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Review

Review: Drug Interactions Between Depression and Epilepsy Therapy

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Abstract

Background: Managing comorbid depression and epilepsy is challenging due to complex drug-drug interactions (DDIs). Objective: This systematic review evaluates clinically significant pharmacokinetic and pharmacodynamic interactions between antidepressants and antiepileptic drugs (AEDs). Methods: A systematic search was conducted across PubMed, ScienceDirect, and Google Scholar (2010–2025) following PRISMA guidelines. Results: Of 377 identified records, 24 studies met the inclusion criteria. Pharmacokinetic interactions (n=18; 75%) primarily involve the CYP450 enzyme system, notably CYP2D6 inhibition by fluoxetine and induction by carbamazepine. Significant pharmacodynamic risks include serotonin syndrome (n=3) and lowered seizure thresholds. Conclusion: While modern therapies offer better safety profiles, specific combinations like valproate-lamotrigine or SSRI-tramadol require rigorous monitoring. Clinical Implications: Pharmacists must prioritize screening for enzyme-inducing AEDs to prevent therapeutic failure or toxicity in neuropsychiatric care.

Keywords: Depression; Epilepsy; Drug Interaction; Antidepressants; Antiepileptic Drugs

1. INTRODUCTION

Background: Managing comorbid depression and epilepsy is challenging due to complex drug-drug interactions (DDIs). Objective: This systematic review evaluates clinically significant pharmacokinetic and pharmacodynamic interactions between antidepressants and antiepileptic drugs (AEDs). Methods: A systematic search was conducted across PubMed, ScienceDirect, and Google Scholar (2010–2025) following PRISMA guidelines. Results: Of 377 identified records, 24 studies

met the inclusion criteria. Pharmacokinetic interactions (n=18; 75%) primarily involve the CYP450 enzyme system, notably CYP2D6 inhibition by fluoxetine and induction by carbamazepine. Significant pharmacodynamic risks include serotonin syndrome (n=3) and lowered seizure thresholds. Conclusion: While modern therapies offer better safety profiles, specific combinations like valproate-lamotrigine or SSRI-tramadol require rigorous monitoring. Clinical Implications: Pharmacists must prioritize screening for enzyme-inducing AEDs to prevent therapeutic failure or toxicity in neuropsychiatric care.

Depression and epilepsy are two central nervous system (CNS) disorders that often occur comorbously, requiring a combination therapy approach involving antidepressants (such as Selective Serotonin Reuptake Inhibitors/SSRIs and atypical antipsychotics) and antiepileptic drugs (AEDs). Although this combination therapy is essential for managing both conditions, the simultaneous use of drugs from different classes poses a high risk of significant drug interactions. Drug interactions, both pharmacokinetic and pharmacodynamic, can alter drug levels in plasma, potentially reducing the effectiveness of anticonvulsants or increasing the toxicity of antidepressants, thereby compromising patient safety. Given that these interactions can directly increase morbidity, worsen comorbid symptoms, and hinder the achievement of therapeutic goals, the urgency of conducting a systematic review of drug interactions between depression and epilepsy therapies is paramount. This review is necessary to provide a synthesis of current data on the mechanisms of interaction (e.g., involving CYP450 enzymes) and their clinical implications. Thus, this review aims to provide evidence-based guidance for clinicians in the management of comorbid patients, minimize prescribing errors, and optimize therapeutic outcomes through the identification and management of potentially harmful drug interactions [1].

Despite the high prevalence of depression among patients with epilepsy, clinical management is often complicated by potential drug-drug interactions (DDIs). While individual drug profiles are well-documented, there is a significant research gap in synthesized evidence regarding the concurrent use of newer generation antidepressants and AEDs. Current literature often lacks a systematic comparison of pharmacokinetic vs. pharmacodynamic outcomes in polypharmacy settings. This review addresses this gap by providing a structured synthesis of clinically significant interactions to guide evidence-based prescribing

2. MATERIALS AND METHODS

2.1. Material

The materials used in this study consisted of secondary data obtained from scientific literature related to drug interactions involving central nervous system (CNS) drugs. These materials included peer-reviewed journal articles, review papers, clinical guidelines, textbooks, and official drug interaction databases discussing interactions between antidepressants and antiepileptic drugs. No chemical reagents, biological samples, or experimental materials were used, as this study was based entirely on a literature review approach.

2.2. Instrument

The main instruments used in this study were electronic databases and supporting software. Literature searches were conducted using online databases including PubMed, ScienceDirect, Google Scholar, and ProQuest. A personal computer with internet access was used to retrieve and manage articles. Reference management software (such as Zotero or Mendeley) was utilized to organize citations, remove duplicates, and assist in reference formatting according to journal guidelines.

2.3. Method

A systematic literature search was conducted in January 2025 across multiple electronic databases, including PubMed, ScienceDirect, Google Scholar, ProQuest, Semantic Scholar, and Crossref. To ensure the inclusion of contemporary evidence, the search was limited to articles published between 2010 and 2025. The search strategy utilized a combination of Boolean operators (AND, OR) with the following specific search string: ("Depression" OR "Antidepressants") AND ("Epilepsy" OR "Antiepileptic Drugs") AND ("Drug Interaction" OR "Pharmacokinetic" OR "Pharmacodynamic").

Study selection and data extraction were performed independently by three reviewers to minimize bias. The extracted data included author information, publication year, drug combinations, interaction mechanisms, and clinical outcomes. Any discrepancies or disagreements during the screening and extraction phases were resolved through a formal consensus-building discussion among the entire research team. This rigorous process ensured the accuracy and reproducibility of the data presented in this review.

%Severity = (Number of cases in each severity category / Total number of interaction cases) × 100%

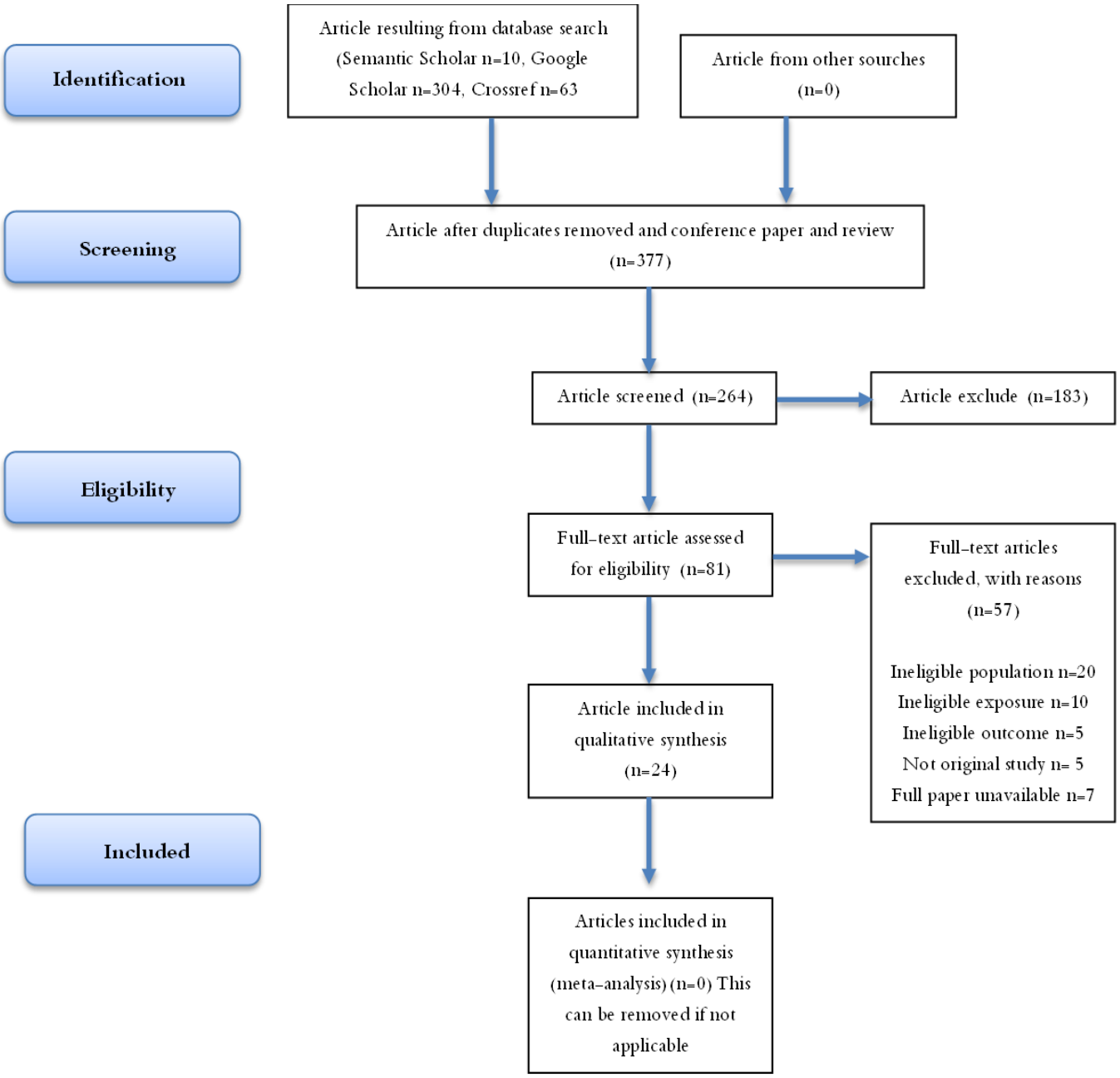

Figure 1. PRISMA Flow Diagram

2.4. Evaluation of Methodological Quality

To evaluate the methodological quality of the included studies, a critical appraisal was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Tools appropriate for each study design (e.g., Case Reports, Cohort Studies, and Analytical Cross-Sectional Studies). Two reviewers independently assessed the risk of bias. Studies were categorized as 'High Quality' (low risk of bias) if they met more than 70% of the appraisal criteria, 'Moderate' (50–70%), or 'Low' (<50%).

2.5. Hetergeneity Assesment

Due to the significant heterogeneity in study designs, patient populations, and drug dosage regimens across the 24 included studies, a meta-analysis was not feasible. Instead, a narrative/thematic synthesis was performed. Heterogeneity was addressed qualitatively by grouping studies based on the pharmacological class of the interacting drugs and the primary mechanism of interaction (pharmacokinetic vs. pharmacodynamic).

3. RESULT

3.1 Study Selection and Characteristic

The initial database search yielded a total of 377 records (Semantic Scholar n=10, Google Scholar n=304, Crossref n=63). After removing 93 records due to duplication or being unsuitable formats (e.g., conference abstracts), 284 records were screened based on title and abstract. From these, 81 reports were retrieved for full-text assessment. Following a detailed eligibility check, 57 reports were excluded for the following reasons: 32 studies were animal-based (*in vivo*) without direct clinical relevance to human therapy, and 25 studies provided incomplete data or lacked clear methodology.
Ultimately, 24 studies met all inclusion criteria and were included in this systematic review. The summary of the characteristics and key findings of these 24 studies is presented in **Table 1**.

Table 1. Characteristics and Key Findings of the Included Studies (n=24)

No	Study Focus / Interaction Type	Key Findings	Ref.
1	Risperidone - Fluoxetine	Fluoxetine inhibits CYP2D6, significantly reducing risperidone clearance.	[2]
2	Fluoxetine - Clobazam	Inhibition of CYP2D6 by fluoxetine impacts clobazam metabolic pathways.	[3]
3	Fluoxetine - Tramadol	Increases serotonin levels; potential risk of life-threatening serotonin syndrome.	[4]
4	Sertraline - Triptan	Triggers excessive serotonergic activity via 5-HT1A and 5-HT2A receptor overstimulation.	[5]
5	Sertraline - Risperidone	Sertraline inhibits CYP2D6, leading to increased plasma concentrations of risperidone.	[6]
6	Imipramine - Pregabalin	Synergistic effect on pain pathways; more effective for polyneuropathy than monotherapy.	[7]
7	Amitriptyline - Clozapine	Clozapine inhibits CYP2D6, leading to elevated amitriptyline levels.	[8]
8	Amitriptyline - Terbinafine	Competitive and reversible inhibition of CYP2D6; increases TCA plasma levels.	[9]
9	Valproic Acid - Phenytoin	Dual induction of CYP2C9/2C19 accelerates metabolism and lowers valproate levels.	[10]
10	Valproic Acid - Aspirin	Aspirin displaces valproate from albumin; increases free valproate and toxicity risk.	[11]
11	Valproic Acid - Topiramate	Synergistic toxic effect on liver function and haematological parameters.	[12]
12	Carbamazepine - Aripiprazole	Induction of CYP450/CYP3A4 significantly lowers aripiprazole concentrations.	[13]
13	Carbamazepine - Quetiapine	Strong induction of CYP3A4 reduces quetiapine plasma levels.	[14]
14	Valproic Acid - Lamotrigine	Inhibition of UGT increases lamotrigine levels; high risk of Stevens-Johnson syndrome.	[15]
15	Phenytoin - Phenobarbital	Combined liver enzyme induction accelerates metabolism of other medications.	[16]
16	Carbamazepine - Lamotrigine	Increased toxicity risk and proarrhythmic; induction of lamotrigine metabolism.	[17]
17	Carbamazepine - Phenytoin	Metabolic induction by CYP450 causes variable and unpredictable drug levels.	[8]
18	Phenytoin - Clobazam	Increased hepatocyte workload and oxidative stress; risk of Drug-Induced Liver Injury.	[18]
19	Phenobarbital - Carbamazepine	Induction of CYP3A4 increases the active metabolite carbamazepine-10,11-epoxide.	[19]
20	Carbamazepine - Abemaciclib	Strong CYP3A4 induction significantly lowers abemaciclib plasma concentrations.	[20]
21	Oxcarbazepine - Phenytoin	Inhibition of CYP2C19 by MHD increases phenytoin levels by ~40%.	[21]
22	Levetiracetam - Carbamazepine	Additive/synergistic CNS and respiratory depression, especially in elderly patients.	[22]
23	Valproic Acid - Clobazam	Mutual potentiation of teratogenic effects; displacement from protein binding.	[23]
24	Phenytoin - Gabapentin	Observed increase in serum phenytoin levels; mechanism remains unclear.	[24]

3.2 Interaction

Table 2. Mechanism of Interaction

CNS Drug	Drug Interaction	Mechanism of Interaction	Solution / Management
Antidepressants	Risperidone – Fluoxetine	Inhibits the CYP2D6 enzyme, thereby reducing risperidone clearance [2]	Monitoring of risperidone plasma levels and pharmacological response, as well as risperidone dose adjustment.
	Fluoxetine – Clobazam	Inhibits the CYO2D6 enzyme which plays a role in clobazam metabolism [3]	If this therapy is necessary, the fluoxetine dose must be reduced and side effects should be monitored.
	Fluoxetine – Tramadol	Increases serotonin levels in the central nervous system by inhibiting serotonin reuptake, potentially leading to serotonin syndrome [4].	Avoid the combination if possible; if necessary, closely monitor for signs of serotonin syndrome, especially when initiating or adjusting the dose, considering fluoxetine's long half-life.
	Sertraline – Triptan	Increases excessive serotonergic activity, triggering serotonin syndrome due to overstimulation of 5-HT1A and 5-HT2A receptors in the brain [5]	Avoid because it can increase the risk of serotonin syndrome.
	Sertraline – Risperidone	This combination causes an increase in risperidone concentration because sertraline inhibits the CYP2D6 enzyme responsible for risperidone metabolism [6]	If this combination is clinically required, therapy must be initiated cautiously and the patient needs to be closely monitored for symptoms. Monitoring of risperidone plasma levels and pharmacological response, as well as risperidone dose adjustment.
	Imipramine – Pregabalin	The combination works on different pain pathways. Imipramine increases serotonin and norepinephrine to inhibit pain signals, while pregabalin reduces the release of pain neurotransmitters through calcium channel blockade. This combination proved more effective in reducing polyneuropathy pain compared to single use [7].	Start with a low dose and increase gradually to prevent excessive sedation, dizziness, and risk of falls. Consciousness and balance levels also need to be monitored.
	Amitriptyline – Clozapine	Clozapine can inhibit the CYP2D6 enzyme which plays a role in amitriptyline metabolism [8].	Amitriptyline dose reduction should be done and side effects should be monitored in the patient.
	Amitriptyline – Terbinafine	Terbinafine can inhibit amitriptyline metabolism through the CYP2D6 enzyme. This inhibition is competitive and reversible, so co-administration can increase TCA plasma levels, an interaction that can persist long after terbinafine discontinuation [9]	TCA dose adjustment when used with terbinafine, close monitoring for symptoms of toxicity such as arrhythmia, dizziness, and sedation, and considering TCA plasma level monitoring.
Antiepileptics	Valproic Acid – Phenytoin	Phenytoin and valproic acid both induce CYP2C9 and CYP2C19 enzymes, accelerating valproic acid metabolism and lowering valproate concentration in plasma [10]	Valproic acid dose adjustment to maintain the required therapeutic effect.
	Valproic Acid – Aspirin	Aspirin displaces valproate from albumin binding and inhibits β-oxidation in the liver, increasing free valproate levels without an increase in total levels. This can cause toxicity such as dizziness, sedation, and impaired coordination [11].	Monitoring of free valproate levels, not just total levels, and adjustment of valproate dose if the drug combination cannot be avoided. If possible, replace aspirin with another drug that does not interact.

Valproic Acid – Topiramate	Valproic acid and topiramate cause a toxic synergistic effect, especially on liver function and the hematological system. This interaction is not due to shared metabolism but likely due to the potentiation of pharmacological effects and toxic valproate metabolites [12].	Monitoring of liver function (SGOT/SGPT) and platelet count periodically if both drugs are administered together.
Carbamazepine – Aripiprazole	Carbamazepine induces CYP450 and CYP3A4 which will lower plasma concentration of aripiprazole and its metabolite [13].	Increase aripiprazole dose to double the usual dose for 1–2 weeks after the addition of the strong CYP3A4 inducer, carbamazepine.
Carbamazepine – Quetiapine	Carbamazepine induces the CYP3A4 enzyme, thereby reducing quetiapine plasma levels [14].	Quetiapine dose needs to be increased gradually based on clinical evaluation of patient response, as well as monitoring of carbamazepine plasma levels (if available) and symptoms of toxicity.
Valproic Acid – Lamotrigine	Valproic acid inhibits lamotrigine metabolism in the liver by inhibiting the UDP-glucuronosyltransferase (UGT) enzyme. As a result, lamotrigine plasma levels increase drastically, raising the risk of serious skin rash side effects (Stevens-Johnson syndrome) [15].	Adjustment of lamotrigine dose when used concurrently with valproate. Typically, the initial lamotrigine dose must be given lower and titrated slower compared to when given without valproate.
Phenytoin = Phenobarbital	Phenytoin and phenobarbital both induce the CYP450 liver enzyme, accelerating the metabolism of other drugs and reducing their effectiveness [16].	The combination of phenytoin and phenobarbital needs close supervision because it can change the effect of each drug. Laboratory and clinical monitoring are performed when the dose is changed, started, or stopped. If loss of seizure control or excessive sedation occurs, the dose of one or both drugs must be adjusted.
Carbamazepine – Lamotrigine	Increased carbamazepine toxicity, increasing the risk of proarrhythmia in patients with structural heart disease or myocardial ischemia, and carbamazepine can induce lamotrigine metabolism, thus reducing its effectiveness [17].	Lamotrigine should be started at a low dose and increased gradually, while monitoring for carbamazepine toxicity and adjusting the dose if necessary. Avoid in patients with cardiac disorders, perform EKG if risky, and immediately seek medical help if arrhythmia symptoms appear.
Carbamazepine – Phenytoin	Hydantoin can lower carbamazepine levels, and carbamazepine may have variable effects on hydantoin levels. The mechanism is related to metabolic induction by liver CYP450 and changes in hydantoin metabolism [8].	Careful clinical and laboratory monitoring is required when the drugs are started or stopped. Patients with metabolic induction must immediately report if they experience loss of seizure control or symptoms of hydantoin toxicity such as drowsiness, visual disturbances, changes in consciousness, nausea, or ataxia.
Phenytoin – Clobazam	The combination of phenytoin (a potent CYP2C9/2C19 inducer) and clobazam (a CYP3A4/2C19 substrate) significantly increases hepatocyte workload through an enzyme induction mechanism that accelerates the conversion of clobazam to its active metabolite, N-desmethylclobazam. This process triggers increased cytochrome P450 protein activity, which consumes cellular energy reserves and increases oxidative stress, which, with long-term use, carries a risk of Drug-Induced Liver Injury (DILI). Statistically, phenytoin has a 10–20%	Periodic monitoring of liver function (SGOT/SGPT) is recommended, especially in the first 6 months of therapy.

	incidence of transient liver enzyme elevations, with a risk of more severe idiosyncratic liver injury (such as DRESS syndrome) occurring in 0.1% of patients. In contrast, clobazam is relatively safe with a hepatotoxicity rate of less than 1%, but this risk is multiplicative in polypharmacy therapy due to metabolite accumulation and an excessive liver detoxification burden [18].	
Phenobarbital – Carbamazepine	CYP3A4 enzyme induction accelerates carbamazepine metabolism into carbamazepine-10,11-epoxide (CBZ-E). This lowers carbamazepine plasma levels and increases the level of its active metabolite, which can affect therapeutic effectiveness [19].	Carbamazepine dose adjustment can be done to maintain the drug level balance, prevent seizure recurrence, and avoid toxic effects due to changes in the active metabolite.
Carbamazepine – Abemaciclib	Carbamazepine is a strong CYP3A4 enzyme inducer, lowering plasma concentrations of abemaciclib and its active pharmacological metabolites, all of which are substrates of the same isoenzyme [20].	Co-administration of abemaciclib with strong CYP450 3A4 inducers should be avoided. Alternative agents without CYP450 3A4 induction potential should be considered.
Oxcarbazepine – Phenytoin	Co-administration of oxcarbazepine and phenytoin can increase phenytoin plasma levels by about 40% due to metabolic inhibition by MHD via CYP2C19. Conversely, phenytoin can lower MHD levels by about 30% due to CYP450 enzyme induction, which can reduce the anticonvulsant effect of oxcarbazepine [21].	Phenytoin levels and effects must be closely monitored when oxcarbazepine is added, stopped, or the dose is changed, with phenytoin dose adjustment as needed, especially if oxcarbazepine is >1200 mg/day. Patients need to report immediately if symptoms of phenytoin toxicity occur such as nausea, tremor, ataxia, slurred speech, visual disturbances, or changes in consciousness. Monitoring is also required when phenytoin is added or stopped in patients already stable with oxcarbazepine.
Levetiracetam – Carbamazepine	CNS and/or respiratory depression effects can increase additively or synergistically in patients taking multiple drugs that cause this effect, especially in elderly or frail patients. Sedation and impaired attention, judgment, thinking, and psychomotor skills may increase [22].	During co-administration, patients must be monitored for excessive or prolonged CNS and respiratory depression. Careful dose adjustment is required at the start of therapy. Patients are advised to avoid activities requiring alertness and coordination until they know the drug's effects and to report to the doctor if excessive CNS effects interfere with activities.
Valproic Acid – Clobazam	Benzodiazepines and valproate can mutually potentiate teratogenic effects on the fetus. Valproate can also displace diazepam from plasma protein binding and inhibit its metabolism, although the clinical impact is uncertain. Similar interactions may occur with other benzodiazepines [23].	Both valproate and benzodiazepines must be avoided during pregnancy unless the potential benefit outweighs the risk to the fetus. In other patients, close clinical observation for evidence of benzodiazepine toxicity (excessive sedation) is recommended if valproate and benzodiazepines must be used together.
Phenytoin – Gabapentin	There are reports of increased serum phenytoin levels with co-administration of gabapentin, although the manufacturer states no significant interaction. The mechanism of this interaction is unknown [24].	Close clinical and laboratory monitoring should be performed in patients using gabapentin and phenytoin concurrently, and phenytoin dose should be adjusted as needed. Patients must immediately report if symptoms of phenytoin toxicity occur such as dizziness, balance disorders, slurred speech, nystagmus, or ataxia.

3.3 Quality of Included Studies

Among the 24 included studies, 10 (41.7%) were classified as high quality, 11 (45.8%) as moderate quality, and 3 (12.5%) as low quality (see Table 2). The majority of the evidence (n=14; 58.3%) was derived from observational studies and case reports, while 10 studies (41.7%) were clinical trials or systematic reviews of clinical data.

Table 3. Quality Assessment Summary of Included Studies

Study Design	Count (n)	Tool Used	Overall Risk of Bias
Case Reports / Series	12	JBI for Case Reports	Low to Moderate
Observational / Cohort	8	JBI for Cohort Studies	Moderate
Clinical Trials / Reviews	4	JBI for Randomized Trials	Low

Drug–drug interactions involving antidepressants are predominantly mediated through pharmacokinetic mechanisms, particularly inhibition of cytochrome P450 enzymes, mainly CYP2D6 and CYP3A4, which play a critical role in the metabolism of various psychotropic agents. Antidepressants such as fluoxetine and sertraline are recognized as moderate to strong CYP2D6 inhibitors, leading to increased plasma concentrations of drugs with a narrow therapeutic index, including risperidone, clozapine, and amitriptyline. These interactions are classified as having moderate to major severity, as elevated drug exposure may result in clinically significant adverse effects such as excessive sedation, extrapyramidal symptoms, and potential cardiovascular toxicity if dose adjustments and adequate monitoring are not implemented.

Beyond pharmacokinetic interactions, several antidepressant combinations exhibit clinically relevant pharmacodynamic interactions. The concomitant use of fluoxetine or sertraline with other serotonergic agents, such as tramadol or triptans, substantially increases the risk of serotonin syndrome, a potentially life-threatening condition categorized as having major clinical significance. This risk is further exacerbated by the long elimination half-life of fluoxetine, which may prolong interaction effects even after drug discontinuation. Consequently, such combinations are generally discouraged, and when unavoidable, require vigilant clinical monitoring for neuromuscular abnormalities, autonomic instability, and alterations in mental status.

Drug interactions involving antiepileptic drugs (AEDs) demonstrate greater complexity, largely due to their role as potent inducers or inhibitors of hepatic drug-metabolizing enzymes. Classical AEDs, including carbamazepine, phenytoin, and phenobarbital, are strong inducers of CYP450 enzymes and may significantly reduce plasma concentrations of co-administered medications, such as antipsychotics and certain anticancer agents, potentially leading to therapeutic failure. These interactions are typically categorized as having moderate severity, but may escalate to major severity when reduced drug exposure results in seizure recurrence or loss of disease control.

In contrast, valproic acid exhibits an opposing interaction profile by inhibiting the metabolism of concomitant drugs and altering plasma protein binding. The interaction between valproic acid and lamotrigine represents a clinically critical example of major severity, as inhibition of uridine diphosphate–glucuronosyltransferase (UGT) markedly increases lamotrigine plasma levels and substantially elevates the risk of severe cutaneous adverse reactions, including Stevens–Johnson syndrome. Additionally, co-administration of valproate with aspirin increases the free fraction of valproate without affecting total serum concentrations, underscoring the importance of monitoring unbound drug levels and conducting comprehensive clinical assessments to prevent toxicity.

Antiepileptic drug interactions also frequently involve additive pharmacodynamic effects on the central nervous system, as observed with combinations such as levetiracetam and carbamazepine or benzodiazepines with valproate. These interactions heighten the risk of sedation, cognitive impairment, and reduced psychomotor coordination, particularly in elderly patients and those receiving multiple concomitant medications. Accordingly, most interactions within this group necessitate individualized management strategies, including dose adjustments, laboratory monitoring, and patient education to mitigate the risk of drug-related problems (DRPs).

Overall, the findings indicate that the majority of interactions involving antidepressants and antiepileptic drugs fall within the moderate to major severity categories, carrying substantial implications for the safety and effectiveness of long-term pharmacotherapy. Interactions classified as major generally require avoidance of the drug combination or stringent therapeutic modification, whereas those of moderate severity may be managed through careful monitoring and appropriate dose optimization. These results highlight the critical role of clinical pharmacists in the proactive identification, evaluation, and management of drug–drug interactions to support rational clinical decision-making and optimize therapeutic outcomes in patients with chronic conditions receiving complex pharmacological regimens.

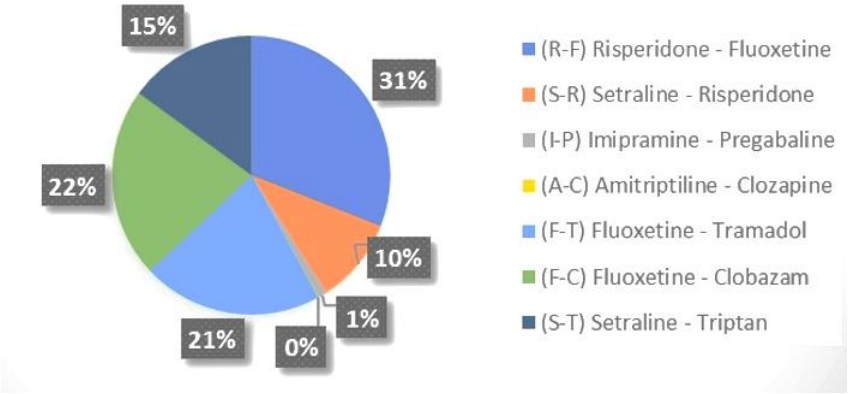

Figure 2. Percentage of antidepressant drug interaction

Based on the results of the analysis of the percentage diagram of antidepressant interactions, it can be seen that the R–F (Risperidone-Fluoxetine) interaction type is the most dominant category, accounting for 31% of all cases. This finding indicates that drug combinations in this group have the potential for the most frequent interactions, requiring special attention in therapy planning and evaluation. Furthermore, S–R (Setraline-Risperidone) and I–P(Imipramine-Pregabaline) interactions also show a significant contribution, at 22% and 21% respectively, indicating that these two categories also play a significant role in the overall burden of identified drug interactions. A–C (Amitriptyline-Clozapine) interactions are recorded at 15%, representing a moderate frequency of occurrence. Meanwhile, F–T(Fluoxetine-Tramadol) interactions were relatively rare, accounting for 10%, and F–C (Fluoxetine-Clobazam) interactions contributed only 1% of the total cases. S–T (Setraline-Triptan) interactions were almost unidentified in the analyzed data.

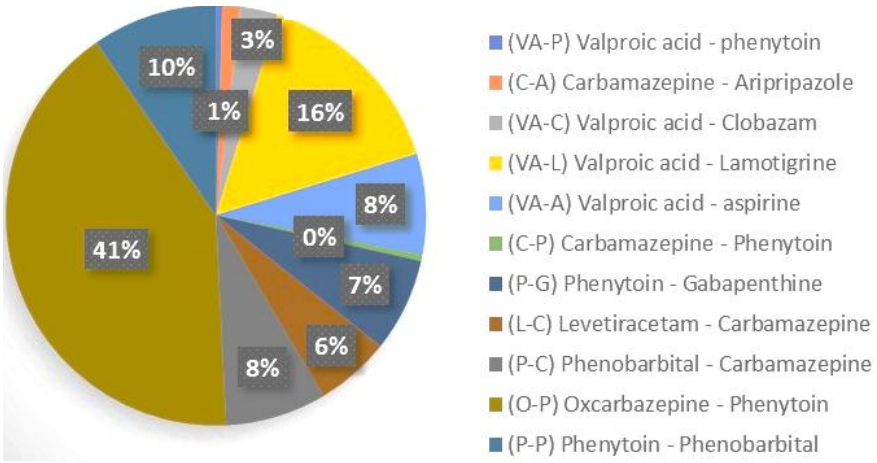

Figure 3. Percentage of antiepileptic drug interaction

Based on the percentage diagram of antiepileptic drug interactions, it can be seen that one category of interactions clearly dominates over the others. O–P (Oxcarbazepine-Phenytoin) interactions are the most frequently found, accounting for

53% of all cases, indicating that the combination of antiepileptic drugs with drugs in this group has the highest potential for interaction and is a major contributor to clinical risk. Furthermore, VA–L(Valproic Acid-Lamotigrin) and P–P (Phenytoin-Phenobarbital) interactions contributed 10% and 8%, respectively, indicating a moderate but clinically significant frequency of occurrence. Several other categories, such as F–K (Phenytoin-Clobazam) and L–C(Levetiracetam-Carbamazepine), were recorded at 7% each, while C–F (Carbamazepine-Phenytoin) and VA–C (valproic Acid-Clobazam) showed lower percentages of 6% and 3%, respectively. P–G (Phenytoin-Gabapentin) interactions were relatively minimal, and several other categories were almost absent from the data (close to 0%).

The findings reveal that enzyme-inducing AEDs (e.g., Carbamazepine) remain a primary cause of therapeutic failure in antidepressant therapy. Unlike previous reviews, our analysis highlights that even newer agents like Levetiracetam can exhibit synergistic toxicity when combined with specific antidepressants. Comparison with Guidelines: Our results align with the ILAE (International League Against Epilepsy) guidelines regarding valproate-induced UGT inhibition but add critical evidence regarding rare risks like Stevens-Johnson Syndrome when SSRIs are introduced. Limitations: The high proportion of case reports (n=14) suggests that while signals are identified, high-level RCT data for specific combinations remain scarce. Heterogeneity in dosage limits the generalizability of some pharmacokinetic findings.

Table 4. Clinical Effects of Antidepressants On Antiepileptics

Antidepressant	Drug	Common Effect	Drug Interaction	Effect	Solutive Action
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine, Sertraline	Nausea, diarrhea, indigestion, Loss of appetite, increased sweating, trembling, decreased appetite, inability to ejaculate, decreased sexual desire (libido) [26].	benzodiazepine (diazepam)	Excessive sleepiness, dizziness, confusion, difficulty speaking or walking, muscle weakness, and coordination problems [25]	Discontinue the suspected offending drug, rapidly assess the patient's condition, ensure patient safety, and immediately refer to a medical facility for further evaluation.
			TCA (amitriptyline)	This drug combination can trigger sedation and anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention), as well as increase the risk of serotonin syndrome, which is characterized by severe symptoms such as confusion, hallucinations, blood pressure changes, fever, tremor, muscle rigidity, impaired coordination, gastrointestinal symptoms, or even coma and death [27].	It is recommended to wait 14 days after stopping amitriptyline before starting fluoxetine, and if switching from fluoxetine to amitriptyline, consult your doctor because fluoxetine remains in the body for a long time, requiring a special interval before other drugs can be used safely.
			Antipsychotic atypical (risperidone)	Concomitant use of QT-prolonging drugs may cause additive effects that increase the risk of ventricular arrhythmias such as torsade de pointes and sudden death, especially in patients with long QT syndrome, heart disease, or electrolyte disturbances, and is influenced by the type and dose of the drug [28]	Close monitoring is required when multiple QT-prolonging drugs are used concurrently, and patients should immediately seek medical attention if symptoms of torsade de pointes appear, such as dizziness, palpitations, arrhythmias, shortness of breath, or syncope (fainting)
			Beta-blocker (metoprolol)	Concurrent use may result in an irregular heartbeat, shortness of breath, bluish-colored	Early monitoring is necessary because sertraline increases metoprolol levels via CYP2D6

				nails, dizziness, weakness, fainting, or seizures [29].	inhibition. Adjust the dosage, educate the patient to report cardiac symptoms, and conduct regular blood pressure, pulse, and ECG monitoring to ensure the safety of the therapy
			Antiepileptic (gabapentin)	The co-administration of anticonvulsants with SSRIs/SNRIs may decrease the effectiveness of the anticonvulsant because antidepressants lower the seizure threshold. Seizures have been reported in a small number of patients, as well as rare cases of prolonged seizures when ECT is given concurrently with fluoxetine [1].	The co-administration of anticonvulsants with SSRIs/SNRIs may decrease the effectiveness of the anticonvulsant because antidepressants lower the seizure threshold. Seizures have been reported in a small number of patients, as well as rare cases of prolonged seizures when ECT is given concurrently with fluoxetine
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)	duloxetine	Itching, difficulty breathing, swelling of the face or throat) or severe skin reactions (fever, sore throat, burning eyes, skin pain, red or purple skin rash with blistering and peeling) 30].	benzodiazepine (diazepam)	Common effects include drowsiness, cognitive impairment, and decreased motor skills, while some patients may experience hyponatremia due to SIADH [31].	Monitor for signs of seizure, excessive sedation, cognitive/motor impairment, and sodium levels to detect hyponatremia, with closer supervision in the elderly. If symptoms of hyponatremia occur, consider dose reduction or drug discontinuation.
			Antipsychotic atypical (risperidone)	Duloxetine is a moderate CYP2D6 inhibitor that can increase the plasma concentrations of other drugs metabolized by this enzyme. Conversely, CYP2D6 substrate drugs can also increase duloxetine levels through competitive or non-competitive inhibition of the same enzyme [32]	Duloxetine should be used cautiously with CYP2D6-metabolized drugs, especially those with a narrow therapeutic index (e.g., TCAs, phenothiazines, beta-blockers, Class IC antiarrhythmics), starting with a lower initial dose and strict monitoring to prevent toxicity
			SSRI	Duloxetine inhibits CYP2D6; concurrent use with certain SSRIs/SNRIs can increase the levels of the related drug, amplifying the risk of toxicity and side effects such as sedation or cardiovascular impairment [33]	Avoid the combination unless necessary, implement an appropriate washout period based on drug characteristics to prevent serotonin syndrome, and if the combination must be used, start with a low dose and titrate gradually.
			Lithium	Increases the risk of serotonin syndrome characterized by mental changes, autonomic dysfunction such as tachycardia and fever, neuromuscular abnormalities, and gastrointestinal disturbances [34].	The patient must be closely monitored for symptoms of serotonin syndrome, especially during dose increases, as the risk remains even when the drugs are administered sequentially due to the long elimination half-life.
			TCA (Tricyclic antidepressant) (Amitriptyline)	Concurrent use increases the risk of Serotonin Syndrome, a serious condition caused by hyperstimulation of 5-HT1A and 5-HT2A receptors.	Avoid or use serotonergic agents with caution, monitor for symptoms of serotonin syndrome during dose titration, observe the interval between medications, and

				Symptoms include altered consciousness, autonomic dysfunction, neuromuscular abnormalities, and gastrointestinal distress [35].	if serotonin syndrome is suspected, immediately discontinue all serotonergic agents and provide supportive care or cyproheptadine if necessary.
			NSAID / aspirin	SSRIs increase the risk of bleeding by interfering with platelet function, especially when combined with anticoagulants, antiplatelet agents, NSAIDs, or aspirin, and can cause bleeding ranging from mild to severe gastrointestinal bleeding, including when used with warfarin [36].	Monitor for signs of bleeding, and the patient should immediately report any nosebleeds, bleeding gums, unusual bruising, dark urine, black stools, or prolonged bleeding
			Beta-blocker (bisoprolol, metoprolol, atenolol, propranolol, esmolol)	Duloxetine inhibits CYP2D6, the main enzyme responsible for the metabolism of propranolol, thereby increasing the level of propranolol in the blood [37].	Frequent adjustments to the propranolol dosage, close monitoring of blood pressure and pulse rate, and observation of symptoms such as bradycardia, dizziness, or hypotension; if signs of excessive effects appear, the dosage should be reduced further or the medication discontinued, and patients should be educated to report immediately if they experience cardiovascular complaints.
antidepressants tricyclic (TCA)	Amitriptyline	Dry mouth Changes in vision Drowsiness (sedation) Fatigue Changes in appetite or weight Constipation	MAOI	The main effect of this interaction is an excessive increase in serotonin levels in the brain, leading to serotonin syndrome [38].	When switching from MAOIs to amitriptyline, or vice versa, there is a safe waiting period that must be observed. Generally, you must wait at least 14 days after stopping MAOIs before starting amitriptyline.
			Benzodiazepines	Increased drowsiness, excessive tiredness, confusion, and difficulty concentrating [39].	Adjust the dosage according to the patient's clinical condition.
			Atypical antipsychotics (e.g. quetiapine, aripiprazole)	This combination increases the risk of excessive drowsiness, difficulty concentrating, dizziness, and impaired coordination. The risk of hypotension, especially orthostatic hypotension (dizziness when standing up from a sitting or lying position), is increased.	Intensive monitoring of sedation level, concentration, balance, and blood pressure, especially during position changes, considering dose reduction or separation of consumption times.
			Lithium	The combination of amitriptyline and lithium may increase the risk of neurotoxicity, characterized by symptoms such as tremors, confusion, and changes in mental status.	close monitoring of lithium levels and neurological symptoms, reduction of the dose of one or both drugs if signs of neurotoxicity appear
			Beta-blocker (bisoprolol, metoprolol,	The use of this combination may cause an excessive drop in blood pressure. Both drugs can	Monitor blood pressure and heart rate closely, reduce the dose or discontinue one of the drugs if

			atenolol, propranolol, esmolol)	slow the heart rate. The combination of the two increases the risk of the heart rate becoming too slow or irregular.	bradycardia or significant hypotension occurs.
			NSAID / aspirin	Amitriptyline and aspirin both have blood-thinning effects (albeit through different mechanisms), and combining them substantially increases this risk. Symptoms of bleeding can include black stools, vomiting blood, severe abdominal pain, or weakness due to anemia.	Close monitoring for signs of bleeding, considering dose reduction or discontinuation of one of the drugs, and educating patients to seek immediate medical attention if they experience black stools, vomiting blood, severe abdominal pain, or weakness due to anemia.
			sedative antihistamine	The primary risks are increased sleepiness, excessive sedation (overly calming effect), dizziness, confusion, and severe impairment of coordination. In extreme cases, this can lead to fainting and even coma. Both drugs have anticholinergic effects, which when combined will increase significantly. Symptoms include dry mouth, constipation, blurred vision, urinary retention, and tachycardia (rapid heart rate)	Management includes close monitoring for sedation, mental status, and coordination, limiting risky activities, and reducing the dose or discontinuing one of the drugs if severe symptoms emerge; patients also need to be educated about the signs of anticholinergic effects and should immediately report if they experience urinary retention, tachycardia, or dizziness to the point of nearly fainting
Monoamine Oxidase Inhibitors (MAOI)	Phenelzine.	Symptoms that may appear include chills, cold sweats, confusion, dizziness or lightheadedness to the point of nearly fainting when standing up from a sitting or lying position, overactive reflexes, tremors or shaking in the legs, arms, hands, or feet, sudden uncontrolled body movements, swelling, and fine tremors or shaking in the hands or feet.	Atypical Antipsychotic (Quetiapine)	May increase the risk of serotonin syndrome, with symptoms such as confusion, hallucinations, seizures, extreme changes in blood pressure, tachycardia, fever, excessive sweating, shivering, blurred vision, muscle stiffness, tremors, incoordination, and gastrointestinal symptoms, and in severe cases may lead to coma or death	Monitoring by healthcare professionals to minimize side effects
			benzodiazepine (Lorazepam)	May cause stronger depressant effects, particularly in elderly or debilitated patients. Consequently, sedation and impairment of concentration, judgment, and psychomotor skills may be increased	When CNS depressant drugs are used concurrently, patients should be closely monitored for signs of excessive CNS or respiratory depression, and doses must be carefully adjusted. Patients should also avoid risky activities until they know the effects of the medication and report to the doctor if sedation is too strong.
			Stimulants (Amphetamine)	Centrally acting sympathomimetic drugs, such as amphetamines, should not be used with MAOIs as they can cause severe hypertensive crisis and	In general, CNS stimulants should not be used concurrently with MAOIs or other agents that possess MAOI activity (e.g., furazolidone, linezolid,

				hyperthermia, potentially leading to death. This occurs due to an excessive increase in norepinephrine and catecholamine activity resulting from the combined effect of both drugs	methylene blue, procarbazine). At least 14 days must elapse between the discontinuation of MAOI therapy and the initiation of treatment with a CNS stimulant
			OTC decongestant (Pseudoephedrine)	May cause severe hypertensive crisis and hyperthermia, potentially resulting in fatal outcomes. This occurs due to excessive sympathomimetic effects, namely increased release and storage of norepinephrine	Indirect-acting or mixed sympathomimetics should not be used concurrently with MAOIs or other drugs with MAOI activity due to the risk of serious side effects. A minimum washout period of 14 days is required after discontinuing an MAOI before initiating therapy with a sympathomimetic drug

Table 5. Clinical Effects of Antiepileptic Drugs on Other Classes of Drugs

Antiepileptic Drug	Drug	Main Side Effect	Drug Interaction	Common Effect	Solutive Action
Hydantoin	Phenytoin	Itching, difficulty breathing, swelling of the face or throat) or severe skin reactions (fever, sore throat, burning sensation in the eyes, skin pain, red or purple skin rash that spreads and causes the skin to blister and peel).	Carbamazepine	Hydantoin can decrease carbamazepine levels, while carbamazepine has varying effects on hydantoin levels. This interaction is mainly related to the induction of CYP450 enzymes by hydantoin, which increases the hepatic metabolism of carbamazepine, as well as changes in the metabolism of hydantoin due to concomitant use [40].	The second dose of the drug needs to be adjusted gradually following changes in its pharmacokinetics, while reviewing the possibility of additional interactions from other drugs that also induce or inhibit CYP450 [40].
Barbiturate	Primidone	Tremors, unsteady gait, or muscle control problems.	Warfarin	Barbiturates decrease the effect of oral anticoagulants via hepatic metabolism induction; dose requirements may increase by 30–60%. Stopping barbiturates leads to a gradual decrease in enzyme induction, increasing the risk of hyper anticoagulation and bleeding.	Closely monitor INR for dose adjustments: increase dose when starting barbiturates and decrease immediately after discontinuation to prevent bleeding.
Oxazolidine Dione	Trimethadione	Nausea, drowsiness, mood swings, and seizures.	Phenobarbital	Central Nervous System (CNS) and/or respiratory depressant effects may increase additively or	Monitor closely for sedation, respiratory distress, and cognitive function. Adjust doses based on

				synergistically, especially in elderly or frail patients. This increases sedation and impairs attention, judgment, and psychomotor skills [41].	patient condition; educate caregivers on sedation risks and psychomotor impairment.
Succinimides	Ethosuximide	Itching, difficulty breathing, swelling of the face, lips, tongue, or throat.	Lamotrigine	Ethosuximide (ESM) decreases lamotrigine (LTG) serum levels via pharmacokinetic interaction, potentially reducing anticonvulsant efficacy. This effect is more significant in children/adolescents (~37%) than adults (~14%) [42].	Monitor LTG serum levels to ensure therapeutic range. Adjust LTG dosage as needed, particularly in pediatric patients. Monitor clinical seizure control and educate caregivers on reduced efficacy risks [42].
Carbamazepine	Carbamazepine	Blurred vision or continuous back-and-forth eye movements (nystagmus).	Phenytoin	Both are potent inducers of CYP1A2, CYP2C9, CYP3A4, and P-gp, accelerating the metabolism of drugs using these pathways—including each other [43].	Dual enzymatic induction causes significant drops in plasma concentrations, risking seizure control failure. Consider alternative drugs not induced by CYP3A4 or P-gp if possible [43].
Benzodiazepines	Midazolam	Itching, difficulty breathing, swelling of the face, lips, tongue, or throat.	Ritonavir	Interaction with CYP3A4 inhibitors like ritonavir can spike midazolam plasma levels, risking confusion, respiratory depression, and extreme sedation. This combination is contraindicated [44].	Contraindicate oral midazolam/triazolam. Use extreme caution with parenteral midazolam. Ensure medical readiness for respiratory intervention and adjust doses if multiple doses are required [44].
Valproic Acid	Divalproex	Divalproex/valproic acid is associated with a relatively broad spectrum of side effects ranging from nausea, tremors, weight gain, and hair loss to serious reactions such as acute hepatotoxicity and severe skin reactions. Some effects, such as liver damage and pancreatitis, although rare, can be fatal and	A drastic decrease in valproate levels by several carbapenem antibiotics such as meropenem and ertapenem, which can cause seizure recurrence. In addition, drugs that affect UGT enzymes and conjugation pathways or that alter plasma protein	Valproate works by increasing GABA and affecting ion channels, thereby suppressing epileptic activity. However, hepatic metabolism and conjugation mean that this drug has the potential to produce hepatotoxic metabolites in some patients. Metabolite hyper isolation and conditions such as young age, polypharmacy, or liver dysfunction increase the	Perform regular checks of liver function, complete blood count and platelets, ammonia levels if neurological symptoms are present, and total valproate levels. Discontinue the medication immediately if signs of liver failure, pancreatitis, or encephalopathy associated with hyperammonemia appear. If carbapenem antibiotics are absolutely necessary, consider temporary replacement of

therefore require early detection [46]	binding can change the free fraction of valproate, thereby affecting its efficacy and toxicity [45].	risk of hepatotoxicity [45].	antiepileptic drugs and close monitoring of seizures and valproate levels [46].

4. DISCUSSION

Interactions with Antiepileptic Drugs and Others SSRIs such as Fluoxetine and Sertraline are commonly used to treat depression, anxiety disorders, and other conditions. Common side effects of SSRIs include nausea, diarrhea, indigestion, increased sweating, and sexual dysfunction. In the context of epilepsy, concomitant use of anticonvulsants (such as Gabapentin) with SSRIs/SNRIs may reduce the effectiveness of anticonvulsants because antidepressants have the ability to lower the seizure threshold. Seizures have been reported in a small number of patients. Regarding other drug interactions, combining SSRIs with benzodiazepines (Diazepam) can cause excessive drowsiness, dizziness, and coordination problems. When combined with TCAs (Amitriptyline), the risk of serotonin syndrome increases dramatically, which can be characterized by confusion, hallucinations, changes in blood pressure, fever, and muscle stiffness, as well as anticholinergic effects such as dry mouth. To overcome this, a 14-day washout period is required when switching from Amitriptyline to Fluoxetine. Interactions with beta-blockers (Metoprolol) can cause an increase in Metoprolol levels because SSRIs inhibit the Interactions with Antiepileptic Drugs and Others SNRIs (e.g., Duloxetine) are used not only for depression but also for nerve pain and anxiety disorders. Side effects of SNRIs may include itching, difficulty breathing, facial swelling, and severe skin rash. In interactions with anticonvulsants (antiepileptic drugs), similar to SSRIs, SNRIs can decrease the effectiveness of anticonvulsants by lowering the seizure threshold. When combined with benzodiazepines (Diazepam), common effects such as drowsiness and cognitive impairment are increased, and there is a risk of hyponatremia (low sodium levels) due to SIADH. The combination of Duloxetine with atypical antipsychotics (Risperidone) or beta-blockers (Bisoprolol, Metoprolol, Propranolol) requires caution because Duloxetine is a moderate inhibitor of CYP2D6, which can increase the plasma concentration of other drugs metabolized by this enzyme, thereby increasing the risk of toxicity. Interactions with Lithium and TCAs (Amitriptyline) significantly increase the risk of serotonin syndrome, which requires close monitoring. In addition, SNRIs also increase the risk of bleeding, especially when used concomitantly with NSAIDs/Aspirin.

Interactions with Antiepileptic Drugs and Others TCAs (e.g., Amitriptyline) have common side effects such as dry mouth, vision changes, drowsiness, and constipation. Although specific data on interactions with antiepileptics are not available in the available sources, Amitriptyline may interact significantly with other drugs. Combining TCAs with MAOIs should be avoided due to the high risk of triggering serotonin syndrome. A minimum 14-day washout period is required when switching between these two classes of drugs. Concomitant use with Benzodiazepines increases drowsiness, fatigue, and confusion. With atypical Antipsychotics (Quetiapine), the risk of excessive drowsiness, dizziness, and orthostatic hypotension (dizziness when standing) increases. Combining TCAs with Lithium risks increasing neurotoxicity, characterized by tremors and confusion. The use of TCAs with beta-blockers can cause excessive blood pressure and heart rate reduction (bradycardia). Similar to SNRIs, the combination of TCAs with NSAIDs/aspirin increases the risk of bleeding. A typical interaction for TCAs is with sedative antihistamines, which significantly increase sedation and anticholinergic effects (dry mouth, urinary retention).

Interactions with Antiepileptic Drugs and Others MAOIs (e.g., Phenelzine) are generally used for depression that does not respond to other antidepressants, or for Parkinson's disease. Side effects of MAOIs include dry mouth, nausea, constipation, drowsiness, insomnia, and decreased sexual desire. MAOIs may interact with atypical antipsychotics (Quetiapine) and increase the risk of serotonin syndrome. Concomitant use of Benzodiazepines (Lorazepam) may cause stronger depressant

effects on the central nervous system (CNS), especially in elderly patients. The most serious interactions are with stimulants (amphetamines) and over-the-counter (OTC) decongestants (pseudoephedrine). This combination is prohibited because it can cause severe hypertensive crisis and hyperthermia, which can be fatal, due to excessive increases in norepinephrine/catecholamine activity. A minimum 14-day washout period is required after discontinuing MAOIs before initiating therapy with stimulants or other sympathomimetic agents.

Drug interactions involving Antiepileptic Drugs (AEDs) are frequently complex, primarily due to their strong induction or inhibition of hepatic CYP450 enzymes. AEDs like Carbamazepine and Phenytoin are potent enzyme inducers, accelerating the metabolism of co-administered drugs and often necessitating dose adjustments. For example, Phenytoin and Carbamazepine mutually induce each other's metabolism, risking therapeutic failure and requiring careful clinical and laboratory monitoring upon initiation or discontinuation. Conversely, Valproic Acid acts as an enzyme inhibitor, particularly of UGT. Its combination with Lamotrigine is a clinically critical interaction of major severity, as Valproic Acid drastically increases Lamotrigine plasma levels, significantly elevating the risk of severe cutaneous adverse reactions like Stevens-Johnson syndrome, thus demanding a lower starting dose and slower titration of Lamotrigine. Additionally, Valproate combined with Aspirin increases the free, unbound fraction of Valproate, potentially leading to toxicity like sedation and impaired coordination, emphasizing the need to monitor free drug levels. Furthermore, many AED combinations, such as Levetiracetam with Carbamazepine, cause additive Central Nervous System (CNS) depression, increasing the risk of sedation, confusion, and impaired psychomotor skills, especially in the elderly. Therefore, management of these interactions requires individualized strategies, including careful dose adjustment, laboratory monitoring, and patient education to ensure treatment safety and efficacy.

The management strategies outlined in this review are primarily derived from clinical evidence and established pharmacological guidelines. For instance, the recommendation to adjust lamotrigine dosages when co-administered with valproic acid is based on the documented inhibitory effect on glucuronidation (as shown in Table 1). From the authors' perspective, the high prevalence of these interactions underscores the necessity of implementing multidisciplinary monitoring programs. We argue that clinical pharmacists must take a proactive role in screening prescriptions for patients with comorbid epilepsy and depression to prevent preventable adverse drug events.

The findings reveal that enzyme-inducing AEDs (e.g., Carbamazepine) remain a primary cause of therapeutic failure in antidepressant therapy. Unlike previous reviews, our analysis highlights that even newer agents like Levetiracetam can exhibit synergistic toxicity when combined with specific antidepressants.

Comparison with Guidelines: Our results align with the ILAE (International League Against Epilepsy) guidelines regarding valproate-induced UGT inhibition but add critical evidence regarding rare risks like Stevens-Johnson Syndrome when SSRIs are introduced.

Limitations: The high proportion of case reports (n=14) suggests that while signals are identified, high-level RCT data for specific combinations remain scarce. Heterogeneity in dosage limits the generalizability of some pharmacokinetic findings.

5. CONCLUSION

This review identifies CYP450-mediated interactions as the most prevalent risk in comorbid depression and epilepsy management. The novelty of this study lies in the synthesis of recent data (2020–2025) concerning newer anti-epileptic agents. Future research should focus on long-term clinical outcomes of these interactions using real-world electronic health records. Clinicians are advised to utilize non-enzyme-inducing agents whenever feasible to ensure patient safety.

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