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## Concomitant prescription of psychotropic and cardiovascular drugs in elderly patients

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### ABSTRACT

**OBJECTIVES:** Cardiovascular disorders and medication are highly prevalent in elderly. Due to age-related changes, the elderly are particularly vulnerable to side effects and adverse drug reactions. Some psychotropic drugs are linked with reports of cardiac side effects. The aim of the study was to investigate the prevalence and nature of concomitant use of cardiovascular drugs among elderly patients taking psychotropic medication.

**METHODS:** A retrospective, descriptive study was conducted among elderly patients ( $n = 1447$ ) admitted to the outpatient clinics at a tertiary care hospital between September 1 and December 31 2013. Medical records including demographics, diagnosis codes, and prescription drug data were evaluated according to the presence or absence of cardiovascular or psychotropic medication.

**RESULTS:** Of the patients, 541 (37.3%) received a prescription for psychotropic medication. One in four psychiatric patients received a prescription for concomitant cardiovascular medication (135/541, 24.9%). No significant difference in prescription of cardiovascular or psychotropic drugs relation to concomitant medication was found. Antidepressant medications were the most common psychotropic medication (47.4%) prescribed among concomitant users, followed by antipsychotics (43.7%) and anxiolytics (28.1%). Nearly half of the elderly patients with cardiovascular and psychiatric disease were prescribed diuretics (53.3%) and angiotensin-converting enzyme inhibitors (45.9%).

**CONCLUSIONS:** There is no specific drug of choice for cardiovascular or psychotropic medication in elderly patients prescribed concomitant medication. Concomitant prescription of cardiovascular drugs and psychotropics is associated with polypharmacy. Close monitoring during treatment and being vigilant for interacting drugs can reduce the risk of adverse reactions on these vulnerable patients.

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### KEYWORDS

Older age; cardiovascular drugs; drug therapy; elderly; psychotropic

## Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients aged 65 years or over, and cardiovascular medicines are the most commonly prescribed drugs in the elderly. The incidence of adverse drug outcomes from using these drugs is also highest in this population. Ageing itself is not a risk factor for adverse drug reactions [1]. However, age-related physiologic changes may alter the pharmacokinetic and pharmacodynamic effects of drugs. Additionally, polypharmacy and the narrow therapeutic windows of many cardiovascular drugs may result in increased likelihood of adverse events.

The most common causative drugs for adverse outcomes in the elderly are cardiovascular drugs and psychotropic drugs [1,2]. Several epidemiological studies indicate that the most common prescription drugs among persons aged 70 years or over are also cardiovascular drugs followed by psychotropic drugs [3,4]. Depression and psychotropic medication increase the

risk of cardiovascular disorders [5,6]. On the other hand, cardiac patients are more likely to suffer from depression [7]. Many cardiac medications have been shown to have psychiatric side effects, such as anxiety, agitation, depression, and insomnia [8,9]. Conversely, cardiac effects are also common in psychotropic medication [10,11]. It is therefore important to understand the effects, side effects, and interactions of these two varied groups of drugs.

The concomitant use of some cardiovascular drugs and psychotropic drugs has been shown to increase the risk of toxicity and hospitalization in elderly [12]. Many drug toxicity in elderly occur as a result of medication known to cause drug–drug interactions. The risk of an adverse event due to drug–drug interactions is substantially increased among older persons and when multiple drugs are taken [13]. Furthermore, prescribers' lack of awareness of patients' medication results in problems such as duplication and drug interactions [14]. In this study, we aimed to investigate the

prescription pattern of psychotropic and cardiovascular drugs in elderly patients.

## Methods

### Study design

The retrospective, descriptive study included elderly patients ( $\geq 65$  years of age) admitted to the outpatient clinics at a tertiary care hospital between September 1 and December 31 2013. Medical records including demographic data, diagnosis codes, admission dates, and prescription drug data were analysed. After exclusion of patients with recurrent admissions and incomplete data, the number of older patients amounted 1447.

### Identification of drug use

The drugs were defined according to the Anatomical Therapeutic Chemical (ATC) classification system. Psychotropic drugs belong to classes of antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants (ATC groups N05A, N05B, N05C, and N06A). Cardiovascular drugs (C) were classified into cardiac therapy and medicines used mainly for hypertension, diuretics, beta blockers, calcium channel blockers and agents acting on the renin-angiotensin system. Preventive medication for cardiovascular diseases included lipid-lowering drugs and low-dose acetylsalicylic acid (ASA).

### Outcome measures

The patients were classified into four groups according to the presence or absence of cardiovascular or psychotropic prescription: concomitant prescription of cardiovascular and psychotropic drugs (CON,  $n = 135$ ), cardiovascular drug prescription (C,  $n = 198$ ),

psychotropic drug prescription (P,  $n = 406$ ), and no prescription of cardiovascular and psychotropic drugs (NO,  $n = 708$ ). Rates of drug prescription in all patient groups were calculated and also stratified by gender and age groups (65–69, 70–74, 75–79, and 80 years and above). The mean number of prescription drugs was calculated and minimum–maximum numbers of drugs were recorded for each group.

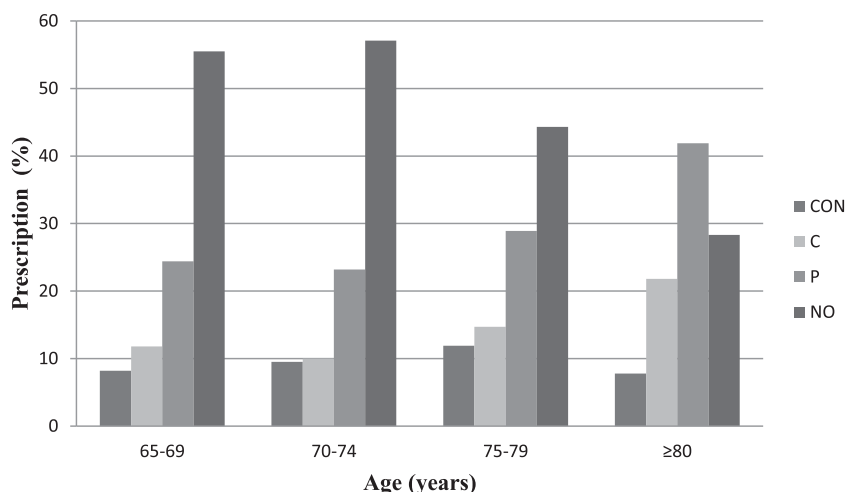
### Statistical analysis

Statistical analysis was performed with SPSS Software Version 16.0. The results were expressed as number and percentages. For the comparison of continuous variables, ANOVA were used. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate. The results were considered statistically significant when  $p$ -values were  $< .05$ .

## Results

A total of 1447 records of the patients admitted to hospital were analysed (Figure 1). Of them, 541 (37.3%) received a prescription for psychotropic medication. One in four psychiatric patients received a prescription for concomitant cardiovascular medication (135/541, 24.9%). Most patients in the age-group 70–74 years were prescribed no cardiovascular and no psychotropic medication ( $n = 216$ , 67.9%). The rate of cardiovascular or psychiatric prescription drugs was higher in the oldest age group (80+ years) compared with the other age groups. On the other hand, no difference in concomitant medication in relation to age was found (Figure 1).

Table 1 shows some characteristics of the patients. A greater share of women than men received medications in all groups. The proportion of men prescribed concomitant medication was significantly higher than those taking cardiac or psychiatric drugs alone ( $p = .0019$ ).



**Figure 1.** Prescription of cardiovascular and psychotropic drugs in elderly patients, stratified by age. CON: concomitant prescription of cardiovascular and psychotropic drugs; C: cardiovascular drug prescription; P: psychotropic drug prescription; NO: no prescription of cardiovascular and psychotropic drugs.

**Table 1.** Characteristics of patients.

	CON	C	P	NO	<i>p</i> value
Male (%)	51 (37.8)	56 (28.2)	38 (11.9)	19 (7.8)	.0019 <sup>a</sup>
Mean age in years (min–max)	73 (65–83)	75 (65–92)	74 (65–98)	71 (65–92)	<.001 <sup>b</sup>
Mean number of drugs (min–max)	6.2 (2–13)	4.1 (1–9)	4 (1–11)	2.6 (0–11)	<.001 <sup>b</sup>

Note: CON: concomitant prescription of cardiovascular and psychotropic drugs; C: cardiovascular drug prescription; P: psychotropic drug prescription; NO: no prescription of cardiovascular and psychotropic drugs.

<sup>a</sup>Chi-square test.

<sup>b</sup>ANOVA.

The median ages of the patients taking cardiac and/or psychiatric drugs were similar. However, the patients prescribed no psychiatric and no cardiac drugs were younger than the others ( $p < .001$ ). The patients on concomitant medication had the highest mean number of all drugs taken (6.2), and the patients prescribed cardiac and/or psychiatric drugs were more likely to receive four or more medicines ( $p < .001$ ).

Antidepressant medications were the most common psychotropic medication (47.4%) prescribed among concomitant users, followed by antipsychotics (43.7%) and anxiolytics (28.1%). Mirtazapine was the most common antidepressant (22.3%) prescribed. Psychotropic medication rates were similar among patients prescribed psychotropic drugs alone (Table 2).

Nearly half of the elderly patients with cardiovascular and psychiatric disease were prescribed diuretics (53.3%) and angiotensin-converting enzyme (ACE) inhibitors (45.9%). Men were more likely than women to be prescribed concomitant lipid-lowering drugs (68.6% vs. 20.2%,  $p < .00001$ ), and women were more likely to be prescribed diuretics (65.4% vs. 33.3%,  $p = .002$ ). Nearly half of the elderly patients with cardiovascular disease (156/333, 46.8%) received a prescription for an ACE inhibitor. Cardiovascular medication rates were similar among patients prescribed cardiovascular drugs alone (Table 3).

**Table 2.** Psychotropic drug prescription.

Drugs	CON, <i>n</i> = 135 (%)	P, <i>n</i> = 406 (%)
Antipsychotics	59 (43.7)	206 (50.7)
Antidepressants	64 (47.4)	209 (51.4)
Anxiolytics	38 (28.1)	118 (29.0)
Other	16 (11.8)	58 (14.2)

Note: CON: concomitant prescription of cardiovascular and psychotropic drugs; P: psychotropic drug prescription

**Table 3.** Cardiovascular drug prescription.

Drugs	CON, <i>n</i> = 135 (%)	C, <i>n</i> = 198 (%)
ASA	50 (37.0)	81 (40.9)
Nitrates	14 (10.3)	31 (15.6)
Beta blockers	40 (29.6)	56 (28.2)
ACEI	62 (45.9)	94 (47.4)
CCB	34 (25.1)	53 (26.7)
Diuretics	72 (53.3)	101 (51.0)
Digitalis	19 (14.0)	21 (10.6)
LLD	52 (38.5)	67 (33.8)
ARB	43 (31.8)	73 (36.8)

Note: CON: concomitant prescription of cardiovascular and psychotropic drugs; C: cardiovascular drug prescription; ASA: acetylsalicylic acid; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; LLD: lipid-lowering drugs; ARB: angiotensin II receptor blockers.

## Discussion

Cardiovascular medications are most commonly used drugs in the elderly patients [3]. In our study, we found that nearly one in every four elderly patients was prescribed cardiovascular drugs, and nearly half of them were prescribed psychotropic medication concomitantly. Psychotropic drugs and psychiatric diseases have been implied in causing cardiovascular effects. Conversely, cardiovascular drugs have also been shown to have psychiatric side effects and drug interactions with psychotropic medications [9]. To reduce the risk of adverse drug effects in the elderly, clinicians should check for potential side effects and drug–drug interactions.

Psychotropic medications are also more common among older adults than other age groups. We found that a large proportion, 37% of the patients in our study group, was prescribed psychotropic medications, and one in four elderly patients prescribed psychotropics received a prescription of a cardiovascular drug. It seems that concomitant prescription of psychotropic and cardiovascular drugs is connected with polypharmacy. There is no consistent cut point that defines polypharmacy. Polypharmacy, defined by the World Health Organization as “the administration of many drugs at the same time or the administration of an excessive number of drugs,” is often used to mean taking four or more medicines [15]. Concomitant use of cardiovascular and psychotropic drugs seems to be associated with an increased number of drugs taken. We found that the mean numbers of drugs were 4 and 4.1 in groups of patients prescribed psychotropic or cardiovascular drugs alone, whereas concomitant users were prescribed significantly more drugs than the other groups (mean: 6.2,  $p < .001$ ).

Use of psychotropic medication is high among very old patients. As in earlier studies [16,17], use of psychotropics increased with advancing age in our study group. We found that half of the oldest patients (80+ years) were prescribed psychiatric medication with and without cardiovascular medication (121/243). Most of the patients prescribed psychiatric or cardiovascular medication were 80 years of age or older. A meaningful proportion of the patients aged between 65 and 74 years had no cardiovascular and no psychotropic medication ( $p < .00001$ ). We found no statistically significant difference in patients on concomitant

medication in relation to age. However, the percentage of patients on concomitant medication in the oldest age group (80+ years) was somewhat lower when compared with the other groups. This minimal difference could be explained by clinicians' awareness about potentially inappropriate medications for very old patients.

Since the majority of the patients in the study were female, we found a higher percentage of women than men in all types of medication. A significantly lower proportion of men received a prescription for cardiovascular or psychotropic drugs alone in comparison with other groups ( $p < .0019$ ). It seems that co-occurring cardiovascular and psychiatric diseases in men are more common than these conditions alone. Several studies suggest a relationship between psychiatric disorders and increased cardiac outcomes [18,19]. These patients with psychiatric disorders require a more active management which may potentially reduce morbidity and mortality associated with cardiovascular problems.

In many studies, no significant differences between genders in the use of cardiovascular drugs were found [20,21]. According to a Canadian study women aged 75 and older more often used beta blockers than men [22]. A Finnish study showed that elderly women were more likely than men to use of ACE inhibitors, diuretics, and digitalis [23]. In our study, ACE inhibitors, diuretics, lipid-lowering drugs, and ASA were the most frequently prescribed cardiovascular drugs. We found that women were more likely to receive a prescription for diuretics than men, and men more often received a prescription for lipid-lowering drugs than women. The significant difference between genders in the prescription for cardiovascular drugs existed in all groups of patients prescribed cardiovascular medication with or without psychotropic medication.

Several studies have indicated less lipid-lowering drug use at older ages and in women [24–26]. We also found that the proportion of lipid-lowering drugs was lower in women (19% vs. 71%) prescribed cardiovascular medication and in women (20.2% vs. 68.6%) prescribed concomitant psychotropic medication. The underlying cause of gender differences could be differences in the prescription pattern of physicians and differences in indications of prescribed medications.

Cardiovascular medications can cause psychiatric side effects and medicine interactions. This is even more evident for high-risk populations such as older adults. About 2% of patients taking ACE inhibitor discontinued the medication because of neuropsychiatric side effects, including anxiety, insomnia, mania, paresthesias, sedation, fatigue, and hallucinations [8]. Because ACE inhibitors interfere with the pharmacokinetics of lithium, concurrent use of both agents can cause an important increase in lithium concentrations

and lithium toxicity in patients taking ACE inhibitors. Lithium and diuretics may also interact, and lithium levels can increase resulting in lithium toxicity [27]. Diuretics, when used concomitantly with antidepressants, may also promote clinically relevant hyponatremia, especially in elderly patients [28]. Careful assessment and sometimes simply switching to a different medication can eliminate the side effects. Drug-induced psychiatric disorders can result in significant morbidity and mortality [29]. Cardiovascular drugs, such as ACE inhibitors and cholesterol-lowering statins, have been implicated in causing depression and suicide ideation in reports, but the evidence is inconclusive. Some studies have supported this association [30,31]. The other authors have indicated that ACE inhibitors and statins might be effective in the treatment of major depression [32,33].

Many cardiovascular and psychotropic drugs lower blood pressure, additive hypotensive effects can occur when they are used concomitantly, as for example tricyclic antidepressants in conjunction with antihypertensives. This side effect, particularly in elderly, may cause acute coronary syndromes, cerebral hypoperfusion, and falls [11]. Antidepressants, particularly tricyclic compounds, have been shown to have cardiovascular effects including postural hypotension, tachycardia, arrhythmias, the long QT syndrome, or heart block. Tricyclic antidepressants should be avoided in cardiovascular conditions, in ischaemic heart disease in particular, and they should be not use with antiarrhythmic and antihypertensive agents. Selective serotonin reuptake inhibitors are considered relatively safer, but they are bound to plasma proteins and can lead to increased drug effect or toxicity of the active substrate. Antipsychotic drugs have been shown to cause electrocardiographic modifications including prolongation of the PR and QT intervals, ST depression, T wave changes, ventricular arrhythmias, and heart block. Myocarditis and cardiomyopathy were also associated with antipsychotic use, particularly clozapine. Regular and close monitoring in elderly patients receiving clozapine, antipsychotics, and tricyclic antidepressants should be done [34].

The main weakness of the study is the retrospective design. Clinical outcomes were assessed through medical records of the patients. While this provides an overview of the medication prescription rates among elderly patients, the evaluations did not include the possible use of over the counter drugs without a prescription. Moreover, elderly patients may not adhere to their medication regimens as prescribed. Our sample is from a single outpatient clinic, and the applicability of findings may differ among geographic regions or specialties. As the data dated back to 2013 contain the drug prescription patterns during a short study period of 4 months, it may not reflect the most recent year's data correctly.



Age-related pharmacokinetic and pharmacodynamic changes make the elderly particularly sensitive to the adverse effects and interactions of many medications. According to our study, there is no specific drug of choice for cardiovascular medication in elderly patients taking antidepressants or other psychotropic drugs, and use of cardiovascular and/or psychotropic drugs seems to be associated with polypharmacy. Careful assessment and sometimes simply switching to a different medication may help prevent adverse drug events. Close monitoring during treatment and being vigilant for interacting drugs can reduce the risk of potentially harmful side effects on these vulnerable patients.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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