journal of global health Neurology and Psychiatry

Khanna A, Özkan Ö, Pajiyar A, et al. Memantine as Adjunctive Therapy in Lennox–Gastaut Syndrome With Neuropsychiatric Comorbidity: A Case Report. *JoGHNP*. Published online July 15, 2026. doi:10.7189/001c.164973

RESEARCH ARTICLE

Memantine as Adjunctive Therapy in Lennox–Gastaut Syndrome With Neuropsychiatric Comorbidity: A Case Report

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Keywords: Lennox–Gastaut Syndrome, attention-deficit/hyperactivity disorder, memantine, antiepileptic drug resistance, neuropsychiatric comorbidity

https://doi.org/10.7189/001c.164973

Journal of Global Health Neurology and Psychiatry

Introduction

Lennox–Gastaut Syndrome (LGS) is a severe childhood-onset epileptic encephalopathy characterised by multiple daily seizures of varying semiology, intellectual disability, and a characteristic electroencephalographic pattern. Neuropsychiatric comorbidities - including attention-deficit/hyperactivity disorder (ADHD), autistic spectrum manifestations, and learning difficulties - are well documented in this population. Management is challenging owing to poor seizure response to conventional antiepileptic medications and the complexity introduced by co-occurring psychiatric disorders.

Case Presentation

We report the case of a patient with LGS severely resistant to antiepileptic therapy and complicated by worsening ADHD symptoms. Following years of trialling multiple antiseizure medications with limited benefit, memantine was initiated alongside other medications and was associated with meaningful improvement in seizure frequency, cognition, and behavioural manifestations. ADHD medications were subsequently reintroduced, were well tolerated, and further improved the patient's attention and behaviour.

Conclusion

This case highlights a novel application of memantine - an agent most commonly used in the management of Alzheimer's disease - and suggests its potential utility as adjunctive therapy for improving both seizure control and neuropsychiatric symptoms in patients with LGS. Further research is warranted to evaluate this therapeutic approach systematically.

1. Introduction

Lennox–Gastaut Syndrome (LGS) was first described as a "petit mal variant" by Lennox and later formalised by Gastaut, and constitutes a severe developmental and epileptic encephalopathy (DEE) with onset in childhood.[1] It is characterised by three core features: multiple seizure types, including at least one tonic-clonic seizure; distinct electroencephalographic (EEG) abnormalities, such as slow spike-wave complexes at under 2.5 Hz and rapid bursts of activity (10–20 Hz, typically observed during non-REM sleep); and evidence of intellectual and behavioural impairment.[2]

LGS is typically diagnosed in childhood, often before the age of eight years, with the highest incidence occurring between three and five years of age.[3] The prevalence of LGS ranges from 2.9 to 28 per 100,000 individuals,[4] accounting for one to two percent of the total epilepsy population, with a prevalence of one to ten percent among children with epilepsy.[5]

Many patients with LGS present with psychiatric conditions or symptoms, including difficulties with attention, aggression, agitation, hyperactivity, intellectual disability, and autism spectrum manifestations.[6] These behavioural abnormalities may result from pathological neurodevelopmental processes, the effects of epileptic activity on brain function, and the adverse effects of antiepileptic medications.[7,8]

Owing in part to its drug-resistant nature, LGS is frequently associated with cerebral palsy, status epilepticus, seizure-related injuries, and sleep disturbances. The high comorbidity burden contributes substantially to reduced quality of life and increased psychosocial strain in affected individuals.[9] These challenges underscore the need for novel therapeutic approaches to prevent severe and permanent neurological damage. Memantine, an NMDA receptor antagonist that reduces excitotoxicity, represents one such alternative. Excitotoxicity is a recognised contributor to cognitive decline in epilepsy, and memantine offers a mechanism of action distinct from conventional pharmacological and non-pharmacological strategies for seizure control.[10,11]

This report presents a case of LGS complicated by severe ADHD symptoms, characterised by uncontrolled seizures, aphasia, and agitation refractory to an established antiepileptic treatment regimen.

2. Case Presentation

We present a fifteen-year-old male patient with a twelve-year history of Lennox–Gastaut Syndrome, diagnosed at the age of three years following the initial onset of atonic seizures, subsequently evolving to tonic and tonic-clonic episodes, with generalised slow spike-and-wave discharges on EEG and developmental delay. He was referred to our psychiatry clinic at the age of ten for evaluation of executive function deficits, including inattention, impaired concentration, hyperactivity, and impulsivity. Until that point, the patient had been followed exclusively by neurology and was receiving valproate 1500 mg daily, with no reliable history of prior antiepileptic medications available. At the time of his first psychiatric visit, seizure frequency was three to six episodes per week, comprising clonic, tonic, absence, and tonic-clonic seizures. No significant change in seizure type had been documented over the course of the illness, with early seizure frequency reported as one to five episodes per week.

At the time of his initial psychiatric evaluation, aged eleven, the patient presented with classic features of attention-deficit/hyperactivity disorder (ADHD). Parents described him as impulsive and unable to sustain attention on any given task, with similar observations reported from school. Treatment was initiated with clonidine 0.1 mg daily alongside Applied Behaviour Analysis therapy.

At reassessment twelve months later, ADHD symptoms had shown only mild improvement, with some behavioural progress noted at school but no improvement in academic performance. Seizure control remained unsatisfactory, with episodes occurring at near-daily frequency (five to seven per week). The treatment plan was revised: clonidine was discontinued and viloxazine 100 mg daily was introduced, in accordance with the neurologist's recommendation to avoid stimulant medications and clonidine given the patient's seizure profile.

Seizure control continued to deteriorate, with tonic-clonic (grand mal) episodes becoming increasingly frequent. Plasmapheresis was initiated with weekly sessions, alongside intravenous immunoglobulin therapy, and the valproate dose was increased to 1750 mg daily. This resulted in a mild reduction in seizure frequency to fewer than four episodes per week.

This regimen produced a modest reduction in seizure frequency, particularly grand mal episodes, sustained over approximately twelve months, during which the patient demonstrated marginal behavioural improvements at home and school. After twelve months, however, his condition began to deteriorate: seizure frequency returned to near-daily levels, and his behaviour, productivity, and physical functioning were markedly affected. At reassessment two months into this period of decline, the patient was found to be aphasic and socially withdrawn, with prominent anhedonia and agitation.

Given the recurrence of frequent and refractory seizures, cenobamate 50 mg daily and fenfluramine 20 mg daily were initiated. Fenfluramine was considered a contributing factor to the partial improvement in seizure frequency observed, as well as to the resolution of anhedonia and social withdrawal. Memantine 5 mg daily was subsequently added to the regimen, and follow-up neurological and psychiatric evaluation was scheduled for four weeks later.

At that follow-up visit, both seizure control and behaviour had improved substantially. Seizure frequency had decreased to fewer than three episodes per week, with no further grand mal seizures, and aphasia and anhedonia had resolved. Methylphenidate 10 mg daily was then introduced; one month later, it was well tolerated with no adverse impact on seizure control and a mild positive effect on attention and school productivity.

At the time of this report, the patient has been maintained on memantine alongside the aforementioned medications for approximately ten weeks. The clinical improvement has been sustained and no adverse effects have been reported.

3. Discussion

This case report describes an uncommon but clinically instructive presentation of LGS complicated by severe, treatment-refractory ADHD, in which the introduction of memantine as adjunctive therapy was associated with meaningful improvements in both seizure control and neuropsychiatric symptoms. To the best of our knowledge, the use of memantine in this context, as part of a multimodal regimen targeting both epileptic and behavioural manifestations of LGS, has not been previously described in the paediatric literature. The subsequent safe reintroduction of stimulant medication following neuropsychiatric stabilisation further adds to the clinical significance of this case, as stimulants are generally approached with caution in patients with epilepsy. These findings highlight the potential value of targeting NMDA receptor-mediated excitotoxicity as a therapeutic strategy in LGS and invite broader consideration of memantine in the management of epileptic encephalopathies with neuropsychiatric comorbidity.

The aetiology of LGS is commonly categorised as either unknown or identifiable.[12] Identifiable causes are further classified as genetic, structural, or metabolic, and include central nervous system (CNS) infections, perinatal asphyxia, head injury, and hereditary metabolic disorders, among others.[12] Neuroimaging is strongly recommended to identify underlying structural causes such as cortical malformations, tuberous sclerosis, or acquired brain injury.[12] Genetic testing is recommended when no structural lesion is identified, as numerous cases have been associated with de novo pathogenic variants, including 15q duplication associated with Prader–Willi/Angelman syndrome.[13]

Developmental and behavioural problems may precede or follow seizure onset and generally progress to developmental slowing, plateau, or regression, resulting in moderate to severe intellectual disability in more than 90% of cases.[14] Consistent with the published literature, our patient was diagnosed with LGS at the age of three years, initially presenting with absence seizures that subsequently evolved to atonic, clonic, and tonic-clonic seizures. His condition was further complicated by disruptive behaviour and restlessness in the school setting, which on assessment met diagnostic criteria for ADHD.

Longitudinal neuroimaging studies have demonstrated progressive cortical thinning in patients with persistent seizures, particularly when compared with those who achieve seizure freedom.[15] In childhood epilepsies, beyond the risk of neuronal loss, affected individuals may develop attentional, behavioural, and psychiatric difficulties in adolescence.[15] Recent studies have

also highlighted the role of mitochondrial dysfunction and chronic oxidative stress in the development of seizures and epilepsy.[16] In patients with ADHD, stimulant medications may potentially increase seizure activity owing to shared neurobiological mechanisms.[17]

Despite treatment with multiple antiseizure medications, many patients with LGS continue to experience seizures.[12] Although LGS accounts for only approximately five percent of childhood epilepsy cases, it represents nearly half of all healthcare expenditure on paediatric epilepsy in the United States, with seizures accounting for 18 to 20% of the total cost per patient.[18] Seizure-related accidents represent the most common cause of poor long-term prognosis, making seizure management a central component of LGS treatment.[19]

Non-pharmacological treatment options for LGS include the ketogenic diet, deep brain stimulation, corpus callosotomy, and vagus nerve stimulation. Pharmacological options include valproic acid, lamotrigine, rufinamide, topiramate, clobazam, felbamate, and cannabidiol, among others.[20] Nevertheless, rates of resistance to antiseizure medications have historically been high, with epileptic activity persisting into adulthood in the majority of cases.[11]

Given the persistence of seizures despite multiple antiseizure medications, alternative therapeutic strategies were considered in our patient. As described above, both plasmapheresis and intravenous immunoglobulin were trialled on the basis of evidence supporting their efficacy in seizures of autoimmune origin, which, although never confirmed in this patient, was strongly suspected.[10] Memantine, an N-methyl-D-aspartate receptor (NMDA-R) antagonist most commonly used in the treatment of Alzheimer's disease, has demonstrated improvement in both seizure control and encephalopathy in a randomised controlled trial, with no reported adverse effects.[11]

Mutations in NMDA receptors have been identified in some studies, leading to disruption of normal brain signalling and contributing to childhood epilepsy syndromes such as LGS. This provides a plausible mechanistic basis for the clinical improvement observed with memantine in our patient.[21] Additional studies have reported reductions in seizure frequency with memantine and other NMDA receptor antagonists, particularly in epilepsy and autoimmune encephalopathy,[22] and evidence suggests that overactivation of NMDA receptors may contribute to epilepsy and encephalitis syndromes through excitotoxic neuronal injury.[22] However, the precise mechanism remains incompletely understood and warrants further investigation. Memantine has also been reported to reduce aggression in patients with Alzheimer's disease, an effect similarly observed in our patient.[23]

In the present case, memantine was initiated while the patient was already receiving fenfluramine, cenobamate, and valproate. A synergistic effect among these agents may account for the marked improvement observed in expressive aphasia, speech, and overall communication. Improved seizure control and neuropsychiatric stabilisation subsequently permitted the safe reintroduction of a stimulant medication, which in turn contributed to meaningful improvement in ADHD symptoms.

Fenfluramine has a distinctive mechanism of action among antiseizure medications, acting through serotonergic pathways and sigma-1 receptor modulation. It is postulated to restore the balance between GABAergic inhibition and glutamatergic excitation, thereby contributing to the reduction in seizure activity observed in this case.[24]

Acknowledging the inherent limitations of single case reports and the complex pharmacological profile of this patient, a potential synergistic effect between memantine and antiepileptic medications may be inferred as capable of achieving meaningful seizure control alongside positive behavioural and cognitive outcomes in this patient population. Controlled clinical trials are needed to further evaluate this therapeutic approach and its underlying mechanisms.

4. Conclusion

Patients with Lennox–Gastaut Syndrome and comorbid psychiatric conditions such as ADHD frequently face significant challenges in the management of neuropsychiatric symptoms, compounded by the burden of recurrent seizures. This case highlights the potential role of memantine as an adjunctive therapeutic option in patients with LGS who continue to experience refractory seizures and associated neuropsychiatric comorbidity.

In our patient, improvement in seizure control following the introduction of memantine permitted the safe reintroduction of ADHD pharmacotherapy, which was well tolerated and associated with meaningful behavioural and cognitive gains. Taken together, these findings suggest that memantine may represent a viable adjunctive option in selected cases of LGS with neuropsychiatric comorbidity, warranting further investigation in both neurology and psychiatry settings.

Future prospective studies and controlled clinical trials are needed to establish the long-term safety and efficacy of memantine in the paediatric epilepsy population, and to better delineate the patient profiles most likely to benefit from this therapeutic approach.

Ethical Statement

No ethical review or approval was required for this study in accordance with local legislation and institutional requirements. Written informed consent was obtained from the patient's guardian for the publication of this case report.

Conflict of Interest Statement

The authors declare no conflicts of interest relevant to this study.

Acknowledgements

The authors wish to thank the patient and his family for their consent to publish this case and for their cooperation throughout the process.

Submitted: June 02, 2026 BST. Revised: July 22, 2026 BST. Accepted: July 11, 2026 BST. Published: July 15, 2026 BST.

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