Case report

DOI: https://doi.org/10.4038/sljpsyc.v17i1.8668

Rare case of perampanel-induced psychosis in an epileptic patient: A clinical alert

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SL J Psychiatry 2026; 17(1): 66-67

Introduction

Perampanel is a selective, noncompetitive AMPA receptor antagonist approved by the U.S. Food and Drug Administration for focal-onset seizures and as adjunctive therapy for generalized tonic-clonic seizures. Although behavioural adverse effects have been described, frank psychosis remains infrequently reported. Presenting a rare case report of a man with epilepsy who developed psychosis due to perampanel.

Case report

We present a case of a 42-year-old single man with chronic epilepsy since age 4 (GTCS and partial seizure) who was reasonably well maintained on valproate and perampanel and had been seizure free for 15 months. He reportedly had frontal lobe surgery about 5 years ago which reduced the frequency of seizures significantly.

He first developed psychotic symptoms (auditory and visual hallucinations and paranoid thoughts) 12 months ago. He was working at the time. There was no use of illicit substances. He was a chronic smoker and was consuming 1 to 2 standard drinks of alcohol every couple of days. There was no family h/o mental illness or past episode of psychosis.

He started hearing derogatory and commanding 2nd person auditory hallucinations, voices of people saying things like "that's him, we are going to get him" etc, as a result he became paranoid. He also had visual hallucinations of seeing people walking in the front yard, that scared him. His paranoia kept on increasing gradually which made him feel depressed and suicidal. He was started on aripiprazole and mirtazapine. His psychosis worsened with time.

He left the job as symptoms got worse. He advised that he had been on fycompa (perampanel) for about 14 months due to partially controlled seizures; the dose was increased by the Neurologist to 8 mg per day a few weeks before onset of psychosis.

He was admitted to the psychiatric ward. Aripiprazole was ceased and replaced with olanzapine; dose was increased to 20 mg. There was minimum change in his psychosis. He was fearful of the voices and had referential ideas that people were talking about him.

Perampanel was ceased after a review by his private Neurologist. A few weeks later, his visual hallucinations disappeared, auditory hallucinations were significantly reduced. After a couple of months paranoid and referential ideas subsided significantly and he was quite insightful. His mood also improved.

He is maintained on sodium valproate 1gm per day, lacosamide 100 mg at night, mirtazapine 15 mg and olanzapine 20 mg per day. He remains compliant with medications. He has been seizure and psychosis free for a while.

This case highlights the temporal correlation between introduction of the perampanel and the development of psychosis in a male especially after increasing the dose from 4 to 8 mg/day. There are only a limited number of cases reported of psychosis from perampanel, all were female (1,11,12,14).

Discussion

Perampanel is a novel non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor of glutamate, the main mediator of excitatory neurotransmission in the central nervous system (5,7). Most common side effects of perampanel are dizziness, fatigue, headache, somnolence, irritability, vertigo, vomiting, weight gain, contusion, nausea, abdominal pain, and anxiety. The development of acute psychotic disorders as a side effect rarely occurs, ranging from 0.1% to 1.3% according to different studies and is poorly described (1.9,14).

The reduction in glutamatergic transmission through AMPA receptors is hypothesised to be perampanel associated PBAEs (psychiatric and behavioural adverse

events) associated with symptoms such as impulsive aggression caused by increased glutamate levels in the amygdala, hypothalamus, and periaqueductal grey matter (2,3,4). The variables related to epilepsy implicated in treatment emergent adverse events of antiepileptic medications can include limbic system dysfunction, hippocampal sclerosis, neuronal channel dysfunction or forced normalization (16). The presence of complex partial seizures and anti-epileptic drug polytherapy are also significantly associated with the development of psychosis (17).

It carries a black-box warning for serious psychiatric and behavioural adverse reactions of aggression and irritability, and overall rate of psychiatric treatment-emergent adverse events was higher in higher doses of perampanel (8 mg and 12 mg) (1,10).

Conclusions

Heightened pharmacovigilance, early identification of behavioural changes, and close collaboration between neurology and psychiatry teams are critical to mitigate morbidity. Patients with seizures should be counselled about the potential risk of developing psychosis and behavioural disturbances associated with perampanel. Close monitoring is recommended, particularly during dose titration and at higher dosage levels.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

1. Ali Sulais , Abdullah Alhedaithy, Fouad Alghamdi , Yasser Ad-Dab'bagh. On Seizures and Knives: Perampanel-Induced Psychosis: A Case Report and Literature Review. J Epilepsy Res, 2024 30; 14(1): 37-41.
2. Jon Soo Kim, Won Seop Kim, Won Young Sung, Hyewon Woo. Psychiatric and behavioural concerns of perampanel with concomitant levetiracetam in children with epilepsy. Epilepsy & Behavior 154 (2024) 109740.
3. Hansen CC, Ljung H, Brodtkorb E, Reimers A. Mechanisms underlying aggressive behaviour induced by antiepileptic drugs: Focus on topiramate, levetiracetam, and perampanel. Behav Neurol 2018; 2018: 2064027.
4. Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S, et al. Epilepsy, antiepileptic drugs, and aggression: An evidence-based review. Pharmacol Rev 2016; 68: 563-602.
5. Frampton JE. Perampanel: a review in drug-resistant epilepsy. Drugs. 2015; 75(14): 1657-68.
6. Fycompa (Perampanel) prescribing information. Woodcliff Lake, New Jersey: Eisai R&D Management (Eisai Ltd.); 2016.
7. Franco V, Crema F, Iudice A, et al. Novel treatment options for epilepsy: focus on perampanel. Pharmacol Res. 2013; 70(1): 35-40.
8. Jessica Greenwood, Jose Valdes. Perampanel (Fycompa) A Review of Clinical Efficacy and Safety in Epilepsy. P&T. 2016; 41(11): 683-98.
9. United States Department of Health and Human Services . Fycompa (Perampanel) prescribing information [Internet] Washington (DC): United States Department of Health and Human Services; 2016.
10. Ettinger AB, LoPresti A, Yang H, et al. Psychiatric and behavioral adverse events in randomized clinical studies of the noncompetitive AMPA receptor antagonist perampanel. Epilepsia. 2015; 56: 1252-63.
11. Pujal Rodríguez E, Pons-Cabrera MT, Giménez A, et al. Perampanel-induced psychosis in a young woman: a case report. Clin Neuropharmacol. 2021; 44: 240-2.
12. Leite RA, Borges J, Macedo P, Santos T. Perampanel-induced psychotic disorder: a case report. Arch Clin Psychiatry. 2021; 48: 184-5.
13. Zaccara G, Giovannelli F, Cincotta M, Ludice A. AMPA receptor inhibitors for the treatment of epilepsy: the role of perampanel. Expert Rev. Neurother. 2013; 13(6): 647-55.
14. Shoko M. Yamada MD, Yusuke Tomita, Yoshinori Takaya. Features of psychological reactions induced by perampanel: A case report. Journal of clinical Pharmacy and Therapeutics 2020.
15. Villanueva V, Garcés M, Lopéz-González FJ, Rodriguez-Osorio X, Toledo M, Salas-Puig J, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: The FYDATA study. Epilepsy Research. 2016; 126: 201-10.
16. Mula M. Treatment-emergent psychiatric adverse events of antiepileptic drugs in epilepsy: how can we avoid them? Neuropsychiatry. 2011; 1: 371-6.
17. Schmitz B. Psychiatric syndromes related to antiepileptic drugs. Epilepsia. 1999; 40(10): 65-70.