FABAD J. Pharm. Sci., 50, 3, 655-670, 2025
Doi: 10.55262/fabadeczacilik.1791969
RESEARCH ARTICLE

Evaluation of Drug Interactions with Psychotropic Drugs Causing QTc Prolongation – A Study in Palliative Care Patients

Fadain ABISHOV[*], Ozgenur GERIDONMEZ[**], Yahya SEKIN[***], Kamer TECEN-YUCEL[****°]

Evaluation of Drug Interactions with Psychotropic Drugs Causing QTc Prolongation – A Study in Palliative Care Patients

SUMMARY

The use of multiple QTc-prolonging psychotropic drugs or agents affecting their metabolism can lead to significant drug-drug interactions (DDIs). This study aims to compare the severity ratings of potential DDIs (pDDIs) specified in two interaction databases and identify clinically relevant interactions associated with QTc prolongation in palliative care patients. This prospective study was conducted in a palliative care unit of a state hospital between October 2023 and May 2024. Potential DDIs and their severities were assessed according to Micromedex® and Lexicomp® databases. Electrocardiograms (ECGs) were performed on patients flagged as having the risk of QTc prolongation. The Drug Interaction Probability Scale (DIPS) was applied to evaluate the clinical relevance of the detected interactions. A clinical pharmacist provided recommendations based on DIPS assessments. A total of 209 pDDIs involving 77 different drug pairs were identified among 120 patients. Interrater reliability between the two databases was poor for major pDDIs (kappa = –0.034) and overall (kappa = –0.052). A pDDI involving a psychotropic drug was detected in 61.7% of patients. QTc prolongation was observed in 66.7% of patients who underwent ECG (n=58). According to DIPS, 122 clinically relevant DDIs (63 unique pairs) were identified. Physicians accepted 10.5% of the clinical pharmacist's recommendations, leading to modifications in psychotropic drug regimens. Follow-up ECGs revealed no QTc prolongation after the interventions. The findings highlight the frequent exposure of palliative care patients to psychotropic drug interactions that may prolong QTc. Although drug interaction databases provide guidance, discrepancies in severity ratings and clinical relevance necessitate individualized patient evaluation by a multidisciplinary team, including clinical pharmacists, to ensure medication safety.

Keywords: *Psychotropic drugs, drug interaction programs, clinically relevant drug interactions, palliative care patients.*

QTc Uzamasına Neden Olan Psikotrop İlaçlarla İlaç Etkileşimlerinin Değerlendirilmesi – Palyatif Bakım Hastalarında Bir Çalışma

ÖZ

QTc uzatan psikotrop ilaçların veya metabolizmalarını etkileyen ajanların birlikte kullanımı, önemli ilaç-ilaç etkileşimlerine (İİE) yol açabilmektedir. Bu çalışmanın amacı, iki ilaç etkileşim veri tabanı tarafından tanımlanan potansiyel ilaç-ilaç etkileşimlerinin (pİİE'ler) şiddet derecelerini karşılaştırmak ve palyatif bakım hastalarında QTc uzaması ile ilişkili klinik olarak anlamlı etkileşimleri belirlemektir. Bu prospektif çalışma, Ekim 2023 ile Mayıs 2024 tarihleri arasında bir devlet hastanesinin palyatif bakım ünitesinde yürütülmüştür. Potansiyel ilaç etkileşimleri ve şiddetleri, Micromedex® ve Lexicomp® veri tabanları kullanılarak değerlendirilmiştir. QTc uzaması riski taşıdığı belirlenen hastalar için elektrokardiyogram (EKG) çekilmiştir. Saptanan etkileşimlerin klinik önemini değerlendirmek için İlaç Etkileşimi Olasılık Ölçeği (DIPS) uygulanmıştır. Klinik eczacı, DIPS değerlendirmelerine dayanarak hekime öneride bulunmuştur. 120 hasta arasında toplam 77 farklı ilaç etkileşim çiftini içeren 209 pİİE tespit edildi. İki veri tabanı arasında gözlemciler arası güvenilirlik, majör şiddetteki pİİE (katsayı = –0,034) ve genel pİİE şiddeti için (katsayı = –0,052) düşüktü. Psikotrop bir ilaç içeren pİİE, hastaların %61,7'sinde (n=74) tespit edildi. EKG çekilen hastaların %66,7'sinde (n=58) QTc uzaması gözlendi. DIPS'e göre, 122 klinik olarak anlamlı ilaç etkileşimi (63 farklı ilaç etkileşim çifti) tespit edildi. Hekimler, klinik eczacının önerilerinin %10,5'ini kabul etti ve bu da psikotrop ilaç tedavisinde değişikliklere yol açtı. Eczacı müdahalelerinden sonra takip edilen EKG'lerde QTc uzaması gözlenmedi. Bulgular, palyatif bakım hastalarının QTc'yi uzatabilen psikotrop ilaç etkileşimlerine sık sık maruz kaldığını vurgulamaktadır. İlaç etkileşim veri tabanları rehberlik sağlasa da, şiddet derecelendirmelerindeki ve etkileşimin klinik önemiyle ilgili farklılıklar, ilaç güvenliğini sağlamak için klinik eczacıların dahil olduğu multidispiliner bir ekip tarafından bireyselleştirilmiş hasta değerlendirmesini zorunlu kılmaktadır.

Anahtar Kelimeler: *Psikotrop ilaçlar, ilaç etkileşimi programları, klinik olarak önemli ilaç etkileşimleri, palyatif bakım hastaları.*

Recieved: 27.09.2025
Revised: 5.10.2025
Accepted: 7.10.2025

[*] ORCID: 0009-0004-1925-2571, Anadolu University, Faculty of Pharmacy, Department of Clinical Pharmacy, 26470, Eskişehir, Türkiye
[**] ORCID: 0000-0002-8223-2723, Hacettepe University, Faculty of Pharmacy, Department of Clinical Pharmacy, 06100, Ankara, Türkiye & Anadolu University, Faculty of Pharmacy, Department of Clinical Pharmacy, 26470, Eskişehir, Türkiye
[***] ORCID: 0009-0002-8670-5126, Yunus Emre State Hospital, Palliative Care Service, Eskisehir, Türkiye
[****] ORCID: 0000-0002-5381-0950, Anadolu University, Faculty of Pharmacy, Department of Clinical Pharmacy, 26470, Eskişehir, Türkiye

[°] Corresponding Author; Kamer Tecen-Yucel
E-mail: kamertecen@anadolu.edu.tr

INTRODUCTION

Palliative care services focused on comfort and symptom control are vital for those with terminal illnesses. Current estimates indicate that around 25-42% of individuals nearing the end of life could gain from palliative care. The increasing population of older individuals and the rising incidence of chronic illnesses in various nations suggest that a greater number of individuals may require palliative care in the future (Etkind et al., 2017).

Behavioral symptoms, such as anxiety, restlessness, depression, and delirium, are common in the end stages of life and can be extremely distressing for both patients and caregivers. Psychotropic drugs, including antipsychotics and benzodiazepines, are commonly prescribed in palliative care for the management of both behavioral and physical symptoms, such as nausea (Gerlach et al., 2021). The prescription of psychotropic drugs in elderly patients poses challenges due to prevalent comorbidities and polypharmacy, which frequently lead to numerous drug interactions. The interaction of these two factors, along with the changes in pharmacokinetics and pharmacodynamics that come with getting older, as well as the higher risk of tolerance and dependence-related conditions, leads to a higher risk of side effects, especially corrected QT (QTc) prolongation (Mangoni & Jackson, 2004).

The guidelines established by the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) indicate that a QTc interval exceeding 470 ms in adult males and 480 ms in adult females is considered abnormal. The risk of developing torsades de pointes (TdP) increases when the QTc interval is ≥ 500 ms in patients (Drew et al., 2010). According to research, the risk of heart problems in people with long QT syndrome (LQTS) goes up by about 5% for every 10 ms increase in the QTc interval (Khatib et al., 2021).

The influence of psychotropic drugs on cardiac repolarization is becoming increasingly recognized. Numerous antipsychotic and antidepressant drugs are associated with QT prolongation (Funk & Bostwick, 2013). Haloperidol presents an increased risk of QTc prolongation when administered intravenously (Beach, Celano, Noseworthy, Januzzi & Huffman, 2013). While atypical antipsychotics are associated with QTc prolongation, they pose a lower risk compared to typical antipsychotics (Beach et al., 2013). Antidepressants like Citalopram, Escitalopram, and Sertraline are known to drastically elevate QTc intervals (Funk & Bostwick, 2013). Citalopram has been linked to numerous instances of TdP, resulting in the establishment of dosage restrictions by the FDA (Åström-Lilja, Odeberg, Ekman & Hägg, 2008).

Evidence indicates that the simultaneous administration of various QTc-prolonging drugs, or other treatments that may alter the metabolism of a QTc-prolonging agent, can lead to detrimental drug-drug interactions (DDIs) (Wysowski, Corken, Gallo-Torres, Talarico & Rodriguez, 2001). For a more accurate assessment of QTc prolongation risk, it is important to look at how pharmaceutical agents and patient-specific factors interact with each other. Patient-specific risk factors encompass sex, age, cardiac conditions, dyselectrolytemia, and the administration of diuretics and antiarrhythmics.

Drug interaction programs are regarded as essential tools for alerting physicians to identify DDIs. Previous studies have identified significant discrepancies in the outcomes generated by drug interaction programs concerning potential drug-drug interactions (pDDI) (Tecen-Yucel et al., 2020). Numerous pDDIs can be identified using drug interaction programs; however, limited research has assessed their clinical relevance.

This study aimed to characterize the differences in severity levels of pDDIs identified by two drug interaction programs for psychotropic drugs, as well as to identify clinically relevant DDIs in palliative care patients receiving psychotropic drugs.

METHOD

Study design, setting and participants

The study was conducted prospectively in the palliative care unit of a state hospital, where an average of 110 patients are followed up annually. The participants completed a written informed consent form. This study aimed to identify potential and clinically relevant drug interactions between two psychotropic drugs or between psychotropic drugs and non-psychotropic drugs used in palliative care patients by using the Micromedex® and Lexicomp® drug interaction programs and to assess the risk of these interactions causing QTc prolongation.

According to the sample size calculation (Raosoft sample size calculator), a minimum of 86 patients were planned to participate in the study with a 95% confidence interval and a 5% margin of error.

Patients who were hospitalized in the palliative care unit between October 2023 and May 2024 who were over 18 years old, used at least one psychotropic drug, and had one or more electrocardiograms (ECGs) performed during their initial and follow-up visits were included in the study. Patients who did not meet these criteria were excluded from the study.

Study procedure

A clinical pharmacist participated in clinic visits with physicians and examined patient demographics (age, gender, number of prescribed medications per patient, and diagnosis), drug treatments, and ECG results from the preceding month.

Initially, pDDIs were observed with psychotropic drugs that cause QTc prolongation, and their severity levels were detected from a patient's treatment schedule utilizing Micromedex® and Lexicomp® drug interaction programs. These two drug interaction programs are frequently utilized by physicians in hospitals. The Lexicomp® database (by Wolters Kluwer) and the Micromedex® database (by IBM) necessitate subscriptions for access to medication interaction information (Wolters Kluwer (n.d.), IBM, (n.d.)).

Table 1 was categorized pDDIs into five classifications for analysis: severe (contraindicated), major, moderate, minor, and none. When a drug interaction combination was categorized into multiple classifications by the programs, the most severe category was chosen for comparison between the Micromedex® and Lexicomp® programs. If the possible drug interaction was classified as severe/contraindicated, major, moderate, or minor to produce QTc prolongation in any program, an ECG was performed. The calculated QTc was derived using the Bazett Formula (QTc = QT/(RR)0.5). QTc intervals ranging from 450 to 500 ms in males and from 470 to 500 ms in females were deemed borderline prolonged. QTc ≥ 500 ms or a variation over 60 ms from baseline was classified as prolonged. The cutoffs were selected based on the research in the scientific literature indicating an increased risk of sudden cardiac death or arrhythmias (Das, Ramasubbu, Agnihotri, Kumar & Rawat, 2021).

Upon determining that a patient's clinical status aligned with the effects (related signs and symptoms) of a pDDI, the Drug Interaction Probability Scale (DIPS) criteria were employed for a causal assessment of the specific interaction. A clinical pharmacist ultimately intervened to address identified clinically relevant drug interactions using the DIPS, a tool including 10 questions that evaluate the likelihood of a causal association between an observed occurrence and the effects of a drug interaction. The assessment of DDI encompasses the following criteria: (1) prior reliable reports; consistency with the established characteristics of (2) precipitant or (3) object drug; (4) temporal progression; (5) dechallenge; (6) rechallenge; (7) alternative explanations; (8) concentration of the object drug in blood or other fluids; (9) additional objective evidence aside from drug concentration; and (10) alteration in the interaction with the precipitant drug dosage modification. Each question may be responded to with "yes," "no," or "unknown/not applicable," accompanied by a designated numeric score for each inquiry. The final score corresponds to a qualitative

scale that indicates the likelihood of the reaction being a medication interaction. The likelihood of drug interaction was classified as uncertain (<2), possible (2-4), probably (5-8), or highly probable (>8) (Horn, Hansten & Chan, 2007).

Table 1. Classification of potential drug-drug interactions based on severity as indicated by drug interaction programs

Severity of Interaction (Category)	Micromedex	Lexicomp
Severe (5)	Contraindicated	(X) Avoid combination
Major (4)	Major	(D) Consider therapy modification
Moderate (3)	Moderate	(C) Monitor therapy
Minor (2)	Minor	(B) No action needed
None (1)	Unknown	(A) No known interaction

Statistical analysis

Data were analyzed using descriptive statistics (including mean, standard deviation, median, interquartile range, frequency, and percentages). The statistical analysis of the study was performed using SPSS version 23 (IBM, Armonk, NY). The normality of the data was determined using Shapiro-Wilk tests.

The Fleiss' kappa statistic was used to summarize the agreement in the category of pDDI provided by 2 drug interaction programs. The Fleiss' kappa is a measure of interrater reliability that removes agreement expected by chance and is suitable for 2 or more raters. A kappa value varies between −1 and 1, with 1 indicating perfect agreement, −1 indicating perfect disagreement, and 0 indicating agreement expected by chance (Fleiss, 1971). The interpretation of Fleiss' kappa values is based on guidelines established by Landis and Koch, such that <0.0 is poor agreement; 0.0-0.2 is slight agreement; 0.21-0.40 is fair agreement; 0.41-0.60 is moderate agreement; 0.61-0.80 is substantial agreement; and 0.81-1.00 is almost perfect agreement (Landis & Koch, 1977). P values were calculated for the kappa, with a $P<0.05$ meaning that rater agreement was unlikely to be because of chance. A high level of concordance across evaluators does not necessarily imply that the response is accurate, nor does a lack of agreement guarantee its inaccuracy. All Fleiss' kappa values were computed utilizing the R software package "irr," version 0.84.1 (Gamer, Lemon, Fellows & Singh, 2019).

Ethics committee approval

This study was approved by the Anadolu University Scientific Research and Publication Ethics Committee (Protocol number: 744611).

RESULTS AND DISCUSSION

A total of 120 patients were included in the study; 62.5% (n=75) were women, and the mean age was 77.7±12.7 years. The most common diseases were hypertension (58.3%), dementia (46.7%), and diabetes (36.7%). Polypharmacy, defined as the regular use of 5 or more medications at the same time (Varghese, Ishida, Patel & Haseer Koya, 2024), was observed in 94.2% of the patients, and the most commonly prescribed psychotropic drugs were quetiapine (60.0%), haloperidol (24.2%), and donepezil (24.2%) (Table 2).

Table 2. Demographic characteristics of the patients (n=120)

Variables	**Participants** (n=120)
Age (Mean±SD)	77.7±12.7
Gender	
Female	75 (62.5%)
Male	45 (37.5%)
No. of drugs prescribed per patient	
≤5	7 (5.8%)
6-9	41 (34.2%)
10-14	50 (41.7%)
≥15	22 (18.3%)
Diagnosis	
Hypertension	70 (58.3%)
Dementia	56 (46.7%)
Diabetes Mellitus	44 (36.7%)
Cerebrovascular Accident	26 (21.7%)
Kidney Disease	20 (16.7%)
Heart Disease	20 (16.7%)
Cancer	16 (12.3%)
Asthma & COPD	14 (11.7%)
Pneumonia	12 (10.0%)
General Condition Disorder	12 (10.0%)
Parkinson's Disease	8 (6.7%)
Respiratory Failure	7 (5.8%)
Thyroid Disease	5 (4.2%)
Epilepsy	4 (3.3%)
Dyspnea	4 (3.3%)
ALS	3 (2.5%)
Others*	18 (15.0%)
Psychotropic drugs	
Quetiapine	72 (60.0%)
Haloperidol	29 (24.2%)
Donepezil	29 (24.2%)
Memantine	24 (20.0%)
Levetiracetam	24 (20.0%)
Tramadol	19 (15.8%)
Escitalopram	12 (10.0%)
Levodopa/Carbidopa/Entacapone	11 (9.2%)
Olanzapine	8 (6.7%)
Citalopram	6 (5.0%)
Sertraline	6 (5.0%)
Mirtazapine	5 (4.2%)
Modafinil	5 (4.2%)
Diazepam	5 (4.2%)
Valproic Acid	4 (3.3%)
Alprazolam	4 (3.3%)
Aripiprazole	4 (3.3%)
Trazodone	3 (2.5%)
Others**	15 (12.5%)

*Other (diagnosis): subarachnoid hemorrhage (n=2), prostate (n=2), intracranial hemorrhage (n=1), history of myocardial infarction (n=1), rheumatoid arthritis (n=1), atrial fibrillation (n=1), bipolar disorder (n=1), nutritional disorder (n=1), pulmonary embolism (n=1), multiple trauma (n=1), bradycardia (n=1), schizophrenia (n=1), cholecystitis (n=1), pleural effusion (n=1), anemia (n=1), vertigo(n=1)

**Other (psychotropic drugs): chlorpromazine (n=2), rasagiline (n=2), phenytoin (n=2), carbamazepine (n=2), gabapentin (n=2), duloxetine/paroxetine (n=2), amantadine (n=1), levodopa/benserazide (n=1), rivastigmine (n=1)

Two drug interaction programs detected 209 pDDIs, including 77 different drug interaction pairs that may cause QTc prolongation in patients. While 52 pDDIs (20 different interaction pairs) were observed only with the Micromedex® drug interaction program and 48 pDDIs (16 different interaction pairs) were observed only with the Lexicomp® drug interaction program, 109 pDDIs (40 different drug interaction pairs) were common to both programs (Figure 1). The interrater reliability was poor (kappa = −0.034) for major pDDI; in addition, the overall interrater reliability was only poor (kappa = −0.052). Table 3 shows the number of pDDIs by severity level in Micromedex® and Lexicomp® programs.

The most common pDDI pair seen was haloperidol-quetiapine (n=22 patients, 18.3%). Of those 22, 16 patients could get an ECG, and QTc prolongation was seen in 12 (75.0%) of them. Along with other common possible interactions, donepezil-quetiapine was seen in 12 patients (10.0%), and QTc prolongation was found in 8 of 9 patients (88.0%) for whom an ECG could be done. A potential interaction between levetiracetam and quetiapine was observed in 11 patients (9.2%), and QTc prolongation was detected in 6 (60.0%) of 10 patients for whom an ECG could be conducted. Table 4 shows the drug interaction pairs observed with drug interaction programs in each of the 120 patients, as well as the ECG results performed on the patients in whom these interactions were observed.

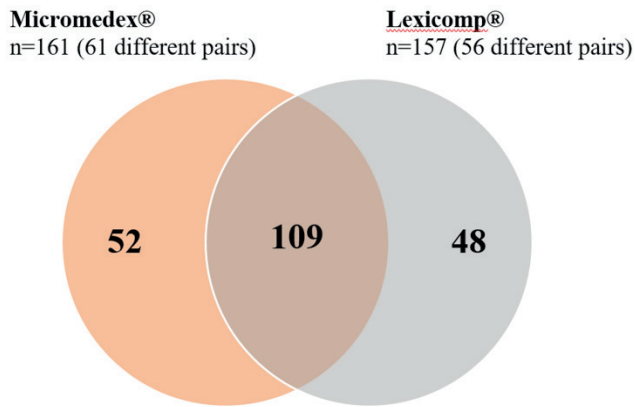

Figure 1. Overlap of pDDIs pairs between Micromedex® and Lexicomp® drug interaction programs

Table 3. The number of pDDIs observed with psychotropic drugs by the drug interaction programs

	Minor	Moderate	Major	Severe	Total number of pDDIs, n
Lexicomp®	30 (16 different pairs)	77 (28 different pairs)	43 (6 different pairs)	7 (6 different pairs)	157 (56 different pairs)
Micromedex®	0	0	161 (61 different pairs)	0	161 (61 different pairs)

p*DDI= potential drug-drug interaction*

Table 4. QTc prolongation on ECG according to drug interaction pairs (n=120)

DDIs pairs (number of patients, %)	Severity in Lexicomp®	Severity in Micromedex®	QTc prolongation in ECG		
			Yes	No	No ECG was taken
Haloperidol-Quetiapine (n=22, 18.3%)	D	Major	12	4	6
Donepezil-Quetiapine (n=12, 10.0%)	-	Major	8	1	3
Levetiracetam-Quetiapine (n=11, 9.1%)	C	-	6	4	1
Quetiapine-Ondansetron (n=9, 8.0%)	D	Major	5	2	1
Quetiapine-Salbutamol (n=7, 5.8%)	C	-	4	2	1
Quetiapine-Memantine+ Donepezil (n=7, 5.8%)	-	Major	4	1	2
Haloperidol-Ipratropium+ Salbutamol (n=6, 5.0%)	C	-	1	3	2
Haloperidol-Olanzapine (n=5, 4.1%)	C	Major	3	1	1
Donepezil-Escitalopram (n=5, 4.1%)	B	Major	2	2	1
Escitalopram-Quetiapine (n=5, 4.1%)	D	Major	4	1	-
Olanzapine-Quetiapine (n=5, 4.1%)	D	Major	4	1	-
Haloperidol-Memantine+ Donepezil (n=5, 4.1%)	C	Major	2	1	2
Aripiprazol-Memantine+ Donepezil (n=4, 3.3%)	-	Major	-	1	3
Donepezil-Haloperidol (n=4, 3.3%)	C	Major	2	-	2
Escitalopram-Ipratropium+ Salbutamol (n=4, 3.3%)	B	-	2	-	2
Mirtazapine-Quetiapine (n=4, 3.3%)	C	Major	2	-	2
Quetiapine-Sertraline (n=3, 2.5%)	C	Major	3	-	-
Aripiprazole-Haloperidol (n=3, 2.5%)	-	Major	-	1	2
Aripiprazole-Quetiapine (n=3, 2.5%)	-	Major	-	1	2
Donepezil-Ondansetron (n=3, 2.5%)	B	Major	2	1	-
Donepezil-Sertraline (n=3, 2.5%)	-	Major	3	-	-
Haloperidol-Levetiracetam (n=3, 2.5%)	C	-	2	1	-
Haloperidol-Ondansetron (n=3, 2.5%)	-	Major	2	1	-
Levetiracetam-Domperidone (n=3, 2.5%)	B	-	2	1	-
Citalopram-Haloperidol (n=3, 2.5%)	C	Major	2	1	-
Citalopram-Quetiapine (n=3, 2.5%)	C	Major	2	1	-
Escitalopram-Levetiracetam (n=2, 1.6%)	B	-	1	1	-
Escitalopram-Olanzapine (n=2, 1.6%)	C	Major	1	-	1
Escitalopram-Trazodone (n=2, 1.6%)	-	Major	1	-	1
Haloperidol-Solifenacin (n=2, 1.6%)	C	Major	1	-	1
Olanzapine-Salbutamol (n=2, 1.6%)	B	-	1	-	1
Olanzapine-Solifenacin (n=2, 1.6%)	-	Major	1	-	1
Sertraline-Ondansetron (n=2, 1.6%)	-	Major	1	1	
Haloperidol-Salbutamol (n=2, 1.6%)	C	-	1	-	1
Haloperidol-Mirtazapine (n=2, 1.6%)	C	Major	-	-	2
Haloperidol-Moxifloxacin (n=2, 1.6%)	C	Major	-	-	2
Quetiapine-Metronidazole (n=2, 1.6%)	C	Major	-	-	2
Quetiapine-Moxifloxacin (n=2, 1.6%)	X	Major	1	-	1
Citalopram-Ipratropium+ Salbutamol (n=2, 1.6%)	B	-	1	1	-
Dexmedetomidine-Haloperidol (n=1, 0.8%)	-	Major	-	1	-
Dexmedetomidine-Ondansetron (n=1, 0.8%)	B	Major	-	1	-

Dexmedetomidine-Quetiapine (n=1, 0.8%)	-	Major	-	1	-
Donepezil +Memantine- Famotidin (n=1, 0.8%)	-	Major	1	-	-
Donepezil+ Memantine-Solifenacin (n=1, 0.8%)	-	Major	1	-	-
Escitalopram-Haloperidol (n=1, 0.8%)	C	Major	-	-	1
Escitalopram- Domperidone (n=1, 0.8%)	X	Major	-	1	-
Levetiracetam-Amiodaron (n=1, 0.8%)	C	-	1	-	-
Olanzapine-Memantine +Donepezil (n=1, 0.8%)	-	Major	1	-	-
Quetiapine-Amiodaron (n=1, 0.8%)	X	Major	1	-	-
Quetiapine-Ciprofloxacin (n=1, 0.8%)	C	Major	-	1	-
Quetiapine-Trazodone (n=1, 0.8%)	C	Major	1	-	-
Quetiapine-Solifenacin (n=1, 0.8%)	C	Major	1	-	-
Quetiapine-Domperidone (n=1, 0.8%)	X	Major	-	1	-
Citalopram-Dexmedetomidine (n=1, 0.8%)	B	Major	-	1	-
Citalopram-Ondansetron (n=1, 0.8%)	C	Major	-	1	-
Escitalopram-Moxifloxacin (n=1, 0.8%)	C	Major	-	-	1
Mirtazapine-Olanzapine (n=1, 0.8%)	-	Major	-	-	1
Mirtazapine-Solifenacin (n=1, 0.8%)	-	Major	-	-	1
Mirtazapine-Moxifloxacin (n=1, 0.8%)	B	Major	-	-	1
Escitalopram-Solifenacin (n=1, 0.8%)	B	Major	-	-	1
Olanzapine-Moxifloxacin (n=1, 0.8%)	C	Major	-	-	1
Donepezil-Trazodone (n=1, 0.8%)	-	Major	-	-	1
Donepezil-Mirtazapine (n=1, 0.8%)	-	Major	-	1	-
Quetiapine-Levofloxacin (n=1, 0.8%)	D	Major	-	1	-
Escitalopram-Memantine+ Donepezil (n=1, 0.8%)	B	Major	1	-	-
Escitalopram-Salbutamol (n=1, 0.8%)	B	-	1	-	-
Mirtazapine-Memantine+ Donepezil (n=1, 0.8%)	-	Major	1	-	-
Citalopram-Amiodaron (n=1, 0.8%)	X	Major	-	1	-
Citalopram-Sertraline (n=1, 0.8%)	-	Major	-	1	-
Amiodaron-Sertraline (n=1, 0.8%)	C	Major	-	1	-
Escitalopram-Ondansetron (n=1, 0.8%)	C	Major	-	1	-
Quetiapine-Chlorpromazine (n=1, 0.8%)	X	Major	1	-	-
Haloperidol- Chlorpromazine (n=1, 0.8%)	D	Major	1	-	-
Levetiracetam- Chlorpromazine (n=1, 0.8%)	C	-	1	-	-
Levetiracetam-Ondansetron (n=1, 0.8%)	B	-	1	-	-
Levetiracetam-Citalopram (n=1, 0.8%)	B	-	1	-	-
Rivastigmine-Domperidone (n=1, 0.8%)	B	-	1	-	-

74 (61.7%) of 120 palliative care patients had pDDIs with psychotropic drugs that could cause QTc prolongation (Table 5). 57 of 74 patients (77.0%) underwent ECG. Despite having a pDDI, 17 patients could not undergo an ECG due to discharge, death, or ward change.

Table 5. Prevalence of potential QTc prolonging drug-drug interactions in palliative care patients

Type of prevalence	Patients (n)	%
Overall prevalence	74	61.7
QT-DDI per patient		
1-2	42	35.0%
3-4	17	14.2%
>4	15	12.5%
Gender-wise prevalence		
Male	25	20.8%
Female	49	40.9%
Age-wise prevalence		
<60	4	3.3%
60-69	9	7.5%
70-79	16	13.3%
80-89	37	30.8%
>90	8	6.8%

QT-DDI: QT prolonging drug-drug interactions

Of the 57 patients with ECG, 38 (66.7%) showed QTc prolongation. Table 6 presents the QTc prolongation and DIPS scores according to drug interaction pairs in 57 patients who underwent ECG.

In order to evaluate the clinical significance of potential drug interactions in patients with ECG, DIPS scoring was implemented. Accordingly, 8 (4.9%) of 161 potential drug-drug interactions detected in Micromedex® were classified as "probable," and 77 (47.8%) were classified as "possible" with a score between 2-8 in DIPS. Of the 157 potential drug-drug interactions in Lexicomp®, 11 (7.0%) were classified as "probable" and 76 (48.4%) as "possible" according to DIPS. A total of 122 (58.3%) out of 209 potential drug interactions were clinically relevant. Micromedex® and Lexicomp® drug interaction programs identified 52.7% and 55.4% of the potential drug interactions as clinically relevant, respectively.

A total of 38 patients were recommended for medication change due to suspicion of potential drug interaction-induced QT prolongation. Some of these recommendations were rejected due to patient discharge status, service change, hospital drug shortages, and patient inapplicability. In only 4 patients (10.5%), the clinical pharmacist's recommendations were accepted by the physician, and in all of these patients, no QT prolongation was observed in ECGs taken after drug discontinuation or switching. Two of these patients stopped taking haloperidol, and three of them started taking alprazolam instead of quetiapine. Additionally, in one patient, memantine was switched to rivastigmine, and in another patient, duloxetine was switched to escitalopram.

Table 6. Potential drug-drug interactions observed with psychotropic drugs by the drug interaction programs and the drug interaction probability scale (n=57)

DDIs pairs (number of patients, %)	Number of patients with QT prolongation	DIPS (number of patients)			
		Highly Probable	Probable	Possible	Doubtful
Haloperidol-Quetiapine (n=16, 28.1%)	12 (75.0%)	0	2	14	0
Donepezil-Quetiapine (n=9, 15.8%)	8 (66.7%)	0	1	7	0
Levetiracetam-Quetiapine (n=10, 17.5%)	6 (60.0%)	0	1	5	0
Quetiapine-Ondansetron (n=7, 12.3%)	5 (71.2%)	0	0	5	0
Quetiapine-Salbutamol (n=6, 10.5%)	4 (66.7%)	0	0	4	0
Quetiapine-Memantine+Donepezil (n=5, 8.8%)	4 (80.0%)	0	0	4	0
Haloperidol-Ipratropium+ Salbutamol (n=4, 7.0%)	1 (25.0%)	0	1	0	0
Haloperidol-Olanzapine (n=4, 7.0%)	3 (75.0%)	0	1	2	0
Donepezil-Escitalopram (n=4, 7.0%)	2 (50.0%)	0	0	2	0
Escitalopram-Quetiapine (n=5, 8.8%)	4 (80.0%)	0	1	3	0
Olanzapine-Quetiapine (n=5, 8.8%)	4 (80.0%)	0	2	2	0
Haloperidol-Memantine+ Donepezil (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Aripiprazol-Memantine+ Donepezil (n=1, 1.8%)	0 (0%)	0	0	0	0
Donepezil-Haloperidol (n=2, 3.5%)	2 (100%)	0	1	1	0
Escitalopram-Ipratropium+ Salbutamol (n=2, 3.5%)	2 (100%)	0	1	1	0
Mirtazapine-Quetiapine (n=2, 3.5%)	2 (100%)	0	0	2	0
Quetiapine-Sertraline (n=3, 5.3%)	3 (100%)	0	0	3	0
Aripiprazole-Haloperidol (n=1, 1.8%)	0 (0%)	0	0	0	0
Aripiprazole-Quetiapine (n=1, 1.8%)	0 (0%)	0	0	0	0
Donepezil-Ondansetron (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Donepezil-Sertraline (n=3, 5.3%)	3 (100%)	0	0	3	0
Haloperidol-Levetiracetam (n=3, 5.3%)	2 (66.7%)	0	1	1	0
Haloperidol-Ondansetron (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Levetiracetam-Domperidone (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Citalopram-Haloperidol (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Citalopram-Quetiapine (n=3, 5.3%)	2 (66.7%)	0	0	2	0
Escitalopram-Levetiracetam (n=2, 3.5%)	1 (50%)	0	0	1	0
Escitalopram-Olanzapine (n=1, 1.8%)	1 (100%)	0	1	0	0
Escitalopram-Trazodone (n=1, 1.8%)	1 (100%)	0	0	1	0
Haloperidol-Solifenacin (n=1, 1.8%)	1 (100%)	0	0	1	0
Olanzapine-Salbutamol (n=1, 1.8%)	1 (100%)	0	0	1	0
Olanzapine-Solifenacin (n=1, 1.8%)	1 (100%)	0	0	1	0
Sertraline-Ondansetron (n=2, 3.5%)	1 (50%)	0	0	1	0
Haloperidol-Salbutamol (n=1, 1.8%)	1 (100%)	0	0	1	0
Quetiapine-Moxifloxacin (n=1, 1.8%)	1 (100%)	0	0	1	0
Citalopram-Ipratropium+ Salbutamol (n=2, 3.5%)	1 (50%)	0	0	1	0
Dexmedetomidine-Haloperidol (n=1, 1.8%)	0 (0%)	0	0	1	0
Dexmedetomidine-Ondansetron (n=1, 1.8%)	0 (0%)	0	0	1	0
Dexmedetomidine-Quetiapine (n=1, 1.8%)	0 (0%)	0	0	1	0
Donepezil +Memantine- Famotidin (n=1, 1.8%)	1 (100%)	0	0	1	0

Donepezil+ Memantine-Solifenacin (n=1, 1.8%)	1 (100%)	0	0	1	0
Escitalopram- Domperidone (n=1, 1.8%)	0 (0%)	0	0	1	0
Levetiracetam-Amiodaron (n=1, 1.8%)	1 (100%)	0	0	1	0
Olanzapine-Memantine +Donepezil (n=1, 1.8%)	1 (100%)	0	0	1	0
Quetiapine-Amiodaron (n=1, 1.8%)	1 (100%)	0	0	1	0
Quetiapine-Ciprofloxacin (n=1, 1.8%)	0 (0%)	0	0	1	0
Quetiapine-Trazodone (n=1, 1.8%)	1 (100%)	0	0	1	0
Quetiapine-Solifenacin (n=1, 1.8%)	1 (100%)	0	0	1	0
Quetiapine-Domperidone (n=1, 1.8%)	0 (0%)	0	0	1	0
Citalopram-Dexmedetomidine (n=1, 1.8%)	0 (0%)	0	0	1	0
Citalopram-Ondansetron (n=1, 1.8%)	0 (0%)	0	0	1	0
Donepezil-Mirtazapine (n=1, 1.8%)	0 (0%)	0	0	1	0
Quetiapine-Levofloxacin (n=1, 1.8%)	0 (0%)	0	0	1	0
Escitalopram-Memantine+ Donepezil (n=1, 1.8%)	1 (100%)	0	0	1	0
Escitalopram-Salbutamol (n=1, 1.8%)	1 (100%)	0	0	1	0
Mirtazapine-Memantine+ Donepezil (n=1, 1.8%)	1 (100%)	0	0	1	0
Citalopram-Amiodaron (n=1, 1.8%)	0 (0%)	0	0	1	0
Citalopram-Sertraline (n=1, 1.8%)	0 (0%)	0	0	1	0
Amiodaron-Sertraline (n=1, 1.8%)	0 (0%)	0	0	1	0
Escitalopram-Ondansetron (n=1, 1.8%)	0 (0%)	0	0	1	0
Quetiapine-Chlorpromazine (n=1, 1.8%)	1 (100%)	0	0	1	0
Haloperidol- Chlorpromazine (n=1, 1.8%)	1 (100%)	0	0	1	0
Levetiracetam- Chlorpromazine (n=1, 1.8%)	1 (100%)	0	0	1	0
Levetiracetam-Ondansetron (n=1, 1.8%)	1 (100%)	0	0	1	0
Levetiracetam-Citalopram (n=1, 1.8%)	1 (100%)	0	0	1	0
Rivastigmine-Domperidone (n=1, 1.8%)	1 (100%)	0	1	0	0

Our findings reveal common prescriptions of drug interactions involving psychotropic drugs associated with known risks of QTc prolongation in patients receiving palliative care. A significant proportion of palliative care patients experienced both minor and major polypharmacy, which included agents known to induce high-risk QTc prolongation. In the study, polypharmacy was observed in 94.2% of the patients. Similar to our study, McNeil et al. found 94% polypharmacy in patients near the end of life (McNeil, Kamal, Kutner, Ritchie & Abernethy, 2016). A meta-analysis involving patients aged 65 years and older (2005–2020) indicated that the frequency of polypharmacy varied from 4% to 96.5%, depending on the healthcare setting and region (Pazan & Wehling, 2021).

In the present study, the most frequently prescribed psychotropic drugs were quetiapine, haloperidol, and donepezil, respectively. Azab et al. (2024) indicated that antipsychotics were the most frequently prescribed psychotropic drugs, which is consistent with our finding (Azab, Novella, Ianes & Pasina, 2024). Since the implementation of Medicare's documentation requirements for medications in hospice care, an evaluation conducted in 2016 identified lorazepam, morphine, and haloperidol as the most commonly prescribed medications (Mohamed, Uvais, Moideen, Cp & Saif, 2024). Unlike our finding, Santos-Peres et al. (2021) found that anxiolytics/hypnotics were the most frequently prescribed psychotropic drugs (Santos-Pérez, Salgueiro-Vázquez, Sáinz-Gil & Martín-Arias, 2021).

This study assessed drug interactions with psychotropic drugs using two commonly utilized drug interaction programs. The findings indicated signifi-

cant differences among these programs regarding the identified number of pDDIs. The interrater reliability was poor (kappa = −0.034) for major pDDI; in addition, the overall interrater reliability was only poor (kappa = −0.052). Health care professionals must recognize the variety of potential pDDIs identified by various drug interaction programs.

Drug interaction programs compile information from scientific literature and categorize it for healthcare professionals. However, there is growing concern among these professionals regarding the variability in quality and effectiveness of the information provided by different programs. Also, these programs can't take into account the specific needs of each patient, which means they can't adjust doses for each person and don't provide specific safety instructions for healthcare professionals (Hammar, Hamqvist, Zetterholm, Jokela & Ferati, 2021).

In clinical practice, physicians receive numerous pDDI alerts, many of which can be rapidly disregarded. Excessive alerts may obscure the significance of a specific DDI. Consequently, pharmacists' vigilant oversight of palliative care patients can facilitate the identification and prevention of drug-drug interactions, potentially enhancing patient health outcomes (Russ-Jara et al., 2023). Research conducted by Robleck et al. (2016) demonstrated that pharmacist intervention significantly reduces the number of patients with clinically significant DDIs (Roblek et al., 2016).

The interaction of psychotropic drugs with each other or with other drugs increases the risk of QTc prolongation. This study identified numerous QTc-prolonging drug-drug interactions involving combinations of antipsychotics with antipsychotics, antipsychotics with antidepressants, and antidepressants with antidepressants. Combining antipsychotic and antidepressant drugs in polypharmacy has been shown to cause torsades de pointes (TdP) and a significant prolongation of the QTc. The concurrent administration of antipsychotic and antidepressant medications leads to a cumulative effect on the QTc interval. The arrhythmogenic potential of antipsychotics varies significantly (Das et al., 2021).

In the current study, quetiapine, haloperidol, and olanzapine were the antipsychotics most frequently associated with QTc-prolonging drug-drug interactions in the palliative care patients. In this study involving geriatric patients, escitalopram and citalopram were the antidepressants most frequently associated with QTc-prolonging drug-drug interactions. The most frequently observed pDDIs pairs in the study were haloperidol-quetiapine and donepezil-quetiapine, respectively. Similar to our study, Wang et al. indicated that more than 10% of patients receiving quetiapine and haloperidol therapy developed QTc prolongation (Wang et al., 2024). The study by Vogel et al. found that adding 20 mg of donepezil to the treatment of a person who was taking quetiapine made the QT interval longer, which is also consistent with our finding (Vogel, Mican & Smith, 2019).

Consequently, drug interactions with psychotropic drugs must be thoroughly evaluated and subsequently confirmed by healthcare professionals in palliative care patients by utilizing suitable and validated instruments such as DIPS to ensure the treatment's efficacy. The Naranjo algorithm, another tool utilized in the literature, evaluates the likelihood of adverse drug reactions instead of drug interactions (Naranjo et al., 1981). The DIPS algorithm facilitates objective, reliable, and transparent evaluation of causation in clinically relevant DDIs.

In the study, a pDDI with psychotropic drugs that could cause QTc prolongation was detected in 74 out of 120 palliative care patients (61.7%). QTc prolongation was observed in 66.7% of the patients (n=38) who had an ECG performed (n=58).

The Micromedex® program provided 161 of the identified pDDIs with psychotropic drugs that could cause QTc prolongation, and the Lexicomp® program provided 157. Clinically relevant pDDIs constituted 52.7%, and 55.4% of these totals, respectively. In this study, 122 clinically relevant DDIs (63 different pairs) were identified, which were also recognized in prior research (Das et al., 2021, Wang et al., 2024).

In only 4 (10.5%) out of 38 patients, the recommendations made by the clinical pharmacist were accepted by the physician. The accepted recommendations were the discontinuation of haloperidol, which had no indication, starting alprazolam instead of quetiapine, switching from rivastigmine to memantine, and from escitalopram to duloxetine. The patients underwent another ECG one week later, showing no signs of QTc prolongation.

This study has some limitations. At the beginning of the study, we did not know the patients' ECG (baseline) results. In addition, other risk factors of the patients, apart from laboratory results, were frequently not systematically documented. In instances where patient risk factor documentation was insufficient, we engaged our clinical collaborators to obtain this information. Unfortunately, our recommendations to the attending physician have often been rejected due to the risk of QTc prolongation resulting from drug interactions. The main reason the physician rejected the pharmacist's recommendations was that the patients were terminally ill, limiting the available drug alternatives. However, it is still observed that QTc prolongation is resolved in patients who accept the clinical pharmacist's recommendations. A further limitation is the comparison of categories related solely to severity (severe, major, moderate, minor, and none) of pDDIs. The investigation did not encompass additional features, functions, or user-friendliness of the drug interaction programs. Furthermore, in certain instances, it was challenging to ascertain whether the observed adverse reaction resulted from a drug-drug interaction or from a single drug alone. This limitation was addressed through a consensus decision regarding the certainty of DDI-related adverse reactions with the treating physician.

CONCLUSION

This study's results demonstrate that a considerable number of palliative care patients receive drug combinations that may result in drug interactions with psychotropic drugs, which are linked to a risk of QTc prolongation. In palliative care services, requests for ECG and other pertinent laboratory tests are typically not made. Current international guidelines are not implemented in clinical practice, and there is an absence of guidelines specific to Turkey. This situation necessitates the implementation of ECG monitoring protocols and associated laboratory investigations. The AHA and the ACCF recommend conducting an ECG before initiating a QTc-prolonging medication, 8-12 hours following dose escalation of such medications, or in instances of overdose involving a QT-prolonging drug. Reliable evidence-based online drug information resources, including the AzCERT/CredibleMeds Drug Lists, Lexicomp® drug interaction program, and Micromedex® interaction program, can aid clinical professionals in the selection of medications for psychiatric patients. The probability of identifying clinically relevant DDIs remains low, regardless of the chosen interaction program by a health institution. Consequently, patient monitoring must be conducted by a multidisciplinary healthcare team including a clinical pharmacist.

AUTHOR CONTRIBUTION STATEMENT

Concept: FA., K.T.Y; Design: F.A., Ö.G., Y.S., K.T.Y; Supervision: K.T.Y., Y.S.; Data Collection and/or Processing: F.A., Ö.G.; Analysis and/or Interpretation: Ö.G., Y.S., K.T.Y.; Literature Review: F.A., K.T.Y.; Writing the Article: F.A., Ö.G., K.T.Y.; Critical Review: Y.S., K.T.Y.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Azab, M., Novella, A., Ianes, A., & Pasina, L. (2024). Potentially inappropriate psychotropic drugs in nursing homes: An Italian observational study. *Drugs & Aging*, *41*(2), 187–197. doi:10.1007/s40266-023-01083-9

Åström-Lilja, C., Odeberg, J. M., Ekman, E., & Hägg, S. (2008). Drug-induced torsades de pointes: A review of the Swedish pharmacovigilance database. *Pharmacoepidemiology and Drug Safety*, *17*(6), 587–592. doi:10.1002/pds.1607

Beach, S. R., Celano, C. M., Noseworthy, P. A., Januzzi, J. L., & Huffman, J. C. (2013). QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics*, *54*(1), 1–13. doi:10.1016/j.psym.2012.11.001

Das, B., Ramasubbu, S. K., Agnihotri, A., Kumar, B., & Rawat, V. S. (2021). Leading 20 drug–drug interactions, polypharmacy, and analysis of the nature of risk factors due to QT interval prolonging drug use and potentially inappropriate psychotropic use in elderly psychiatry outpatients. *Therapeutic Advances in Cardiovascular Disease, 15*, 17539447211058892. doi:10.1177/17539447211058892

Drew, B. J., Ackerman, M. J., Funk, M., Gibler, W. B., Kligfield, P., Menon, V.,....Zareba, W. (2010). Prevention of torsade de pointes in hospital settings: A scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Journal of the American College of Cardiology, 55*(9), 934–947. doi:10.1016/j.jacc.2010.01.001

Etkind, S. N., Bone, A. E., Gomes, B., Lovell, N., Evans, C. J., Higginson, I. J., Murtagh, E. M. (2017). How many people will need palliative care in 2040? Past trends, future projections and implications for services. *BMC Medicine*, *15*(1), 102. doi:10.1186/s12916-017-0860-2

Fleiss, J. (1971). Measuring nominal scale agreement among many raters. *Psychological Bulletin*, 76(5), 378–382. doi:10.1037/h0031619

Funk, K. A., & Bostwick, J. R. (2013). A comparison of the risk of QT prolongation among SSRIs. *Annals of Pharmacotherapy, 47*(10), 1330–1341. doi:10.1177/1060028013501994

Gamer, M., Lemon, J., Fellows, I., & Singh, P. (2019). *irr Various coefficients of interrater reliability and agreement (R package version).* Retrieved from https://cran.r-project.org/web/packages/irr/irr.pdf

Gerlach, L. B., Kales, H. C., Kim, H. M., Zhang, L., Strominger, J., Covinsky, K.,...Maust, D. T. (2021). Prevalence of psychotropic and opioid prescribing among hospice beneficiaries in the United States, 2014–2016. *Journal of the American Geriatrics Society*, *69*(6), 1479–1489. doi:10.1111/jgs.17085

Hammar, T., Hamqvist, S., Zetterholm, M., Jokela, P., & Ferati, M. (2021). Current knowledge about providing drug–drug interaction services for patients—A scoping review. *Pharmacy*, *9*(2), 69. doi:10.3390/pharmacy9020069

Horn, J. R., Hansten, P. D., & Chan, L. N. (2007). Proposal for a new tool to evaluate drug interaction cases. *Annals of Pharmacotherapy*, *41*(4), 674–680. doi:10.1345/aph.1H423

IBM Micromedex with Watson (n.d.). [Database]. Retrieved from https://www.ibm.com/products/micromedex-with-watson

Jackson, S. H., & Mangoni, A. A. (2004). Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *British Journal of Clinical Pharmacology*, *57*(1), 6–14. doi:10.1046/j.1365-2125.2003.02007.x

Khatib, R., Sabir, F. R. N., Omari, C., Pepper, C., & Tayebjee, M. H. (2021). Managing drug-induced QT prolongation in clinical practice. *Postgraduate Medical Journal*, *97*(1149), 452–458. doi:10.1136/postgradmedj-2020-138661

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159–174. doi:10.2307/2529310

Mangoni, A. A., & Jackson, S. H. (2004). Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *British journal of clinical pharmacology*, *57*(1), 6–14. https://doi.org/10.1046/j.1365-2125.2003.02007.x

McNeil, M. J., Kamal, A. H., Kutner, J. S., Ritchie, C. S., & Abernethy, A. P. (2016). The burden of polypharmacy in patients near the end of life. *Journal of Pain and Symptom Management, 51*(2), 178–183.e2. doi:10.1016/j.jpainsymman.2015.09.003

Mohamed, F., Uvais, N. A., Moideen, S., Cp, R. R., & Saif, M. (2024). Psychotropic medication prescriptions for home-based palliative care oncology patients. *Primary Care Companion for CNS Disorders*, *26*(2), 23m03668. doi:10.4088/PCC.23m03668

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., ... Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics*, *30*(2), 239–245. doi:10.1038/clpt.1981.154

Pazan, F., & Wehling, M. (2021). Polypharmacy in older adults: A narrative review of definitions, epidemiology and consequences. *European Geriatric Medicine*, *12*(3), 443–452. doi:10.1007/s41999-021-00479-3

Roblek, T., Deticek, A., Leskovar, B., Suskovic, S., Horvat, M., Belic, A., Mrhar, A., & Lainscak, M. (2016). Clinical-pharmacist intervention reduces clinically relevant drug–drug interactions in patients with heart failure: A randomized, double-blind, controlled trial. *International Journal of Cardiology*, *203*, 647–652. doi:10.1016/j.ijcard.2015.10.206

Russ-Jara, A. L., Elkhadragy, N., Arthur, K. J., DiIulio, J. B., Militello, L. G., Ifeachor, A. P.,...Weiner, M. (2023). Cognitive task analysis of clinicians' drug–drug interaction management during patient care and implications for alert design. *BMJ Open*, *13*(12), e075512. doi:10.1136/bmjopen-2023-075512

Santos-Pérez, M. I., Fierro, I., Salgueiro-Vázquez, M. E., Sáinz-Gil, M., & Martín-Arias, L. H. (2021). A cross-sectional study of psychotropic drug use in the elderly: Consuming patterns, risk factors and potentially inappropriate use. *European Journal of Hospital Pharmacy*, *28*(2), 88–93. doi:10.1136/ejhpharm-2019-001927

Tecen-Yücel, K., Bayraktar-Ekincioglu, A., Yildirim, T., Yilmaz, S. R., Demirkan, K., & Erdem, Y. (2020). Assessment of clinically relevant drug interactions by online programs in renal transplant recipients. *Journal of Managed Care & Specialty Pharmacy*, *26*(10), 1291–1296. doi:10.18553/jmcp.2020.26.10.1291

Varghese, D., Ishida, C., Patel, P., & Haseer Koya, H. (2024). Polypharmacy. In *StatPearls*. Treasure Island, FL: StatPearls Publishing.

Vogel, S. M., Mican, L. M., & Smith, T. L. (2019). Donepezil-induced QTc prolongation: A case report. *Mental Health Clinician*, *9*(3), 128–132. doi:10.9740/mhc.2019.05.128

Wang, C. L., Wu, V. C., Lee, C. H., Wu, C. L., Chen, H. M., Huang, Y. T., & Chang, S. H. (2024). Incidences, risk factors, and clinical correlates of severe QT prolongation after the use of quetiapine or haloperidol. *Heart Rhythm*, *21*(3), 321–328. doi:10.1016/j.hrthm.2023.10.027

Wolters Kluwer. Lexicomp (n.d.). [Database]. Retrieved from https://www.wolterskluwercdi.com/lexicomp-online/

Wysowski, D. K., Corken, A., Gallo-Torres, H., Talarico, L., & Rodriguez, E. M. (2001). Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. *American Journal of Gastroenterology, 96*(5), 1698–1703. doi:10.1111/j.1572-0241.2001.03927.x