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Potential Drug-Drug Interactions of Medications Used in Alzheimer's Disease: Comparative Analysis Across Four Databases

Alzheimer Hastalığında Kullanılan İlaçların Potansiyel İlaç-İlaç Etkileşimleri: Dört Veri Tabanında Karşılaştırmalı Analiz

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ABSTRACT Objective: The aim of this study is to identify how potential drug-drug interactions related to medications commonly used in the treatment of Alzheimer's disease such as donepezil, rivastigmine, and memantine are classified across 4 different drug interaction databases, and to analyze the discrepancies among these classifications. **Material and Methods:** A total of 129 prescriptions containing Alzheimer's medications, belonging to 117 patients, were obtained from community pharmacies located in the Patnos district of Ağrı Province, Türkiye. These prescriptions were analyzed using 4 different drug interaction databases. The potential interactions between commonly prescribed drugs for Alzheimer's disease and other co-prescribed medications were evaluated through the drug interaction resources Drugs.com, RxMediaPharma®, Medscape, and Lexicomp. **Results:** Many interactions were identified in the databases. The Kendall's W coefficient was calculated as 0,317, indicating a low level of agreement and demonstrating that the classifications of drug interaction severity significantly differed among the 4 databases. Pearson correlation findings revealed striking discrepancies in the concordance of evaluations between the databases. Furthermore, chi-square analyses showed statistically significant differences in all comparisons among the drug interaction databases. **Conclusion:** The findings indicate significant inconsistencies among the databases, suggesting that relying on a single database may lead to overlooking some potentially important drug interactions. This issue is particularly critical in elderly patient populations experiencing polypharmacy, where such discrepancies can contribute to the unnoticed development of adverse drug reactions or interactions.

Keywords: Alzheimer's disease; drug-drug interaction; potential drug-drug interactions; interaction database

ÖZET Amaç: Bu çalışmanın amacı, Alzheimer hastalığının tedavisinde yaygın olarak kullanılan donepezil, rivastigmin ve memantin gibi ilaçlara ilişkin potansiyel ilaç-ilaç etkileşimlerinin 4 farklı ilaç etkileşim veri tabanında nasıl sınıflandırıldığını belirlemek ve bu sınıflandırmalar arasındaki tutarsızlıkları analiz etmektir. **Gereç ve Yöntemler:** Türkiye'nin Ağrı iline bağlı Patnos ilçesindeki serbest eczanelerden 117 hastaya ait, Alzheimer ilaçlarını içeren toplam 129 reçete temin edilmiştir. Bu reçeteler, ilaç etkileşimlerine yönelik 4 farklı veri tabanı (Drugs.com, RxMediaPharma®, Medscape ve Lexicomp) aracılığıyla değerlendirilmiştir. Alzheimer hastalığında sık kullanılan ilaçlarla eşzamanlı reçetelenen diğer ilaçlar arasındaki potansiyel etkileşimler bu veri tabanları üzerinden analiz edilmiştir. **Bulgular:** Veri tabanlarında, çok sayıda etkileşim tespit edildi. Veri tabanlarının etkileşim şiddeti sınıflandırmaları arasında anlamlı farklılıklar olduğu saptanmış; Kendall's W katsayısı 0,317 olarak bulunarak veri tabanları arasındaki düşük düzeyde uyuma işaret etmiştir. Pearson korelasyon analizi, veri tabanlarının değerlendirme tutarlılığı açısından belirgin uyumsuzluklar gösterdiğini ortaya koymuştur. Ayrıca ki-kare analizleri, veri tabanları arasındaki tüm karşılaştırmalarda istatistiksel olarak anlamlı farklılıklar olduğunu göstermiştir. **Sonuç:** Çalışma bulguları, ilaç etkileşim veri tabanları arasında önemli düzeyde tutarsızlıklar bulunduğunu ortaya koymaktadır. Özellikle çoklu ilaç kullanımının yaygın olduğu yaşlı bireylerde, yalnızca tek bir veri tabanına dayanılarak yapılan değerlendirmeler bazı klinik açıdan önemli etkileşimlerin göz ardı edilmesine neden olabilir. Bu durum, potansiyel olarak ciddi advers ilaç etkileşimlerinin fark edilmeden gelişmesine yol açabilir.

Anahtar Kelimeler: Alzheimer hastalığı; ilaç-ilaç etkileşimi; potansiyel ilaç-ilaç etkileşimleri; etkileşim veri tabanı

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Alzheimer's disease (AD) is the most common neurodegenerative disorder in the elderly, characterized by progressive impairments in memory, language, executive functions, and activities of daily living.[1] Globally, an estimated 7.2 million individuals aged 65 years and older are projected to be living with Alzheimer's dementia in 2025, with this number expected to increase to 13.8 million by 2060.[2] The pathophysiology of the disease primarily involves a reduction in acetylcholine levels and dysfunction of the glutamatergic system. Current pharmacological treatments target these neurochemical disturbances, with acetylcholinesterase inhibitors (donepezil, rivastigmine) and the NMDA receptor antagonist memantine being the most used agents in clinical practice.[3-5]

These drugs aim to alleviate symptoms by regulating neurotransmitter levels. However, polypharmacy, which is common among elderly patients, may affect the efficacy and safety of these treatments. Polypharmacy is defined as the use of 5 or more medications and is observed in 30-60% of patients with AD.[2] Polypharmacy increases the likelihood of drug-drug interactions (DDIs) as well as the prescription of potentially inappropriate medications. DDI is defined as a pharmacological or clinical response to a combination of drugs that differs from the expected effect when each drug is administered individually.[6] DDIs can affect both pharmacokinetics and pharmacodynamics, which are clinically important in older adults. The risk of DDIs increases in elderly patients taking multiple medications. In adults aged 75 and older, the likelihood of clinically significant DDIs rise sharply with the number of medications prescribed.[7] Since most individuals diagnosed with AD are elderly patients with multiple comorbidities, polypharmacy rates are considerably high. This represents a significant clinical risk factor for potential DDIs (pDDIs).[8] The agents used in AD treatment, especially when combined with other centrally acting medications (e.g., antipsychotics, antidepressants, beta-blockers, anticholinergics, antihypertensives, and anticoagulants), further increase the potential for both pharmacokinetic and pharmacodynamic interactions.[9,10]

pDDIs are critically important for safety in clinical practice. Reliable and comprehensive databases serve as essential tools for the early identification of these potential interactions.[11] However, these databases are not without limitations. Differences in terminology, classification systems, and the criteria used to evaluate clinical relevance often lead to discrepancies among databases.[12]

There are studies in which different drug interaction databases have been used, either individually or in combination, to investigate potential DDIs in AD. In one study, the medication profiles of 115 AD patients were analyzed using Lexicomp, revealing that 77.4% of patients had at least one pDDIs.[13] Consequently, polypharmacy significantly increases the risk of pDDIs in AD patients. Another study examining the medications of 100 AD patients via Lexicomp found a positive correlation between the number of medications and the risk of pDDIs.[14]

Interactions among pre-admission medications of 134 patients with multiple comorbidities were compared using Drugs.com, Lexicomp, and Medscape databases. While all programs identified numerous interactions, discrepancies existed among them. This study suggested that free tools like Medscape and Drugs.com tend to report more interactions, whereas Lexicomp may apply more conservative criteria.[15] Previous research investigating drug interactions of donepezil, rivastigmine, and memantine primarily utilized the Lexicomp database.[13,14,16]

In this study, prescriptions of AD patients were analyzed using drug interaction databases such as Drugs.com, RxMediaPharma®, Medscape, and Lexicomp, and the differences among these databases were evaluated. In our study, for the first time, interactions were examined across 4 different databases, and concordance among them was demonstrated.[17-20] This approach provided healthcare professionals with a comprehensive comparison opportunity.

MATERIAL AND METHODS

This was a retrospective descriptive study. The study was approved by the Scientific Research Ethics Committee of İbrahim Çeçen University (date: May 23, 2023; no: E-95531838-050.99-71311). Our study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 129 prescriptions containing Alzheimer's medications, belonging to 117 patients, were obtained from community pharmacies operating in the Patnos district of Ağrı Province, Türkiye, and analyzed using 4 different drug interaction databases. Patient prescription data-including age, gender, Alzheimer's medications, and other prescribed drugs- were collected potential drug interactions were evaluated using the RxMediaPharma®, Drugs.com, Medscape, and Lexicomp databases. Drugs.com grouped interactions into Major, Moderate, and Minor categories.[17] The RxMediaPharma® database categorized interactions into Level 1, Level 2, and Level 3.[18] Medscape classified interactions as Monitor Closely, Serious-Use Alternative, and Minor.[19] In the Lexicomp database, drug interactions were classified into categories A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination) (Table 1).[20] Each prescription was individually entered into all 4 databases, and the types and numbers of interactions were identified. The severity, mechanism, clinical significance, and recommended precautions of these interactions were comparatively assessed.

STATISTICAL ANALYSIS

The collected data were analyzed using IBM SPSS Statistics version 20.0. Descriptive statistics were presented as means±standard deviations for continuous variables and frequencies with percentages for categorical variables. The agreement among the 4 drug interaction databases regarding interaction severity classifications was assessed using Kendall's W coefficient. Pearson correlation analysis was conducted to evaluate the relationships between the databases' interaction assessments. Additionally, chi-square tests were performed to determine statistically significant differences in interaction categorizations across the databases. A p value of less than 0.05 was considered statistically significant.

TABLE 1: Classification levels of drug interaction databases

Database	Interaction levels
Drugs.com	Major (severe)
	Moderate
	Minor
RxMediaPharma®	Level 1 (limited clinical impact)
	Level 2 (patient should be monitored)
	Level 3 (combination not recommended)
Medscape	Contraindicated
	Serious-use alternative
	Monitor closely
	Minor
Lexicomp®	A (no known interaction)
	B (no action needed)
	C (monitor therapy)
	D (consider therapy modification)
	X (avoid combination)

RESULTS

In this study, a total of 129 prescriptions belonging to 117 Alzheimer's patients including the commonly used agent's donepezil, rivastigmine, and memantine were analyzed using 4 different drug interaction databases. Among the prescriptions reviewed, none were found to contain galantamine. The mean age of the 117 patients included in this study was 77±5.66 years (range: 67-90). Of the participants, 45.3% (n=53) were female and 54.7% (n=64) were male.

A total of 557 medications were identified in the 129 prescriptions analyzed. The mean number of medications per prescription was calculated as 4.32±0.18, with a minimum of 2 and a maximum of 15 drugs per prescription. Of these 557 drugs, 178 (32%) were agents used in the treatment of AD. The distribution of Alzheimer's medications was as follows: donepezil in 79 prescriptions, memantine in 69 prescriptions, and rivastigmine in 30 prescriptions. Of the total 129 prescriptions, 55 were issued by hospital physicians and 74 by physicians in family health centers. The specialties of the prescribing physicians were distributed as follows: general practitioners (n=56), neurologists (n=42), internists (n=12), psychiatrists (n=7), and family medicine specialists (n=12).

It was observed that Alzheimer's patients frequently had multiple comorbid chronic conditions. In the prescriptions analyzed, comorbidities such as diabetes mellitus, asthma, chronic obstructive pulmonary disease, benign prostatic hyperplasia, generalized anxiety disorder, depression, bipolar dis-

order, hyperlipidemia, Parkinson's disease, rheumatic diseases, and osteoporosis were identified. All prescriptions were individually entered into 4 different drug interaction databases (Drugs.com, RxMediaPharma®, Medscape, and Lexicomp), and pDDIs were identified and quantitatively recorded according to the interaction levels defined by each database. The data obtained from these analyses are presented in Table 2 below. Additionally, the distribution of interaction levels for each database is illustrated in Figure 1, Figure 2, Figure 3, Figure 4.

Drugs.com identified 156 pDDIs, of which approximately 26.3% were associated with antipsychotics, 14.7% with nonsteroidal anti-inflammatory drugs (NSAIDs), 12.2% with antidepressants, 11.5% with beta agonists, 10.9% with anticholinergics, 5.1% with beta-blockers, 5.1% with calcium channel blockers, 3.8% with cholinergic drugs, 3.2% with Ginkgo biloba, 2.6% with antidiabetic drugs, 1.9% with diuretics, 1.3% with antiparkinsonism drugs, and 1.3% with antibiotics. RxPharma Media identified 79 pDDIs, of which approximately 48.1% were associated with antipsychotics, 31.6% with anticholinergics, 11.4% with beta-blockers, 7.6% with cholinergic drugs, and 1.3% with calcium. Medscape identified 98 pDDIs, of which approximately 25.5% were associated with antipsychotics, 19.4% with anticholinergics, 16.3% with antidepressants, 14.3% with beta agonists, 7.1% with NSAIDs, 6.1% with cholinergic drugs, 4.1% with antidiabetic drugs, 4.1% with beta-blockers, and 1.0% each with antiparkinsonism drugs, antibiotics, and calcium. Lexicomp identified 85 pDDIs, of which approximately 45% were associated with antipsychotics, 29% with anticholinergics, 11% with beta-blockers, 8% with antidepressants, and 7% with cholinergic drugs.

TABLE 2: Interactions and counts from prescriptions

Database	Interaction level	Count (n)
Drugs.com	Moderate	112
	Minor	44
	Total	**156**
RxMediaPharma®	Level 1	75
	Level 3	4
	Total	**79**
Medscape	Serious	21
	Monitor	70
	Minor	7
	Total	**98**
Lexicomp	B	7
	C	49
	D	25
	X	4
	Total	**85**

Across all 4 databases, the highest number of pDDIs involved donepezil. However, interactions with rivastigmine were reported to be of greater severity compared to donepezil. For example, beta-blocker interactions with donepezil were generally moderate, whereas those with rivastigmine were classified as serious or contraindicated.

The most frequent interaction in all databases was between quetiapine and donepezil, though severity classifications varied: Lexicomp rated it as C, RxMediaPharma® as Level 1, Medscape as "serious", and Drugs.com as "moderate". Interactions between NSAIDs (aspirin, diclofenac, ketoprofen, indomethacin, flurbiprofen) and donepezil or rivastigmine were inconsistently reported across databases. Aspirin, diclofenac, flurbiprofen, and ketoprofen interactions with donepezil were only noted as "moderate" in Drugs.com, absent in others. Indomethacin and ketoprofen with rivastigmine were labeled "monitor closely" by Medscape and "moderate" by.

Antipsychotic interactions also showed database variability. For instance, olanzapine with rivastigmine was rated D by Lexicomp and Level 1 by RxMediaPharma® but absent in Medscape and "moderate" in Drugs.com. Beta-agonists and anticholinergic asthma medications showed differing interaction levels with donepezil. Salmeterol, for example, was reported as "no interaction" in Lexicomp and RxMediaPharma®, "monitor" in Medscape, and "moderate" in Drugs.com.

Cholinergic Alzheimer drugs (donepezil, rivastigmine) and anticholinergic bladder agents (darifenacin, solifenacin, tolterodine, mirabegron) interactions were reported in all databases. Solifenacin with donepezil was classified as C (Lexicomp), Level 1 (RxMediaPharma®), "serious" (Medscape), and "moderate" (Drugs.com). Among antibiotics,

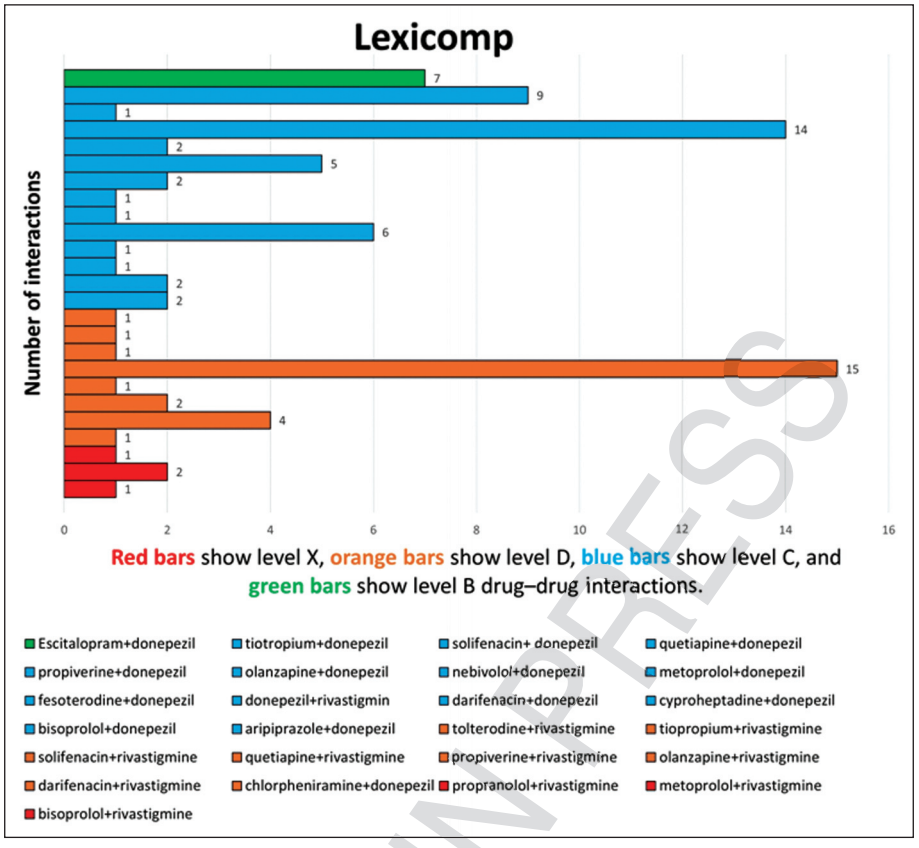

FIGURE 1: PDDIs detected in Lexicomp

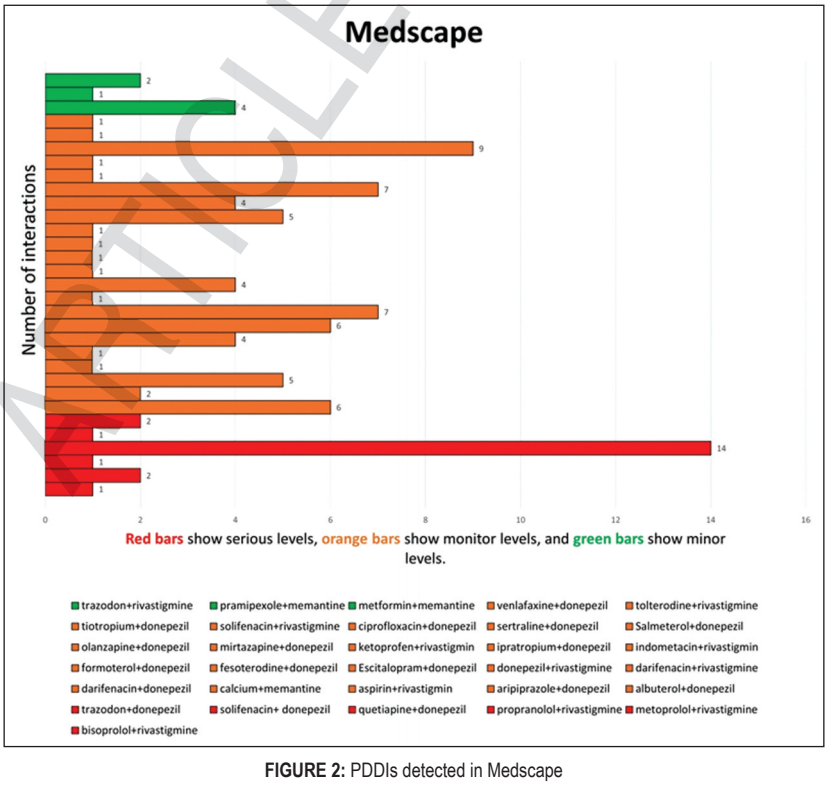

FIGURE 2: PDDIs detected in Medscape

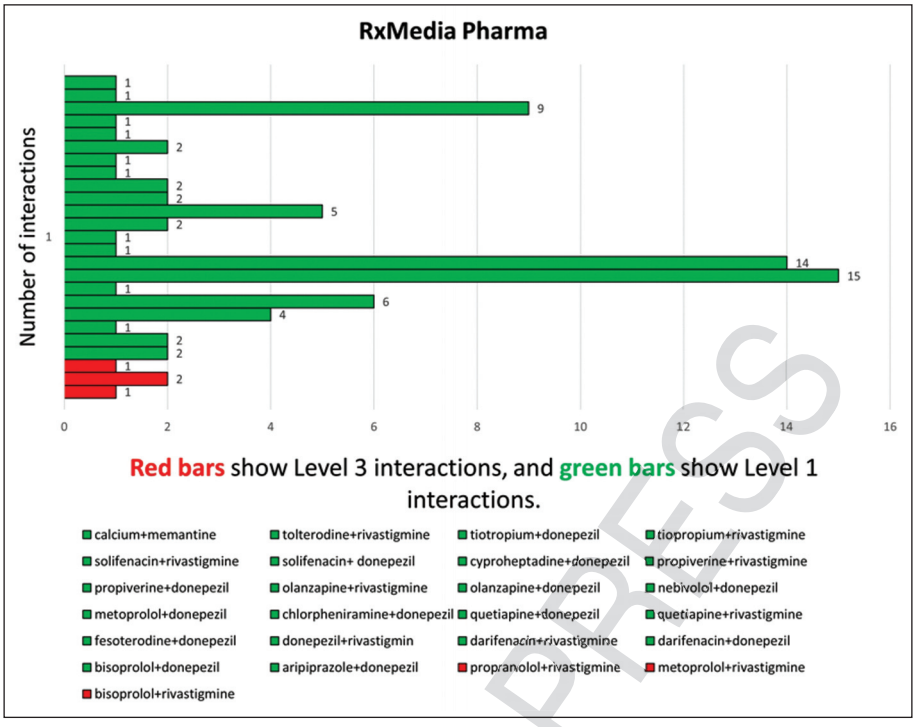

FIGURE 3: PDDIs detected RxMedia Pharma

only quinolones showed interactions. Ofloxacin with rivastigmine was "moderate" only in Drugs.com. Ciprofloxacin with donepezil was "monitor closely" in Medscape and "minor" in Drugs.com, with no records in the other databases. Antidepressants (escitalopram, mirtazapine, sertraline, venlafaxine) exhibited inconsistent interaction reports. Sertraline with rivastigmine was "moderate" in Drugs.com but absent elsewhere. Antihistamines such as cyproheptadine/chlorpheniramine showed interactions with donepezil, varying as C (Lexicomp), Level 1 (RxMediaPharma®), none (Medscape), and moderate (Drugs.com). Ginkgo biloba extract interaction with donepezil appeared only in Drugs.com as "moderate", with no records in other databases. Memantine interactions were limited and generally mild, observed only with levodopa, pramipexole, and metformin.

We created a unified interaction level classification table based on literature reference, aligning with the category definitions of the 4 databases.[20,21] According to this table, interactions were categorized as A (no interaction), B (minor interaction), C (monitoring required), D (alternative should be considered), and X (combination should be avoided) (Table 3). Based on these definitions, Kendall's W test, chi-square test, and Pearson correlation analysis were performed.

The Kendall's W test was conducted to assess the agreement between the classifications of 4 drug interaction databases (Lexicomp, RxMediaPharma®, Medscape, and Drugs.com). The test revealed a statistically significant level of disagreement among the databases, with a Kendall's W coefficient of 0.317, indicating low concordance.

Further statistical evaluation was performed using Pearson correlation analysis and the chi-square test. To assess consistency among the databases, evaluate clinical decision reliability, and provide scientific evidence, a Pearson correlation analysis was conducted. A strong and positive correlation was found between Lexicomp and RxMediaPharma® ($r=0.804$, $p<0.001$), suggesting a similar classification of interaction levels. In contrast, significant negative correlations were observed between Lexicomp and Drugs.com ($r=-0.412$, $p<0.001$), and between RxMediaPharma® and Drugs.com ($r=-0.433$, $p<0.001$), indicating that Drugs.com tends to report

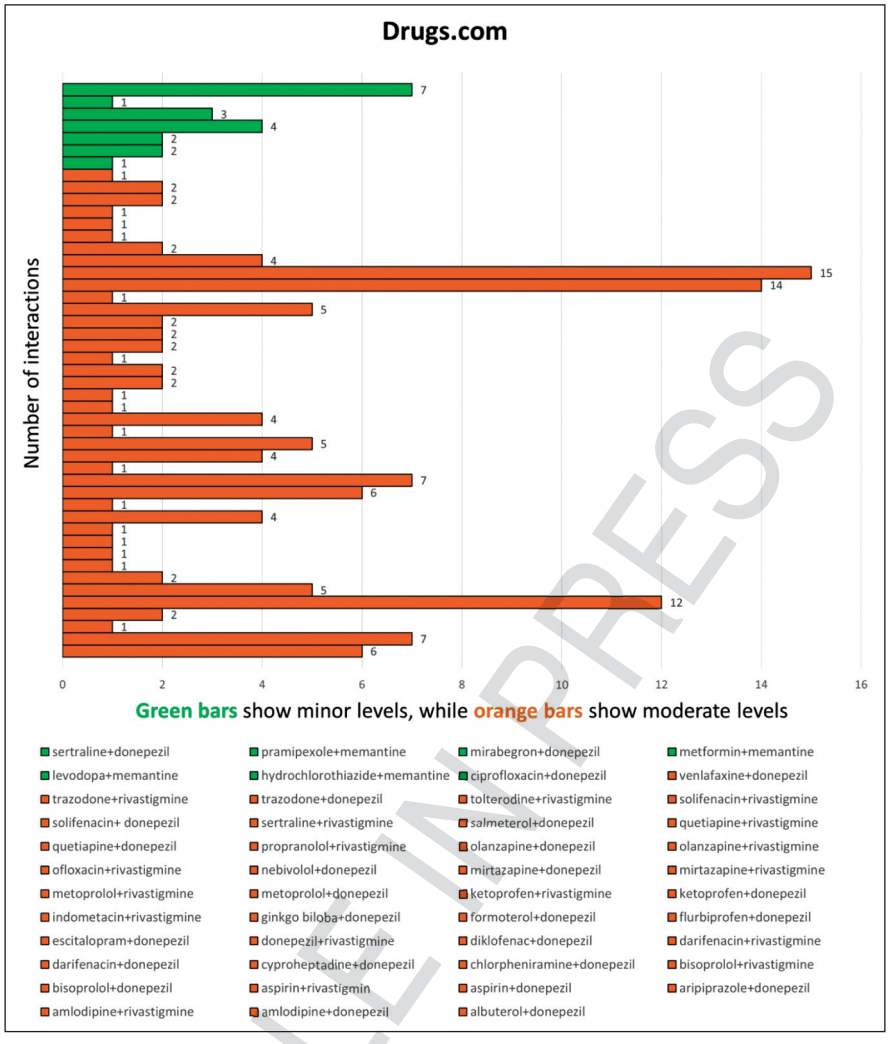

FIGURE 4: PDDIs detected Drugs.com

TABLE 3: Common level classification table

Unified category (proposed)	Definition	RxMediaPharma®	Lexicomp	Drugs.com	Medscape
1. Contraindicated=X	Use should be strictly avoided	Level 3	X	Major	Serious
2. Modification required=D	Dose adjustment or alternative therapy may be needed	Level 2	D	Moderate	Serious
3. Monitoring required=C	Can be used with close monitoring	Level 2	C	Moderate	Monitor closely
4.Minor interaction=B	Clinically insignificant. Generally safe	Level 1	B	Minor	Minor
5. No interaction=A	No known interaction	(Not specified)	A	Unknown	None

higher interaction levels than the other 2. Medscape showed no significant correlation with Lexicomp, RxMediaPharma®, or Drugs.com ($p>0.05$), suggesting a more independent classification approach.

To determine whether significant differences existed among the drug interaction classification systems, crosstabulations and chi-square tests were performed. All comparisons revealed statistically significant differences ($p<0.001$). For example, the chi-square value for Lexicomp vs. RxMediaPharma® was $\chi^2=130.345$, $p<0.001$, indicating variation in interaction level assignments for the same drug combinations. Similarly, Lexicomp vs. Medscape yielded $\chi^2=82.832$, $p<0.001$; Lexicomp vs. Drugs.com $\chi^2=128.983$, $p<0.001$; Medscape vs. Drugs.com $\chi^2=39.463$, $p<0.001$; RxMediaPharma® vs.

Drugs.com χ^2=65.702, p<0.001; and RxMediaPharma® vs. Medscape χ^2=139.305, p<0.001.

DISCUSSION

In this study, the drug interactions of donepezil, rivastigmine, and memantine -commonly used in the treatment of Alzheimer's disease- were evaluated using 4 drug interaction databases: Lexicomp, RxMediaPharma®, Medscape, and Drugs.com. The relationships among these databases were analyzed, and some statistically significant correlations were identified. Kendall's W coefficient was calculated as 0.317, indicating a low level of agreement among the databases. This result suggests that the classification levels of drug interactions differed significantly between the 4 databases. Pearson correlation analysis showed a strong positive correlation between Lexicomp and RxMediaPharma®, indicating that these 2 sources tend to classify drug interactions in a similar way. In contrast, Drugs.com demonstrated a moderate negative correlation with both Lexicomp and RxMediaPharma®, which may imply that Drugs.com uses a different algorithm or evaluation criteria. Clinically, it is important to note that some combinations classified as "no interaction" by certain databases were categorized as "moderate" or even "major" by Drugs.com. This finding highlights the potential risk of relying on a single database during clinical decision-making. Chi-square analysis further supported this concern, showing that sole reliance on one source might lead to overlooking some potential interactions. For instance, some combinations identified as "no interaction" by Lexicomp were reported as "minor" or "moderate" interactions by Drugs.com or Medscape. These differences may arise from variations in algorithms, reference literature, clinical prioritization systems, or risk rating criteria used by each database. Although a certain level of overlap exists among the databases, complete agreement was not observed. This emphasizes that basing clinical decisions on a single source may compromise reliability and underlines the importance of consulting multiple drug information resources.

Like our findings, previous studies have also reported inconsistencies among drug interaction databases.[15-21,22] Such inconsistencies may heighten the risk of unrecognized adverse drug reactions, particularly in elderly patients with polypharmacy. Lexicomp and RxMediaPharma® typically classify interactions as "none" or of low severity, whereas Medscape frequently advises monitoring. Drugs.com more often reports "moderate" interactions and occasionally flags them as "serious." RxMediaPharma® generally assigns a level 1 rating but indicates level 3 interactions in certain drug groups. These variations reflect differing assessment frameworks across databases and should be carefully considered in clinical practice.

Caution is advised when beta-blockers are used with cholinergic agents due to their potential synergistic effects on the cardiovascular system.[23] This study compared interactions between commonly prescribed beta-blockers -metoprolol, bisoprolol, nebivolol, and propranolol- and donepezil or rivastigmine across 4 major drug interaction databases. Most databases identified risks such as bradycardia, AV conduction disturbances, and hypotension. Interactions involving donepezil were generally classified at a lower risk level than those with rivastigmine. For instance, Drugs.com rated rivastigmine combinations as moderate, while other databases marked them as level X. Lexicomp typically labeled donepezil combinations as category C and rivastigmine as X. RxMediaPharma® classified donepezil interactions mostly as Level 1 and rivastigmine as Level 3. Medscape found donepezil interactions to be minimal but flagged rivastigmine combinations as serious. Drugs.com assigned a moderate risk to all combinations.

Interactions between commonly used β2 agonists (albuterol, formoterol, salmeterol) and cholinergic agents donepezil and rivastigmine show mostly no significant interaction across databases. However, "monitor" and "moderate" warnings from Medscape and Drugs.com indicate the need for clinical observation due to potential QTc prolongation.[24,25] Caution is advised especially in elderly patients with cardiac comorbidities. Conversely, the combination of the anticholinergic tiotropium with donepezil or rivastigmine poses a higher pharmacodynamic interaction risk. Lexicomp rates rivastigmine-tiotropium as "D" and donepezil-tiotropium as "C," suggesting possi-

ble antagonism that may reduce therapeutic efficacy and worsen cognitive symptoms.[26] RxMediaPharma® classifies both combinations as Level 1, highlighting clinical significance. Careful monitoring and consideration of alternatives are recommended, particularly in dementia patients.

Significant differences exist between databases regarding interactions of NSAIDs with cholinergic drugs used in Alzheimer's treatment. While Lexicomp and RxMediaPharma® report no interactions for NSAIDs observed in prescriptions, Drugs.com and Medscape recommend monitoring, especially for rivastigmine combined with aspirin, ketoprofen, and indomethacin. Drugs.com classifies these as moderate interaction risks and advises caution. Considering gastrointestinal side effects of NSAIDs and cholinergic agents, careful assessment is necessary, especially for patients at risk of bleeding or GI damage; gastroprotective measures or alternatives may be warranted.[27,28]

Interactions between cholinergic agents (donepezil, rivastigmine) and anticholinergic bladder drugs (darifenacin, solifenacin, tolterodine) are mostly clinically significant in databases. Lexicomp rates many of these as D or C, while RxMediaPharma® assigns Level 1 interaction. Medscape issues "serious" or "monitor" warnings in some cases (e.g., solifenacin+donepezil). Drugs.com labels nearly all as moderate interactions. Due to opposing mechanisms -anticholinergics counteracting cholinesterase inhibitors- simultaneous use can reduce therapeutic effect and increase cognitive side effects.[26,29] These combinations require careful evaluation, dose adjustments, and close cognitive monitoring, especially in elderly patients.

Our study also compared potential interactions between Alzheimer's drugs (donepezil, rivastigmine, memantine) and psychiatric medications (antipsychotics, antidepressants, antiparkinsonian drugs, antihistamines) across 4 major databases. Interactions with donepezil and rivastigmine, especially with antipsychotics and antidepressants, are clinically important in multidisciplinary management.[10,30] Most antipsychotics and antidepressants showed moderate interactions. For example, quetiapine+donepezil and trazodone+donepezil were rated "serious" by Medscape due to risks like QT prolongation, sedation, or cognitive impairment. Some combinations (olanzapine+rivastigmine and chlorpheniramine+donepezil) were rated serious level by Lexicomp and RxMediaPharma®, though Medscape did not indicate this. Parkinson's drugs (levodopa, pramipexole) and mirtazapine showed no significant interactions, allowing individualized therapy in polypharmacy elderly patients.

Amlodipine combined with donepezil or rivastigmine showed no clinically significant interaction in Lexicomp, RxMediaPharma®, and Medscape; however, Drugs.com classified both combinations as moderate risk. This discrepancy may relate to increased cardiovascular effects such as hypotension, bradycardia, AV block, or QT prolongation in elderly patients.[31,32] Monitoring vital signs and dose adjustments are advisable.

Ofloxacin combined with rivastigmine showed no interaction in Lexicomp, RxMediaPharma®, and Medscape but was reported as moderate risk in Drugs.com. Similarly, ciprofloxacin with donepezil was mostly non-interacting, though Medscape recommended monitoring and Drugs.com indicated minor interaction risk. These differences emphasize careful use of fluoroquinolones in elderly due to QT prolongation risks and the importance of monitoring neurological symptoms during treatment.[33]

The combination of donepezil and rivastigmine, frequently prescribed in Alzheimer's treatment, was assessed by all 4 databases as potentially requiring caution. Lexicomp classified it as category C with monitoring advice; RxMediaPharma® rated it Level 1; Medscape advised monitoring; Drugs.com noted moderate interaction. Both drugs being acetylcholinesterase inhibitors may potentiate cholinergic effects, increasing risks of nausea, vomiting, bradycardia, syncope, muscle cramps, and enhanced GI motility.[34,35] Careful patient monitoring and dose titration are essential, especially in the elderly, to prevent adverse cholinergic effects.

LIMITATIONS

This study was designed and conducted as an original associate degree research project supported by the

Scientific and Technological Research Council of Türkiye [Türkiye Bilimsel ve Teknolojik Araştırma Kurumu (TÜBİTAK)]. Due to the nature of student-led research and limited funding, the scope of the study was necessarily narrow. The research was limited to the Patnos district, located in Ağrı province, Türkiye. While this region provides valuable local insights, the findings may not fully apply to other areas or healthcare settings. Additionally, the analysis was based on a limited number of prescriptions collected from local pharmacies. This may have affected the strength and variety of the results. However, the study provides important initial findings that can guide future research. Expanding the sample size and covering more regions in future studies would improve the reliability and usefulness of the results.

CONCLUSION

Clinically, relying on a single drug interaction database may result in overlooking potentially significant interactions. This is particularly critical in elderly patients with polypharmacy, where cross-referencing multiple sources is essential for patient safety. In conditions such as AD, where cognitive function is impaired, adverse effects from drug interactions can severely impact overall health, necessitating careful therapeutic decision-making. We recommend the use of multiple reliable drug interaction databases rather than depending on a single source during clinical decision-making. Prescribing potentially interacting drug combinations should be guided by a personalized approach that considers patient age, comorbidities, and concurrent medications. Healthcare professionals, including clinical pharmacists and physicians, should be made more aware of the inconsistencies across databases. Interactive educational programs should be promoted to support informed pharmacotherapy decisions. Training should be case-based, interdisciplinary, and practical, with separate modules for physicians, clinical pharmacists, nurses, and students. Priority should be given to topics such as effective use of databases, patient-centered risk assessment, and integration with decision support systems to improve clinical reliability. The effectiveness of training should be regularly monitored through pre- and post-tests, appropriate clinical interventions, and patient outcomes to ensure continuous improvement.

We recommend promoting interdisciplinary collaboration among physicians, clinical pharmacists, and other healthcare providers, as well as conducting individualized patient assessments that consider patient-specific factors such as age, renal and hepatic function, existing comorbidities, and the total number of prescribed medications. In the future, international organizations such as the World Health Organization, the United States Food and Drug Administration, and the European Medicines Agency should create harmonized guidelines to improve the consistency and usability of drug interaction databases. These efforts should focus on standardizing classification systems and updating database algorithms to increase reliability and clinical benefit.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Erhan Ballı, Fatma Alganer;* ***Design:*** *Erhan Ballı;* ***Control/Supervision:*** *Erhan Ballı;* ***Data Collection and/or Processing:*** *Fatma Alganer;* ***Analysis and/or Interpretation:*** *Erhan Ballı;* ***Literature Review:*** *Erhan Ballı, Fatma Alganer;* ***Writing the Article:*** *Erhan Ballı;* ***Critical Review:*** *Erhan Ballı;* ***References and Fundings:*** *Erhan Ballı.*

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