passed after withdrawal of care due to poor prognosis. At follow-up (3–17 months), 3 of the remaining 5 patients achieved complete seizure cessation; only 1 patient had poor control of seizures. Pin et al[28] concluded ketamine could likely be used safely as a third-line ASM in neonatal status epilepticus—especially given the alternative mechanism compared to the traditional GABAnergic ASM. While these results and analyses seem promising, caution must be observed as a singular case report may not provide strong data for clinical action. It does, however, yield promise in the potential for larger-scale future studies in neonates.[28]

Ketamine is generally well tolerated when used for SE. Gaspard et al[23] reported a discontinuation rate of 7% (n = 4). One patient developed a propofol-related infusion syndrome-like reaction (4 mg/kg/hour for 4 days). Supraventricular tachycardia (n = 2) and an idiopathic adverse reaction (n = 1) led to ketamine discontinuation as well.[23] Sabharwal et al[29] reported hypothermia incidences in 41 of 79 patients (52%) treated with ketamine; higher ketamine infusion rates and longer durations appeared to be statistically significant (p = 0.001 and p = 0.048, respectively) in those who did and did not experience hypothermia. Jacobwitz et al[24] reported adverse effects requiring intervention in 3 of 69 patients (4%). One patient experienced delirium requiring quetiapine administration; 2 patients experienced hypertension requiring intervention and ketamine infusion wean.[24] Pin et al[28] did not report any side effects in the 8 case reports of ketamine use in neonatal SE.

The retrospective nature of many of these studies presents commonly observed barriers to interpretation—lack of control for comparison, recall bias, potential for missing data, and so on. It should be considered that the severity of the episode may influence the

response or lack of response to ketamine. Alternatively, it cannot be completely ruled out there may be spontaneous resolution of SE or that positive response may be a result of cumulative or delayed effects of concomitant medications.

Ketamine presents a unique opportunity to add to the treatment options for refractory and super refractory status epilepticus in pediatric and neonatal patients. Most seizure rescue medications target inhibitory pathways via GABA and GABA receptors. Ketamine provides an alternative mechanism through the downregulation of excitatory neurologic pathways via NMDA antagonism. Additionally, ketamine could have potential for alternative routes of administration in which other seizure rescue medications are limited. The intranasal route for benzodiazepines for seizure rescue is quite established.[30,31] Intranasal ketamine administration for various indications such as migraine, pain, and depression are reported in the literature.[10,13,14,32] However, only anecdotal reports of intranasal ketamine for seizure rescue exist, indicating an area for future exploration and research that could potentially benefit patients. Ketamine appears to have a relatively mild side effect emergence when used for seizure cessation; side effects may be attenuated by minimizing dose and exposure time if possible. The American College of Emergency Physicians does present potential hesitation for use in infants younger than 3 months of age; the organization considers ketamine use in this population an absolute contraindication due to the higher risk of airway complications.[8] However, in emergent situations where seizure control is of utmost importance, patient airways are often established, and the use of ketamine for a short period of time could prove to have more benefits than risks. Position within the treatment cascade is not yet established, given reports of improved outcomes with early initiation and other studies that show no significant difference in initiation latency. More robust controlled trials are needed, but data are promising and could be considered in patients with particularly refractory seizures unresponsive to at least 2 traditional rescue ASMs.

Memantine. Memantine is presently FDA approved for the treatment of moderate to severe Alzheimer's dementia.[33,34] [see Table 2]Off-label uses include depression, schizophrenia, obsessive-compulsive disorder, substance misuse, pervasive developmental disorders, bipolar disorder, and binge eating (although some data may be lacking).[35] In pediatric patients, memantine is frequently used in the treatment of attention-deficit/hyperactivity disorder and autism spectrum disorder.[35–37] The NMDA receptor antagonist, however, has shown promise in certain types of epilepsy. NMDA receptors are ligand-gated cation channels that mediate a calcium-permeable component within the excitatory pathway.[38] Through NMDA antagonism, pathologic glutamate serum concentrations can be dampened, thus downregulating excitatory neuronal pathways and, possibly, reducing seizures and seizure potential. Additionally, memantine is thought to have some potential anti-inflammatory effects—a particularly interesting characteristic in the treatment of epileptic encephalopathies, as neuroinflammation is thought to play a role in epileptogenesis.[36,39] In some cases, specific genetic mutations associated with the NMDA receptor and identified in cases of epilepsy (e.g., *GRIN1*, *GRIN2a*, *GRIN2b*) may be particularly susceptible to the positive effects of memantine on seizure control.[38]

Table 2. Memantine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[33,34]

Labeled/Reported Dosing	PO	IR: 5–20 mg/day divided 1–2× daily ER: 7–28 mg daily (Indications: Alzheimer's disease, dementia)
Pharmacokinetics	Peak	3–7 hr (IR); 9–12 hr (ER)
	Absorption	Well-absorbed; not affected by food
	Distribution	9–11 L/kg
	Protein binding	45%
	Metabolism	Partially hepatic
	Half-life	~60–80 hr
	Excretion	Urine (74%; ~48% as unchanged drug)
Interactions	Enhanced memantine adverse/toxic effect	NMDA receptor antagonists; trimethoprim (increased risk of myoclonus)
	Increased memantine serum concentration	Alkalinizing agents; carbonic anhydrase inhibitors
Commercially Available US Formulations	Capsule ER 24 hr, oral	7 mg, 14 mg, 21 mg, 28 mg
	Solution, oral	2 mg/mL
	Tablet, oral	5 mg, 10 mg

ER, extended release; PO, oral; IR, immediate release; NMDA, N-methyl-D-aspartate

In 2023, Schiller et al[39] performed a single-center, randomized, double-blind, placebo-controlled crossover clinical trial examining memantine therapy in pediatric patients with developmental and epileptic encephalopathy (DEE)—severe epilepsy with childhood onset characterized by refractory seizures, developmental regression, and EEG abnormalities. Patients with DEE frequently have genetic abnormalities or inflammation after a brain injury; additionally, behavioral disturbances often accompany cognitive deficits, presenting unique and often challenging quality of life considerations for the patients and caregivers. Patients aged 6 to 18 and over 20 kg were included. Patients were randomized to receive memantine followed by placebo or vice versa. Memantine doses were increased in a stepwise manner (5 mg daily × 1 week; 5 mg twice daily × 1 week; 5 mg + 10 mg × 4 weeks); a 2-week washout period was applied between memantine/placebo treatment changes, and a final evaluation was performed at week 16. Investigators assessed treatment response via caregiver seizure diary and EEG obtained after each treatment phase compared with baseline as interval worsening, no significant change, or interval improvement. The primary outcome was responder rate (defined as having 2 of the following: > 50% reduction in seizure frequency, EEG improvement, caregiver impression of improvement, or clear improvement on neuropsychological testing). Ultimately, 27 patients enrolled. Epilepsy syndromes of enrolled patients included DEE of unknown etiology (n = 12), Dravet Syndrome (DS, n = 5), DEE with spike-and-wave activation in sleep (n = 3), and Lennox Gastaut Syndrome (LGS, n = 3); other syndromes reported with an n of 1 were infantile epileptic spasms syndrome, epilepsia partialis continua with regression, epilepsy with myoclonic-atonic seizures, and febrile infection–related epilepsy syndrome. Primary etiologies included *SCN1a* pathogenic variant (n = 6 [22%]) or known or suspected prenatal/perinatal brain injury (n = 5 [19%]); other etiologies with an n of 1 included *GRIN1* pathogenic variant, *GRIN2B* likely pathogenic variant, *DYNC1H1* pathogenic variant, biallelic *POLG* pathogenic variants, *CLCN4* likely pathogenic variant, and brain malformation. A further 10 patients were classified as having an unknown etiology. The memantine group had a statistically significant higher responder rate compared with placebo (9 [33%] vs 2 [7%], $p < 0.04$). Additionally, of those patients on whom EEGs could be obtained (patients were excluded from EEG monitoring if there was a known history of continuous spike wave in sleep), the memantine group had statistically significant EEG improvement and seizure improvement compared with placebo (8 [30%] vs 2 [4%], $p < 0.04$ and 8 [30%] vs 2 [4%], $p < 0.04$, respectively). While perceived behavioral improvements per caregiver impressions were not statistically significant between treatment groups, there was a numerical clinical improvement noted (10 [37%] vs 7 [26%]). Unfortunately, subgroups of epilepsy syndromes and genetic etiologies were too small to perform subgroup analyses. No serious adverse effects were reported. Ultimately, Schiller et al[39] concluded memantine could be a potentially efficacious medication in children with DEE.

Memantine application within the spectrum of epilepsy could potentially be further individualized. Several reports of improved efficacy in the presence of specific genetic mutations have been reported. Bouhadoun et al[36] retrospectively reviewed experiences with 8 pediatric patients aged 2 to 16 years, who were receiving memantine for a neurologic diagnosis.[36] Of these 8 patients, 4 had a diagnosis of epilepsy (2 with DEE; 1 with drug-resistant focal epilepsy and suspected autoimmune encephalitis; 1 with focal epilepsy). Of these 4 patients, all had genetic testing results revealing the following mutations: *GRIN2A* VUS [c.2888 T>C, p.Leu963Pro], Biallelic *PLCB1* pathogenic variants, likely pathogenic *ATP1A2* variant, and variant of uncertain significance in *ATP6*. Only 1 patient's seizures were well controlled at baseline; otherwise, seizure frequency ranged from 3 to 5 seizures per month, with up to 2 to 6 seizure clusters per day. Initial memantine dose in epilepsy patients ranged from 0.1 to 0.17 mg/kg/day (max 5 mg/day); doses were titrated up to a maximum range of 0.2 to 1 mg/kg/day (max 20 mg/day). In 1 patient with DEE, seizure frequency significantly decreased from 3 to 4 seizures per day to approximately 4 seizures per year, while in the other patients, no clear benefit was observed. Of note, the 1 patient with significant response to memantine was the patient with the *GRIN2A* mutation. *GRIN2A* is the gene that encodes the 2A subunit of the NMDA receptor; the authors hypothesized that the clinical benefit in seizure reduction could have been due to the targeted effect on an overactive mutant receptor.[36] Small sample size limits generalizability and limits statistical conclusions due to insufficient power for analyses. However, these findings provide a potential jumping-off point for larger, more robust studies to examine memantine and *GRIN2* mutations.

Similarly, other smaller case studies have reported success with memantine in *GRIN*-related mutations. Mir et al[40] reported success in a pediatric patient with West Syndrome, likely secondary to a *GRIN2A* mutation. The 3-year-old male patient's genetic testing revealed a heterozygous *GRIN2A* variant [c.1083G>A(p.Leu361=]. Of previously trialed ASMs, lacosamide and the ketogenic diet had some benefits, but he continued to have epileptic spasms. He was initiated on memantine 0.15 mg/kg/day and titrated up to 1 mg/kg/day. After memantine initiation, the patient achieved seizure cessation for nearly 10 months. The only recurrence was due to a febrile illness, and the patient returned to a seizure-free state thereafter.[40]

Li et al[38] described their experience with the application of memantine in 2 patients with *GRIN2D*

mutations (c.1999G>A (P.Val667Ile)) in the setting of refractory epilepsy. For the first patient, a 6.5-year-old female, memantine was initiated at 2 mg daily for 1 week and titrated up by 2 mg weekly to a goal dose of 20 mg daily (0.85 mg/kg/day). As no improvement of clinical or subclinical seizures on EEG was noted and memantine was subsequently discontinued; however, after memantine discontinuation, complex focal seizures became more frequent and memantine was restarted and escalated to 20 mg/day (1.3 mg/kg/day). While memantine was well tolerated, the patient did not see any further improvement. Of note, after many medication changes and admissions, oral ketamine and magnesium appeared to resolve subclinical seizures, and the patient remained clinically seizure free. The second patient, a 2.5-year-old female, was initiated on 0.5 mg/kg/day of memantine. At baseline, the patient reported 29 seizures over the 5 days before memantine initiation (5.8 seizures/day). After memantine initiation, during the 5 days preceding discharge, the patient's seizure burden had reduced by 59% (2.4 seizures/day). Moreover, at a 3-week follow-up, the patient had complete seizure freedom, and developmental improvement was noted (e.g., improved visual fixation, motor development progress).[38]

Overall, memantine appeared to be well tolerated among the previous reports. Common side effects noted on medication labeling include confusion, dizziness, headache, agitation, hallucinations, abdominal pain, and urinary retention.[33] Schiller et al[39] described 1 patient with reported "deterioration of behavior" after starting memantine, which led clinicians to discontinue memantine. However, this behavior was felt to be within the patient's baseline behavior fluctuation, and no improvement in behavior fluctuations was seen after memantine discontinuation.[39] Bouhadoun et al[36] reported 1 patient experiencing nocturnal incontinence and another experiencing decreased appetite (neither of which were patients with epilepsy).

Memantine, especially applied in cases of identified genetic mutations, could be especially helpful in the treatment of drug-resistant epilepsies. However, more robust studies are needed to further bolster seemingly safe and effective reports. While current data are promising, responses can be quite variable—even with similar genetic mutations. Factors such as age, mutation-specific impacts, or treatment timing could potentially affect results; thus, more data are needed to truly determine memantine's true role in precision medicine. Many factors (e.g., epileptic syndrome diagnosis, seizure type, genetic mutations, age, etc.) may affect patient response and need and should be weighed seriously when considering memantine in the treatment of drug-resistant epilepsies. Memantine, regardless, appears to show promise in many instances and could be considered in patients with *GRIN* mutation–related epilepsies and patients with DEE when traditional ASMs do not appear to produce an adequate response.

Quinidine. Quinidine is an older medication traditionally used in treating malaria and cardiac arrhythmias. [see Table 3] Specifically, the Class Ia antiarrhythmic has an FDA indication for the treatment of atrial fibrillation/flutter conversion, reduction of frequency of relapse into atrial fibrillation/flutter, and suppression of ventricular arrhythmias.[41,42] It exerts antiarrhythmic activity by depressing rapid, inward depolarizing sodium currents in cardiac muscle and Purkinje fibers ultimately slowing phase-0 depolarization and reducing amplitude without affecting resting potential.[41–43] Use largely ceased when its proarrhythmic potential due to QT prolongation and gastrointestinal intolerance became more widely observed.[44] Recent studies and meta-analyses of quinidine for antiarrhythmic therapy demonstrated increased mortality—especially in those with structural heart disease.[41,42] Of note, the 2 salt formations available (quinidine gluconate and quinidine sulfate) are not interchangeable. Additionally, the IV formulation is discontinued in the United States. In the treatment of malaria, quinidine appears to act primarily as an intra-erythrocytic schizonticide (an agent selectively destructive of the multinucleated form stage of a sporozoan parasite) and is gametocidal to *Plasmodium vivax* and *Plasmodium malariae* (not to *Plasmodium falciparum).*[41,42,45]

Recently, quinidine has been investigated as a treatment for epilepsies secondary to *KCNT1* variants. *KCNT1* encodes a potassium sodium–activated channel subfamily T member 1, and mutations in the gene typically result in channel gain-of-function, the magnitude of which correlates with the clinical severity of epilepsy. This gene has been implicated in several epilepsy syndromes, including autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) and epilepsy of infancy with migrating focal seizures (EIMFS). *KCNT1*-related epilepsy, notably, typically responds poorly to conventional ASM treatment and can significantly negatively affect the patient's (and caregiver) quality of life.[46,47]

An observational, multi-institutional study of 43 *KCNT1*-related epilepsy patients was performed by Fitzgerald et al[48] in 2019. The team sought to compare the response to traditional treatments as well as quinidine in the cohort of *KCNT1* patients (which, remarkably, is one of the world's largest databases of *KCNT1* epilepsy patients). Clinical phenotypes of enrolled subjects included EIMFS (n = 28), early-onset epileptic encephalopathy (EOEE) (n = 9), and ADNFLE (n = 6). To ensure the response to quinidine was not transient, seizure reduction was considered sustained if a percent reduction in seizures lasted for at least 3 months. Quinidine was utilized in 20 patients with daily doses ranging from 30 to over 90 mg/kg/day. Quinidine was not utilized in any of the patients with ADNFLE but was utilized in 17 EIMFS (61%) and 3 early-onset epileptic

Table 3. Quinidine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[41,42]

Labeled/Reported Dosing	IV (gluconate)	Loading: 10 mg/kg over 60–120 min Maintenance: 0.02 mg/kg/min (Indication: malaria [severe/life-threatening])
	PO (sulfate)	15–60 mg/kg/day divided every 6 hr (Indication: tachyarrhythmia [SVT, AFib, AF, VT])
Pharmacokinetics	Peak	2 hr (sulfate); 3–5 hr (gluconate)
	Bioavailability	45%–100% (sulfate); 70%–80% (gluconate)
	Distribution	2–3 L/kg (adults)
	Protein binding	50%–70% (neonates, infants); 80%–88% (older pediatric, adults)
	Metabolism	Hepatic (50%–90%)
	Half-life	3–4 hr (pediatrics); 6–8 hr (adults)
	Excretion	Urine (5%–20% unchanged)
Interactions	Decreased quinidine serum concentration	CYP3A4 inducers (moderate, strong)
	Increased quinidine serum concentration	CYP3A4 Inhibitors (moderate, strong); grapefruit juice
	Increased concomitant medication serum concentration	Carbamazepine; everolimus; fenfluramine; midazolam; sirolimus (X)
	Increased risk of cardiac side effects (bradycardia, QTc prolongation)	Citalopram (X); lacosamide; propofol; quetiapine (X)
Commercially Available Formulations	Tablet ER, oral (gluconate)	324 mg
	Tablet, oral (sulfate)	200 mg, 300 mg

AF, atrial flutter; AFib, atrial fibrillation; ER, extended release; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; PO, oral; SVT, supraventricular tachycardia; VT, ventricular tachycardia; X, contraindicated

encephalopathy (33%) patients. Sustained seizure freedom was observed in only 1 patient (5%); a more than 50% reduction was observed in 4 patients (20%)—all of whom had a *KCNT1* epilepsy phenotype of EIMFS. Worsened seizures were reported in 3 subjects (15%). Also of note, no statistically significant difference in seizure frequency was noted between patients receiving quinidine versus those not receiving quinidine. Those patients who responded to quinidine appeared to be older. The authors additionally evaluated variant-specific responses. The *KCNT1* variant G288S demonstrated both responsiveness and nonresponsiveness to quinidine. Patients with the *R474H* variant saw no quinidine response. Additionally, patients with *R929Q*, *R950Q*, and *R961S* variants demonstrated transient seizure freedom for at least 1 month. These 3 variants are notably immediately distal to the NADP domain within the RCK2 domain on the *KCNT1* protein. This region, the authors note, is "hypothesized to be important in coupling sensitivity to intracellular sodium levels with channel gating." Though results are not as promising as other reports in nontraditional ASMs, authors highlight an important population and that future studies may be targeted at efficacy in patients with *KCNT1* variants *G288S*, *R929Q*, *R950Q*, and *R961S*. It may be difficult, however, because of the small patient population of known patients with *KCNT1* epilepsy.[48]

Mullen et al[49] performed a single-center, randomized, blinded, placebo-controlled crossover trial of oral quinidine in patients with ADNFLE secondary to *KCNT1* mutation.[49] The difference in video EEG-measured seizure frequency between quinidine and placebo was noted as the primary outcome; secondary endpoints included a 50% response rate, tolerability, and paroxysmal arousal rate. Six patients were enrolled and randomized; 4 were adults (ages 28–54), while 2 were pediatric subjects (ages 15 and 17 years). Subjects received either drug or placebo for 2 blocks of 4 days with a 2-day washout period between blocks; a 2-day post-completion inpatient stay was applied to ensure patient safety. Four patients ultimately completed the trial as 2 patients (patient 1 and patient 2) were withdrawn due to dose cardiac toxicity. Patients 1 and 2 were initiated on a dose of 900 and 600 mg/day, respectively. The serum concentrations of these 2 patients were below the normal antiarrhythmic therapeutic range (0.61 and 0.51 mcg/mL, respectively). Subsequent subjects were initiated at a dose of 300 mg/day. The remaining 4 patients did not experience adverse events. Of the 4 patients completing the study, 3 were observed to have

increased focal seizures, and 2 had increased paroxysmal arousals. Seizure frequency was not significantly different between placebo and quinidine groups (p = 0.15). Though the sample size is small, Mullen et al[49] demonstrated quinidine is likely not just inefficacious but can worsen seizures in patients with ADNFLE secondary to a *KCNT1* mutation.

Mikati et al[50] reported 2 patients with EIMFS caused by *KCNT1* mutations. Patient 1, an 11-year-old female, had a heterozygous de novo *KCNT1* mutation (NM_020822.1:c.2386T>C; p.[Tyr796His], *Y796H*) which was previously reported in a family with ADNFLE. The *Y796H* variant resulted in a significantly greater magnitude of peak current in channels compared with the wild type during in vitro testing. When quinidine was applied in vitro, there was significant inhibition of the *Y796H* channel, ultimately reducing currents. Patient 1 was thus admitted on 3 separate occasions for quinidine dose initiation/titration; quinidine was initiated and titrated over 3 days to 11, 40, and 54 mg/kg/day divided into 3 doses. On the last admission, the mean serum quinidine concentrations did not appear to increase, and QT prolongation was noted; the dose was subsequently reduced from 54 to 34 mg/kg/day. The patient did not have a statistically significant reduction in seizure frequency from baseline, though minimal reduction was reported from baseline (3.1 seizures/day) to a quinidine dose of 34 mg/kg/day (2.8 seizures/day). EEGs did not show any significant changes throughout any admission, but investigators reported minimally improved alertness and interaction.[50]

The second case was a 3-year-old male with a de novo *KCNT1* mutation (NM_020822.2:c.1887G>C; p.[Lys629Asn], *K629N*).[50] In vitro functional testing showed the *K629N* variant was also a GOF and increased channel magnitude (greater than that of the *Y796H* variant). Of note, quinidine application was less effective in channel current reduction in the *K629N* mutation compared with the wild type or *Y796H*. At quinidine initiation, the EEG showed interictal multifocal spikes, ictal electrodecremental fast beta rhythms, and multifocal subclinical electrographic seizures. Additionally, multiple daily seizures were present, magnetic resonance imaging showed diffuse atrophy, and the patient had failed 8 ASMs and the ketogenic diet. Three admissions for treatment titration occurred. On the first admission, quinidine was initiated at 12 mg/kg/day divided 3 times per day and was titrated up to 22.6 mg/kg/day in 3 divided doses over 4 days. During the second admission, quinidine was titrated further over 4 days to a dose of 34.4 mg/kg/day in 3 divided doses. Mean quinidine serum concentrations reached 0.3 and 0.77 mcg/mL after the second and third titrations, respectively. The patient experienced an 80% reduction in seizure frequency (mean baseline daily seizure frequency = 4.15 seizures/day vs quinidine treatment 34 mg/kg/day = 0.83 seizures/day). Investigators also noted patient 2 was more alert and more interactive and did not have QT interval changes.[50]

Bearden et al[51] reported another 3-year-old female with EIMFS and a *KCNT1* mutation (c.1283G>A; p.Arg428Gln) treated with quinidine. The patient previously trialed phenobarbital, levetiracetam, phenytoin, topiramate, valproic acid, lamotrigine, clorazepate, gabapentin, clobazam, and ketogenic diet without significant seizure reduction. A baseline seizure frequency of 5 seizures per day and developmental arrest/regression were noted. Upon admission, the ASM regimen consisted of topiramate, levetiracetam, clobazam, gabapentin, and ketogenic diet before quinidine was added up to 100 mg every 6 hours (33 mg/kg/day). After 1 week at the target dose, the patient became seizure free and remained seizure free for the next 6 weeks. Additionally, development appeared to improve and was characterized by improved head control, an increase in spontaneous movement, alertness, and initiation of single-word speech. After 6 weeks, seizures returned at a rate of 0 to 2 seizures/day; quinidine was increased to 42 mg/kg/day, and seizures again resolved. This resolution continued for nearly a year except for slight seizure emergence during times of illness. Quinidine serum concentrations remained within a typical therapeutic range for arrhythmia treatment (1.5–4 mcg/mL). No adverse effects were observed.[51]

Abdelnour et al[52] described 3 cases of quinidine treatment in patients with *KCNT1*-related epilepsy. The authors defined response as a greater than 50% reduction in seizure frequency. Of note, older patients (9 and 13 years old) did not respond to quinidine doses of 60 and 36 mg/kg/day divided 3 times daily and had focal seizures and asymmetric tonic seizures, respectively. However, a 3-month-old patient EIMFS went from 3.2 seizures/hour at baseline to 1 seizure/hour on quinidine 40 mg/kg/day divided 3 times daily. Abdelnour et al[52] concluded that, after analysis of the current literature, response to quinidine might be age dependent and patients younger than 4 years may be more likely to respond to quinidine.

In contrast, Chong et al[53] described a lack of efficacy using quinidine treatment in a 6-year-old male with a gain of function *KCNT1* mutation (*R428Q*) and without a diagnosis of EIMFS. Before quinidine initiation, baseline seizure frequency was 106 ± 13.3 seizures/month. Quinidine was initiated and adjusted to maintain serum quinidine concentration troughs of 1.5 to 3 mcg/mL (maximum dose reached: 73 mg/kg/day). Unfortunately, the authors noted no improvement in seizure frequency after quinidine therapy.[53]

A successful case report of quinidine treatment in a 12-year-old male with LGS with a *KCNT1* mutation (c.625C>T) was described by Jia et al[54] in 2019. The patient had no history of perinatal asphyxia, head injury, or encephalitis and an unremarkable family

history of seizures. In fact, the patient was seizure free until the age of 10 years. The patient was refractory to valproate, levetiracetam, clonazepam, topiramate, and lamotrigine and experienced multiple seizure types, including tonic, atypical absence, myoclonic, and generalized tonic-clonic refractory to valproic acid, levetiracetam, clonazepam, topiramate, and lamotrigine. Given the refractory nature of the patient's seizures and the identification of the *KCNT1* mutation, a trial of quinidine was approved by the institution's ethics committees, guardians, and physicians. In the month before quinidine initiation, 16 tonic, 12 atypical absence, 10 myoclonic, and 1 generalized tonic-clonic seizure(s) were documented. Quinidine was initiated at 5 mg/kg/day in 3 divided doses and was titrated over 4 months up to 13.75 mg/kg/day in 3 divided doses; the patient was maintained at this dose for another 4 months. At the end of the assessment period, tonic seizures were reduced to 4 seizures per month (75% reduction); other seizure-type frequencies remained the same. No side effects were noted, and the QTc interval remained normal throughout therapy.[54]

Quinidine side effects on labeling range from diarrhea (24%), to fever, rash (6%), arrhythmia, abnormal electrocardiogram, dizziness (3%), and cerebral ischemia (2%).[41,42] Fitzgerald et al[48] similarly reported sedation (11%), arrhythmia (5%), elevated liver function tests (5%), and rash (5%). However, the most common side effect with quinidine therapy in the reviewed manuscripts appears to be QTc prolongation—Fitzgerald et al[48] reporting a 47% rate.[50,52] Prolongation may require dose reduction. Specifically, FDA labeling recommends a reduction if the QRS complex widens to 130% of the pretreatment duration; the QTc interval widens to 130% of pretreatment duration and is more than 500 ms; the P waves disappear; or if the patient develops significant tachycardia, symptomatic bradycardia, or hypotension. Monitoring is recommended for 2 to 3 days once the appropriate dose has been attained.[41,42] Otherwise, in the reviewed reports, quinidine appeared to be well tolerated.[50,52]

Quinidine may have some value repurposed to treat *KCNT1*-related epilepsies. There are conflicting reports in regard to age and potential response to quinidine; in the largest observational review, authors concluded older pediatric patients responded more favorably to quinidine than their younger counterparts (median age 4 years vs 11 months, respectively). Patients with a diagnosis of EIMFS appear to respond more favorably compared with other *KCNT1*-related epilepsies based on current available data. Even at higher doses, serum concentrations did not seem to rise above normal antiarrhythmic ranges of 2 to 5 mcg/mL. Rather, the therapy-limiting factor appears to be QTc prolongation, suggesting regular cardiac monitoring would be wise if considering initiation. Unfortunately, most conclusions to date are tenuous as they are gleaned from case studies, case series, or small retrospective reviews. While intriguing, it is arguably still contentious to consider the clinical application of quinidine unless all other reasonable ASMs have been trialed—and even then, great caution and consideration must be taken. While more data are needed to define dosing and substantiate efficacy claims, in patients with *KCNT1*-related epilepsy who have exhausted all traditional ASM options, quinidine could be considered with great thought and caution while closely monitoring for increased seizure frequency with initiation and titration.

Riluzole. A member of the benzothiazole class, riluzole is presently indicated for the treatment of amyotrophic lateral sclerosis; however, riluzole also appears to have some neuroprotective properties in other neurologic diseases (e.g., traumatic brain injury, Parkinson's Disease, Alzheimer's Disease).[55,56] [see Table 4] The exact mechanism of action in the treatment of amyotrophic lateral sclerosis is not fully elucidated; however, riluzole is known to be a glutamate inhibitor; specifically, riluzole exerts action pre- and post-synapse via inhibition on glutamate release and inactivation of voltage-dependent sodium channels.[55–59] Some reports suggest riluzole may inhibit potassium and calcium channel activity and/or protein kinase C.[60] Riluzole may additionally exert an ability to interfere with intracellular events after the binding of neurotransmitters at excitatory amino acid receptors as well as strengthening GABAergic neurotransmission.[55–57] All of these modalities considered, the basis of seizure control may be partially attributed to the balance of excitatory and inhibitory action potentials. The downregulation of excitatory potential could be achieved, in part, with the inhibition of glutamate and glutamatergic receptors and regulation of action potential, and the upregulation of inhibitory potential may be achieved by attenuating the ability to respond to GABA (all aforementioned mechanisms suggested in the efficacy of riluzole in neurologic diseases).

Citraro et al[56] performed EEG analysis on riluzole's effect in Sprague-Dawley rats with limbic seizures (induced by AMPA, kainite, and NMDA receptor agonists) and on Wistar Albino Glaxo/Rijswijk rats with a well-validated genetic model of absence epilepsies. Riluzole was administered before seizure induction. Riluzole appeared to be effective in both models (limbic and absence seizures); furthermore, Citraro et al[56] observed that riluzole acted mainly on the NMDA glutamate receptor. Efficacy appeared to be more sustained with incremental dose increases (0.5 mg/kg < 1 mg/kg < 5 mg/kg < 7.5 mg/kg) with a maximum reduction at 90 minutes.[56]

Tidball et al[61] used generated cell culture lines from 3 patients with sodium voltage-gated channel alpha subunit 8 (*SCN8A*) epileptic encephalopathy to examine the effect of riluzole. *SCN8a* variants present as a spectrum of phenotypes, with a severe DEE

Table 4. Riluzole Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[55,57]

Labeled/Reported Dosing	PO	50 mg BID (Indication: amyotrophic lateral sclerosis)
Pharmacokinetics	Peak	0.8 hr
	Absorption	AUC and peak blood concentrations decreased by high-fat meals
	Bioavailability	~60%
	Distribution	~3.4 L/kg
	Protein binding	96%
	Metabolism	Hepatic (CYP1A2, UGT-HP4)
	Half-life	12 hr
	Excretion	Urine (90%); feces (5%)
Interactions	Decreased riluzole serum concentration	CYP1A2 inducers (moderate)
	Increased riluzole serum concentration	CYP1A2 inhibitors (strong)
Commercially Available Formulations	Film, oral	50 mg
	Suspension, oral	5 mg/mL
	Tablet, oral	50 mg

BID, twice daily; PO, oral

most commonly characterized by refractory seizures, cognitive and motor impairment, and an increased risk of sudden unexpected death in epilepsy. SCN8A DEE phenotypes may largely be associated with gain-of-function variants resulting in severe epilepsy; loss-of-function variants may also produce generalized epilepsy and absence seizures.[62–64] These variants affect sodium channel activity; gain-of-function variants appear to increase sodium channel activity resulting in neuronal hyperexcitability and a higher neuronal firing rate—thus increasing the risk for seizure and seizures themselves.[65] Loss-of-function appears to reduce sodium channel firing, resulting in ataxia and/or myoclonus; in these instances, sodium channel blockers could potentially worsen seizures.[66,67] In the in vitro cellular models described in Tidball et al[61], phenytoin and riluzole were applied. Both phenytoin and riluzole reduced aberrant firing, but riluzole appeared to be more effective in reducing burst spikes and mean firing rates compared with phenytoin. Given these results, riluzole was initiated in 2 of 3 patients whose cells were examined, as well as an additional patient—all 3 subjects were suggested to have an *SCN8a* gain-of-function mutation.[61]

Patient 1, a 16-year-old female with myoclonic and gelastic seizure types, experienced approximately 50% seizure reduction with riluzole added onto phenytoin, clobazam, and topiramate (initial riluzole dose 25 mg/day; titrated up to 50 mg twice a day over 4 weeks).[61] Patient 1 had 164 recorded seizures (8.2 seizures/wk) at baseline and during the first 20 weeks of treatment experienced seizure reduction to 83 seizures (4.2 seizures/wk). Patient 3, a 7-year-old female with myoclonic jerks, experienced an undefined seizure reduction when riluzole was added to levetiracetam treatment (initial riluzole dose: 50 mg; titrated up to 75 mg/day). At 1 month, the patient was free of myoclonic jerks and had a notably improved EEG background. However, because of sleepiness, riluzole was reduced to 50 mg/day; an increase in seizures was noted. Patient 4 (the additional patient) experienced an initial reduction in seizures but returned to the pretreatment baseline after 4 months. Unfortunately, all 3 patients ultimately discontinued riluzole treatment because of side effects (excessive sleepiness, urinary tract infection) or loss of efficacy.[61]

Riluzole labeling specified hepatotoxicity as a potential dose- or therapy-limiting side effect that can appear within the first 3 months of use; therapy is not recommended if the baseline liver function tests are 5 times the upper limit of normal or more.[55,57] Severe neutropenia (ANC < 500/mm^3) has also been reported within the first 2 months of treatment. Other common side effects noted on riluzole labeling include dizziness, somnolence, asthenia, decreased lung function, hypertension, emesis, and urinary tract infection.[55,57] Of note, higher riluzole serum concentrations are linked with a higher risk of adverse effects. Further, patients of Japanese descent are more likely to have higher serum concentrations of riluzole, thus predisposing this particular population to a higher risk of adverse effects.[55,57] Therapy limiting side effects in human epilepsy patients, though small in number, appear to be sleepiness and urinary tract infection.[61]

The data for riluzole application in the treatment of epilepsy are limited and lacking, though potentially promising in certain populations pending more robust human studies. Riluzole, specifically, may yield positive results when patients with refractory epilepsy associated with an *SCN8A* mutation have exhausted all feasible options. Even still, side effects could hinder prolonged treatment durations. Larger retrospective and prospective studies are needed to explore dosing, efficacy, and side effects in the human population. Prescribing riluzole may present its own hurdles. Insurance companies are unlikely to cover riluzole for an indication of seizure treatment; this may subsequently cause undue financial strain on the family and/or affect the patient's ability to remain adherent to a seizure treatment regimen with riluzole. Riluzole, while possibly providing some antiepileptic activity, should be only considered with great caution, given potential access issues and limited information in humans for the treatment of seizures.

Trazodone. Initially approved for the treatment of major depressive disorder in 1981, trazodone has subsequently expanded therapeutic indications over the decades, including depression, migraine, agitation, and insomnia.[68,69] [see Table 5] Of note, sleep disorders appear to be especially prevalent in patients with DS due to a myriad of factors, including, but not limited to, nighttime seizures, medication side effects, enuresis, and dysregulated sleep patterns.[70,71] Licheni et al[71] reported sleep disturbances in 75% (n = 43/57) of studied patients with DS; Van Nuland et al[70] reported sleep was disrupted in 76% (n = 58/76) of DS patients due to non-seizure etiologies and in 53% (n = 40/76) of DS patients due to seizure etiologies.

The 5HT2a receptor antagonist inhibits serotonin reuptake, causes adrenoreceptor sub-sensitivity, induces significant 5-HT presynaptic adrenoreceptor changes, and significantly blocks histamine (H1) and alpha1-adrenergic receptors.[68,69] While depression, migraine, agitation, and insomnia are frequent indications for trazodone use, some recent animal studies suggest trazodone may have some antiseizure effect.[68,69] At first, this may seem unorthodox. The recently reintroduced

Table 5. Trazodone Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[68,69]

Labeled/Reported Dosing	PO	0.75–2 mg/kg/day divided 1–3× daily (maximum 200 mg/dose) (Indications: insomnia/sleep disturbances; major depressive disorder; migraine prophylaxis)
Pharmacokinetics	Onset	1–2 wk (depression)
	Peak	30–100 min; delayed with food
	Absorption	Well-absorbed; increased with food
	Bioavailability	100%
	Protein binding	89%–95%
	Metabolism	Hepatic; active metabolite (mCPP)
	Half-life	5–9 hr (prolonged in obesity)
	Excretion	Urine (~74%, < 1% unchanged); feces (~21%)
Interactions	Increased CNS depression	Barbiturates; benzodiazepines; brivaracetam; cannabinoid-containing products; dexmedetomidine; felbamate; gabapentin; ketamine; lacosamide; lamotrigine; levetiracetam; methsuximide; perampanel; propofol; stiripentol; tiagabine; topiramate; vigabatrin; VPA; zonisamide
	Decreased trazodone serum concentration	Carbamazepine; cenobamate; CYP3A4 inducers (moderate, strong); Fos/phenytoin; phenobarbital
	Increased trazodone serum concentration	CYP3A4 inhibitors (moderate, strong)
	Increased concomitant medication serum concentration	Carbamazepine; Fos/phenytoin
	Increased serotonergic effects	Fenfluramine
Commercially Available Formulations	Tablet, oral	50 mg, 100 mg, 150 mg, 300 mg

CNS, central nervous system; IM, intramuscular; IN, intranasal; IR, immediate release; mCPP, meta-chlorophenylpiperazine; PO, oral; VPA, valproic acid and derivatives

fenfluramine is a seemingly effective antiseizure medication in the treatment of DS and LGS and has potential serotonergic implications.[72–74] Fenfluramine and its metabolite, norfenfluramine, increase extracellular serotonin via serotonin transporter protein interaction and exhibits serotonin 5HT2 receptor agonist activity. Total seizure control may not necessarily be directly attributed to fenfluramine's serotonergic activity, but the pathway is notable and may offer an alternative effective mechanism for seizure control.[72–80] Of note, some studies in patients with temporal lobe epilepsy have shown reduced 5-HT1A receptor binding and that the decreased expression of hippocampal or neocortex 5-HT1a receptors may result in neuronal hyperexcitability and, therefore, seizure activity.[81–84] For these reasons, trazodone has been considered and examined in several preclinical animal studies. Sourbron et al[75] found selective 5-HT1D, 1E, 2A, 2C, and 7 agonists significantly decreased epileptiform activity in zebrafish larvae with homozygous *SCNa1* mutations.[75] Furthermore, local field potential measurements in zebrafish larvae forebrains confirmed antiepileptiform activity of 5-HT1D, 2C, and 2A agonists—especially the latter.[75–77] Griffin et al[85] identified 3 novel analogs of clemizole that exert meaningful epileptiform activity via 5-HT receptors (especially 5-HT2) in DS zebrafish models.

Aygun applied intraperitoneal (IP) trazodone to Wistar rats with penicillin-induced epileptiform activity and Wistar Albino Glaxo/Rijswijk rats (which represent a genetic absence model) at doses of 5, 10, and 30 mg/kg.[86] While 5 mg/kg doses did not affect frequency or amplitude, the 10 and 30 mg/kg doses significantly reduced the frequency of penicillin-induced focal seizure models. Mean epileptiform activity for 5, 10, and 30 mg/kg trazodone doses were reported as 41.57 ± 4.67, 27.87 ± 2.4, and 22.95 ± 2.94 spikes/min, respectively. Conversely, all doses produced an increase in spike-wave discharge frequency and duration in the genetic absence model rats.[86] Translatability of intraperitoneal administration to clinical practice is not feasible for regular administration in humans. Further dose findings with oral trazodone would be more beneficial for consideration in human studies.

Syntaxin-binding protein-1 *(STXBP1)* mutations—missense, nonsense, frameshifts, and deletions—are linked to neurodevelopmental disorders and drug-resistant epilepsies such as Ohtahara syndrome, DS, LGS, West syndrome, and atypical Rett syndrome.[87] Seizures associated with this mutation also include early-onset infantile spasms, focal, tonic-clonic, and absence seizures. Moog et al[87] examined trazodone applied in zebrafish larvae models with homozygous *STXBP1* mutations generated using CRISPR-Cas9 gene editing. A 1-mM trazodone bath was applied to the larvae while continuous local field potential recordings were obtained (baseline: 0–15 min; 45 min after medication exposure = 45–60 min) to monitor for events defined as long-duration (> second), large amplitude (> 0.5 mV) Type II ictal-like multi- or poly-spike events.[87] These were specifically monitored because of previous correlations with whole-body convulsive seizure behaviors. Events were significantly reduced by 83% with the application of trazodone.[87]

In zebrafish *SCN1*lab homozygous mutants, nighttime hyperactivity, decreased time spent in the center of an open arena, and decreased responsiveness to sudden darkness can be used to measure seizure-like activity associated with *SCN1a* mutations.[88] In another preclinical study, Grone et al[88] applied 10-mM solutions of various medications, including trazodone. While other medications proved to have some effect on the reduction of nighttime hyperactivity and increased time spent at the center of the arena, trazodone did not have any effect on either of these data points.[88]

Of note, Borowic et al[89] examined trazodone's antiepileptic activity and effect on the cerebrospinal fluid concentration of other ASMs in mouse models. A single dose of up to 40 mg/kg of trazodone did not affect the electroconvulsive threshold. However, chronic administration of trazodone 40 mg/kg increased the electroconvulsive threshold. Additionally, acute and chronic administration of trazodone increased valproic acid cerebrospinal fluid concentrations and reduced phenytoin concentrations. Chronic administration decreased cerebrospinal fluid concentrations of carbamazepine and phenobarbital.[89]

Human studies in the application of trazodone for epilepsy are notably absent. Trazodone has been shown as relatively safe for use in insomnia, migraine prophylaxis, and major depressive disorder; however, there still is a risk of increased or worsened seizures in patients with epilepsy. More preclinical data are needed to determine possibly safe dosing and safe epilepsy populations before trials in humans can be initiated. However, in the setting of refractory *SCN1a*-related epilepsies, the idea of adding options to the treatment arsenal is promising—especially if trazodone can serve dual purposes for the treatment of insomnia and reduction in seizures. While theoretical for now, future applications of trazodone in these refractory *SCN1a* epilepsies could provide more efficacious results for these patients.

Conclusion

Refractory and super-refractory seizures and epilepsies present significant hurdles for clinicians and patients. When traditional ASMs applied at optimized doses do not produce sufficient seizure reduction to provide improved quality of life, it may feel as though we, as health care practitioners, have failed. Advantageously, some nontraditional ASMs have data to support their use in these instances. [see Table 6]

Of the medications assessed in the present review, ketamine has the strongest data for application in a

Table 6. Dosing, Seizure Efficacy, and Clinical Summary of Nontraditional Antiseizure Medications

Medication	Population	Seizure/ Syndrome Types Studied*	Genetic Mutations with Potential Applications	Antiseizure Dose Range/ Reported Regimen	Efficacy Range Reported†	Relative Strength of Data‡
Ketamine[16–29]	A, N, P	**RSE; SRSE;** generalized; focal; multifocal; mixed type; **neonatal seizure**	n/a	*Loading dose*: 1–5 mg/kg IV • 4.1 mg/kg IM (n = 1) *Continuous rate*: 0.6–10 mg/kg/hr IV	*Responder*: ~32%–100%	++
Memantine[36–40]	P	**DEE**; **West Syndrome**; focal; absence; myoclonic	*GRIN1A; GRIN1B; GRIN2B; GRIN2D*	0.1–1.3 mg/kg/day PO divided 1–2× daily (maximum 20 mg)	*Responder*: 25%–100% • 59%–~100% seizure frequency reduction in responders	+
Quinidine[49–54]	P	ADNFLE; **EIMFS**; **focal; tonic**	*KCNT1*	5 to >90 mg/kg/day PO divided 3–4× daily; 300–900 mg/day	*Responder*: 25%–100% • 75% worsened with ADNFLE • 50%–100% seizure frequency reduction in responders	+/–
Riluzole[56,60,61]	Animal (rats); pluripotent stem cells (human) P	Absence; limbic; **myoclonic**; gelastic	*SCN8a*	0.5–7.5 mg/kg/dose; 25–75 mg, 1–2×daily	*Responder*: 33%–100% • 50%–100% seizure frequency reduction (n = 2)	-
Trazodone[85–89]	Animal (rats, zebrafish)	**DS**; LGS; **focal**; generalized	*SCN1a; STXBP1*	5–40 mg/kg; 1–10 mM bath	*Responder*: 0%–83%	––

A, adult; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; DEE, developmental and epileptic encephalopathy; DS, Dravet Syndrome; EIMFS, epilepsy with migrating focal seizures; LGS, Lennox Gastaut Syndrome; N, neonate; P, pediatric; RSE, refractory status epilepticus; SRSE, super refractory status epilepticus

* **bold** = most efficacy reported
† % response and/or % reduction
‡ ++, most reassuring data; +, some reassuring data; +/-, mixed data; -, minimal or no reassuring data; –, minimal or no reassuring data in humans

clinical setting—specifically in patients with RSE, super-refractory SE, and neonatal seizures. Despite some contradictory findings of ketamine initiation timing within the treatment cascade, one of the largest reviews found ketamine initiation before anesthetic midazolam dosing yielded better patient outcomes and seizure cessation. If patients have failed several benzodiazepine doses, it could be reasonable to consider the incorporation of the alternative mechanism of NMDA-receptor antagonism provided by ketamine into the treatment cascade before or in conjunction with anesthetic midazolam.

Memantine has promising but comparatively weaker evidence. Memantine appears to be generally well tolerated; memantine could be considered as an adjunctive ASM in patients with DEE or West Syndrome—especially in the presence of a *GRIN*-related mutation. Quinidine has even less convincing data compared with memantine and ketamine. While some studies show

promise in *KCNT1*-related EIMFS, worsened seizures were still noted in this population and patients with *KCNT1*-related ADNFLE. Given side effect risk (e.g., QTc prolongation), caution must be taken when considering adjunctive quinidine. Data currently suggest using quinidine in patients with a *KCNT1* mutation, and EIMFS may be most effective; even then, simultaneous diligent cardiac and neurological monitoring for QTc prolongation and seizure frequency, respectively, would be appropriate.

Finally, riluzole and trazodone are unlikely to be reasonable candidates to consider in a clinical setting at this time. Both have compelling data in animals (for riluzole, in human stem cells), but this does not translate into safe human usage. For riluzole, it appears to be most effective for the reduction of myoclonic seizure models, especially in the setting of an *SCN8a* mutation. Trazodone may be effective in DS and focal seizure models, especially in the setting of an *SCN1a* or *STXBP1* mutation. Thus, practitioners interested in using these medications for their patients in the future should closely follow any proposed clinical trials in humans to further bolster presently available data with both riluzole and trazodone. As of the publishing of this manuscript, no studies are presently active within ClinicalTrials.gov concerning either riluzole or trazodone for the treatment of epilepsies or seizures in humans.

The 5 reviewed medications all provide unique opportunities. Some, such as ketamine and memantine, have potential applications in patients today. Of those with less convincing available data, the unique ASM mechanisms of action, potential for use in targeted patient populations, and comparatively reasonable side effect profiles could aid in the design and implementation of larger studies, which may provide more well-defined recommendations for clinical application and implications.

Article Information

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