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Review Article

Antiepileptic Drug Interactions in Polytherapy Patients

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ABSTRACT

Background: Polytherapy remains an essential strategy for patients with refractory epilepsy, where seizure control cannot be achieved with monotherapy alone. However, combining multiple antiepileptic drugs (AEDs) increases the risk of clinically significant drug–drug interactions that can alter therapeutic efficacy and safety. Interactions may be pharmacokinetic, involving metabolic induction or inhibition, or pharmacodynamic, producing additive, synergistic, or antagonistic clinical effects. Older AEDs such as carbamazepine, phenytoin, phenobarbital, and valproate are well-known for extensive hepatic enzyme modulation, whereas newer agents like levetiracetam, lacosamide, and pregabalin exhibit fewer interactions. Yet, challenges persist, especially in patients requiring treatment for comorbid conditions, such as depression, contraception, anticoagulation, or cardiovascular disease. Polytherapy increases the difficulty of predicting serum drug levels, optimizing dosing, and monitoring adverse effects. This review synthesizes current evidence regarding the mechanisms, clinical implications, and management strategies related to AED interactions in polytherapy patients Objective of the review: To analyze the pharmacokinetic and pharmacodynamic interactions among antiepileptic drugs used in polytherapy. To review the clinical implications of AED interactions on efficacy, toxicity, and comorbidity management. To identify strategies to minimize adverse interactions and optimize therapeutic outcomes. To evaluate the role of newer AEDs and pharmacogenomics in reducing interaction-related risks.

INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders globally, affecting over 50 million people, with approximately one-third experiencing seizures resistant to monotherapy (WHO, 2023). For these individuals, polytherapy—defined as the concurrent use of two or more antiepileptic drugs (AEDs)—is often necessary to achieve optimal seizure control. While the rationale behind polytherapy is to combine agents with

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complementary mechanisms of action, the use of multiple AEDs introduces a substantial risk of drug–drug interactions (Patsalos & Perucca, 2003). These interactions may impact pharmacokinetic processes—including absorption, distribution, metabolism, and excretion—or pharmacodynamic effects involving neuronal excitability and neurotransmitter pathways.

Newer AEDs—including levetiracetam, gabapentin, pregabalin, oxcarbazepine, lamotrigine, brivaracetam, and lacosamide—were developed, in part, to minimize interactions by relying on renal elimination, minimal protein binding, or metabolic pathways less susceptible to enzyme modulation. Nevertheless, some newer drugs, such as lamotrigine and oxcarbazepine, may still interact significantly with valproate or carbamazepine, demonstrating that polytherapy interactions remain clinically important.

Drug interactions in epilepsy management have implications that extend far beyond seizure control. AEDs may influence hormone regulation, bone health, cardiovascular function, and psychiatric well-being. For example, hepatic enzyme-inducing AEDs can reduce the effectiveness of hormonal contraceptives, leading to unintended pregnancies. Interactions with anticoagulants, antidepressants, and antipsychotics can complicate the management of comorbidities, which are highly prevalent among epilepsy patients.

Pharmacogenomic factors contribute to interindividual variability in drug response and interaction susceptibility. Variants in CYP2C9, CYP2C19, UGT1A4, and HLA alleles may influence drug metabolism and hypersensitivity. Incorporating pharmacogenomics into AED selection could ultimately enhance therapeutic precision.

MATERIALS AND METHODS

This review article was developed by conducting a narrative analysis of peer-reviewed literature published between 2000 and 2024. Databases including PubMed, Scopus, and Google Scholar were searched using keywords such as antiepileptic drugs, polytherapy, drug interactions, enzyme induction, and therapeutic drug monitoring. Articles were selected based on relevance to AED pharmacokinetics, pharmacodynamics, clinical interactions, and management strategies. Guidelines from recognized bodies such as the International League Against Epilepsy (ILAE) were also consulted. A maximum of 15 high-quality references were included. No ethical approval was required as this study involved secondary data only.

RESULTS

Polytherapy in epilepsy significantly increases the potential for drug interactions, which were categorized in this review into pharmacokinetic, pharmacodynamic, and clinical outcome–related interactions. The results highlight patterns and implications from multiple studies.

1. Pharmacokinetic Interactions

Pharmacokinetic interactions were found to be most prevalent with older AEDs, particularly enzyme-inducers and inhibitors.

Enzyme Induction

Carbamazepine, phenobarbital, and phenytoin remain potent CYP450 inducers. The review revealed:

- **CYP3A4 induction:** Reduces levels of lamotrigine, valproate, topiramate, and hormonal contraceptives.

- **UGT induction:** Accelerates metabolism of lamotrigine, shortening half-life and decreasing serum concentration by as much as 50%.

Induction also affected non-AED drugs. For instance, warfarin efficacy decreased significantly in patients taking carbamazepine, increasing stroke risk if unmonitored.

Enzyme Inhibition

Valproate continues to be the most clinically significant inhibitor among AEDs. It inhibits UGT enzymes, raising lamotrigine serum levels by nearly 200%, predisposing patients to skin reactions including Stevens–Johnson syndrome. Valproate also inhibits CYP2C9, raising phenytoin concentrations and toxicity risk.

Protein Binding Displacement

Valproate's high protein binding leads to displacement of phenytoin and carbamazepine-epoxide, increasing free drug concentrations even when total levels appear normal.

Newer AEDs and Interactions

Newer AEDs demonstrated minimal interactions:

- Levetiracetam showed no meaningful impact on CYP450 or UGT pathways.
- Lacosamide exhibited only mild CYP2C19 interaction potential.
- Brivaracetam, although similar to levetiracetam, showed minor interactions with carbamazepine metabolism.
- Lamotrigine and oxcarbazepine showed moderate interaction risk when combined with inducers or inhibitors.

2. Pharmacodynamic Interactions

Pharmacodynamic interactions influenced therapeutic outcomes independently of serum levels. Additive toxicity was common when combining sodium channel blockers (e.g., phenytoin + carbamazepine), causing dizziness, diplopia, and ataxia. Synergistic efficacy was documented for combinations such as valproate + lamotrigine, attributed to complementary mechanisms on glutamate inhibition and sodium channel modulation. Adverse behavioral effects occurred more frequently when levetiracetam was used with other agents known to affect mood.

3. Clinical Implications

Polytherapy significantly influenced clinical outcomes:

Therapeutic Drug Monitoring (TDM)

TDM was found essential for drugs with narrow therapeutic windows, particularly phenytoin, carbamazepine, valproate, and lamotrigine. Studies consistently recommended routine monitoring when: initiating or stopping an interacting AED, adjusting dose in polytherapy, and managing pregnant patients.

Impact on Comorbidities

AED interactions extended beyond seizure control:

- Endocrine: Enzyme-inducing AEDs reduced hormonal contraceptive efficacy.
- Psychiatric: Carbamazepine reduced serum levels of several antidepressants.
- Cardiovascular: Inducers reduced statin and anticoagulant levels.

Special Populations

Pregnant women, the elderly, and those with hepatic or renal impairment showed greater vulnerability to interaction-related toxicity.

4. Pharmacogenomic Findings

Variants such as CYP2C93 or HLA-B1502 influenced susceptibility to toxicity or hypersensitivity. Though not universally adopted, pharmacogenomic screening is increasingly recognized as valuable.

DISCUSSION

The findings highlight the substantial complexity involved in managing epilepsy patients on polytherapy. The interactions identified underscore the necessity of understanding both the pharmacokinetic and pharmacodynamic properties of AEDs. Older enzyme-inducing AEDs pose the greatest challenges. Their potent effects on hepatic metabolism make drug levels unpredictable, posing risks of subtherapeutic dosing or toxicity. Despite their efficacy and affordability, their extensive interaction potential often makes them less suitable for patients with multiple comorbidities.

Valproate's inhibitory effects are equally important, especially with lamotrigine. Clinicians must carefully titrate lamotrigine when co-administered with valproate to avoid severe skin reactions. These examples illustrate why understanding metabolic pathways is crucial when designing polytherapy regimens.

Newer AEDs have improved the safety profile of polytherapy. Levetiracetam, lacosamide, and brivaracetam offer reliable options with minimal interaction potential. However, absence of metabolic interactions does not eliminate pharmacodynamic concerns, particularly regarding mood changes, sedation, or cognitive impairment.

The concept of rational polytherapy is strongly supported by the literature. Combining drugs with distinct mechanisms—such as a GABAergic agent with a sodium channel blocker—may enhance seizure control while reducing toxicity. In contrast, polytherapy involving multiple sodium channel blockers increases adverse effects without clear therapeutic advantage.

Therapeutic drug monitoring emerges as a cornerstone of safe AED polytherapy. It is particularly valuable when treating vulnerable populations, during physiological changes (e.g., pregnancy), or when interacting medications are added. Pharmacogenomics holds promise, especially in preventing severe adverse reactions and optimizing dosing, although its application remains inconsistent across healthcare settings.

Clinicians should adopt individualized treatment plans that consider seizure type, comorbidities, genetic predispositions, and lifestyle factors. Regular review of medication regimens, patient education, and multidisciplinary collaboration are essential to safely managing polytherapy.

CONCLUSION

Antiepileptic drug interactions remain a significant challenge in patients requiring polytherapy for seizure control. Older AEDs cause extensive metabolic interactions, whereas newer agents largely minimize these risks. Understanding pharmacokinetic and pharmacodynamic principles, applying therapeutic drug monitoring, and selecting rational combinations based on complementary mechanisms are essential strategies to optimize treatment. Pharmacogenomics and personalized medicine represent promising approaches for

further improving outcomes. Effective management of AED interactions enhances seizure control, reduces toxicity, and improves overall quality of life for patients with complex epilepsy.

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CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest.

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REFERENCES

1. Brodie, M.J., & Sills, G.J. (2011). Combining antiepileptic drugs-rational polytherapy? Seizure, 20(5), 369–375.
2. Harden, C. L., et al. (2009). Practice parameter update: Management issues for women with epilepsy. Neurology, 73(2), 126–132.
3. Johannessen, S. I., & Landmark, C. J. (2010). Antiepileptic drug interactions-principles and clinical implications. Current Neuropharmacology, 8(3), 254–267.
4. Patsalos, P. N., & Perucca, E. (2003). Clinically relevant drug interactions in epilepsy. Epilepsia, 44(4), 408–423.
5. Perucca, E. (2006). Clinically relevant drug interactions with antiepileptic drugs. British Journal of Clinical Pharmacology, 61(3), 246–255.
6. WHO. (2023). Epilepsy: Key Facts. World Health Organization.
7. Perucca, E., & Gilliam, F. G. (2012). Adverse effects of antiepileptic drugs. Lancet Neurology, 11(9), 792–802.
8. Schmidt, D., & Schachter, S. C. (2014). Drug treatment of epilepsy in adults. BMJ, 348, g254.
9. French, J. A., et al. (2004). Rational polytherapy in epilepsy. Epilepsia, 45(5), 475–479.
10. Glauser, T., et al. (2013). Updated ILAE evidence review of antiepileptic drug efficacy. Epilepsia, 54(3), 551–563.
11. Perucca, E. (2005). Pharmacological principles as a basis for polytherapy. Acta Neurologica Scandinavica, 112, 31–34.
12. Zaccara, G., et al. (2011). Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disorders, 13(1), 1–15.
13. Patsalos, P. N. (2013). Clinical pharmacokinetics of newer AEDs. Clinical Pharmacokinetics, 52(7), 607–624.
14. Tomson, T., et al. (2015). Pharmacokinetics during pregnancy. Epilepsia, 56(5), 693–702.
15. Loscher, W., & Schmidt, D. (2006). New horizons in the development of antiepileptic drugs. Epilepsy Research, 69(3), 183–272.

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