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SMOKING-DRUG INTERACTIONS WITH MULTIPLE DRUG USAGE IN ELDERLY PEOPLE

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ASSIST.PROF.DR.PHILIP MARTIN CLARK

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DEDICATION

To my precious mother...

Yüksek Lisans (Master) öğrencisi. Gözde KAFTAN'ın çalışması jürimiz tarafından Klinik Eczacılık Anabilim Dalı Master tezi olarak uygun görülmüştür.

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ONAY

Yukarıdaki jüri kararı Enstitü Yönetim Kurulu'nun 05/06/2013 tarih ve ...9-6..... sayılı kararı ile onaylanmıştır.

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ABSTRACT

Kaftan G. Smoking-Drug Interactions In Elderly People With Multiple Drug Usage. Yeditepe University Institute of Health Sciences Clinical Pharmacy Master Thesis. Istanbul, 2013.

Purpose: Smoking-drug interactions in elderly people should be considered as a potential health risk and patients should be monitored closely during the change of smoking habit especially when they use particular drugs, a possible blood-plasma concentration variation may cause serious health consequences. Purpose of this study is to highlight the potential clinical risks of smoking-drug interactions in elderly people.

Materials and Methods: The study was conducted at the Institution of Kayışdağı Darülaceze, a government organization for elderly as a nursing home, in Istanbul, Turkey. Routinely smoking 226 residents with multiple drug usage, are evaluated in our study. Drugs which have the possibility of interaction with smoking, are investigated in this study. Macros and formulas were designed via Microsoft Visual Basic that analyses the data and evaluates statistical outcomes. Correlation of smoking-drug interactions and multiple drug usage is analyzed by SPSS, statistical analysis program.

Results and Discussion: There was a significant increase in the number of drugs that are interacted with smoking as multiple drug usage increase ($p < 0.05$). 27.25% of the patients have cardiovascular diseases, while 25,45% have psychiatric diseases, 14,07% have endocrinologic diseases, 10,78% have respiratory diseases and 5.69% have cognitive diseases. 29 patients were receiving theophylline which is a drug with narrow therapeutic index and use of theophylline might generate health risk due to its interaction potential with smoking during smoking cessation. Some of the antipsychotics might cause health risk in case of any change in their blood-plasma concentrations. Olanzapine was used on 48 patients, chlorpromazine was used on 12 patients and risperidone was used on 16 patients. Variations in dose or plasma concentration of antipsychotics might cause adverse effects or

recurrence of the symptoms of psychiatric diseases might be observed. Although clinical significance of smoking-drug interactions has not been analyzed in detail, possible risks of mentioned drug groups are emphasized in many studies. Substrates of induced enzymes from PAHs such as particular antipsychotics, medicines with narrow therapeutic index and other groups that create risk in case of discontinuation should be monitored closely if patient starts or quits smoking. Especially, elderly patients in nursing homes are much more susceptible to those interactions compared to adults.

Conclusion: Smoking-drug interactions with multiple drug usage in elderly people while changing their smoking habits may cause clinical health risks to patients. This potential risks should be assessed widely by physicians and the importance of patient monitorization for adverse effects should be highlighted by clinical pharmacists. When patients, whose drugs might have affected from smoking through pharmacokinetic and pharmacodynamic pathways, stop smoking; interaction status of the drugs should be investigated, clinical significance of any potential interaction should be determined, possible adverse effects of the drugs should be monitored closely and dose adjustment should be assessed if necessary.

Key Words: smoking-drug interactions, pharmacokinetics, smoking cessation, antipsychotic agents, CYP1A2, adverse effects, contraceptives, insulin, enzyme induction.

ÖZET

Kaftan G. Çoklu İlaç Kullanımı Olan Yaşlılarda Sigara-İlaç Etkileşimlerinin İncelenmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Klinik Eczacılık Yüksek Lisans Tezi. Istanbul, 2013.

Amaç: Yaşlılarda sigara-ilaç etkileşimleri potansiyel bir sağlık riski olarak kabul edilmelidir ve özellikle belli ilaç gruplarını kullanan hastalar, olası bir kan-plazma konsantrasyonu değişimi ciddi sağlık sonuçları doğurabileceğinden sigara içme alışkanlıklarının değişikliği esnasında yakından izlenmelidir. Bu çalışmanın amacı yaşlı kişilerde sigara-ilaç etkileşimlerinin potansiyel klinik riskleri vurgulamaktır.

Materyal ve Metod: Bu çalışma, yaşlı hastalara bakım evi hizmetini sağlayan bir devlet birimi olan İstanbul Kayışdağı Darülaceze Merkezi'nde yürütülmüştür. Çoklu ilaç kullanımı olan 226 kişi bu çalışmada değerlendirilmiştir. Bu çalışmada sigara kullanımı ile etkileşime girme olasılığı olan ilaçlar incelenmiştir. Microsoft Visual Basic programı kullanılarak oluşturulan makrolar ve formüller yardımıyla Darülaceze'deki sakinlerin ilaçları, hastalık sayıları ve sigara kullanımları analiz edilip istatistiksel verilere ulaşılmıştır. Sigara-ilaç etkileşimlerinin çoklu ilaç kullanımı ile olan ilişkileri incelenip SPSS programında analiz edilmiştir.

Bulgular ve Tartışma: Çoklu ilaç kullanımı arttıkça sigarayla etkileşen ilaçların sayısında da anlamlı bir artış görülmüştür ($p<0,05$). Hastaların %27,25'inde kardiyovasküler hastalıklar, %25,45'inde psikiyatrik hastalıklar görülürken %14.07'sinde endokrinolojik, %10.78'inde solunum yolu ve %5.69'unda da kognitif hastalıklar olduğu saptandı. 29 hastada, terapötik aralığı dar bir ilaç olan teofilin kullanıldığı gözlemlendi. Teofilin kullanımının sigara ile etkileşiminden dolayı, sigarayı bırakma esnasında hastalarda bazı sağlık sorunlarına yol açma riski vardır. Sigara ile beraber kullanıldığında kan-plazma konsantrasyonlarının değişme riski bulunan ilaçlardan olanzapinin 48 hastada, risperidonun 16 hastada ve klorpromazinin de 12 hastada kullanımı olduğu gözlemlendi. Antipsikotiklerde doz değişimi ya da kan-plazma

konsantrasyonunun değişimi advers etkilere ya da psikiyatrik hastalıkların semptomlarının artmasına neden olabilir. Sigara-ilaç etkileşimlerinin klinik anlamlılığı detaylı olarak henüz analiz edilmemiş olsa da bir çok çalışmada bahsedilen ilaç gruplarının olası riskleri vurgulanmıştır. Bazı antipsikotiler, dar terapötik aralıklı ilaçlar ve düzenli kullanımına ara verilmesi risk yaratan ilaç grupları gibi PAH'lardan dolayı indüklenen enzimlerin substratlarını kullanan hastalar sigaraya başlama ya da sigarayı bırakma durumlarında yakından takip edilmeliler. Özellikle bakım evlerindeki yaşlı hastalar bu etkileşimlere yetişkinlere göre daha hassaslardır.

Sonuç: Çoklu ilaç kullanımı olan yaşlı hastalarda sigara-ilaç etkileşimleri, sigara kullanım alışkanlıklarını değiştiren hastalarda sağlık riskine neden olabilir. Bu potansiyel riskler hekimler tarafından detaylı olarak değerlendirilmeli ve bu gibi durumlarda klinik eczacılar tarafından advers etkilere karşı hasta takibinin önemi vurgulanmalıdır. Sigara ilaç etkileşimi riski barındıran ilaçları kullanan hastaların sigara bırakmaları durumunda; ilaçların etkileşim durumları araştırılmalı, oluşabilecek potansiyel bir etkileşimin klinik önemi incelenmeli, ilacın olası advers etkilerine karşı hasta yakından takip edilmeli ve gerekliyse doz ayarlaması yapılmalıdır.

Anahtar kelimeler: sigara-ilaç etkileşimleri, farmakokinetik etkileşimler, sigara bırakma, antipsikotik ajanlar, CYP 1A2, advers etkiler, kontraseptifler, insülin, enzim indüksiyonu.

CONTENTS

SYMBOLS AND ABBREVIATIONS

Ah: Aryl hydrocarbon

AIDS: Acquired Immune Deficiency Syndrome

ARE: Ah Responsive Element

CFR: (United States) Code of Federal Regulations

Cmax: Peak plasma concentration

CYP450: Cytochrome P450

DALY: Disability Adjusted Life Years

ED50: (Minimum) Effective Dose

ER: Endoplasmic Reticulum

GI: Gastrointestinal

LD50: (Minimum) Lethal Dose

MoH: Ministry of Health

MI: Myocardial Infarction

OCPs: Oral Contraceptive Pills

QOL: Quality of Life

PAH: Polycyclic Aromatic Hydrocarbons

PPAR: Peroxisome Proliferator Activated Receptor

SSNRI: Selective Serotonine Noradrenaline Reuptake Inhibitor

Tmax: Time to reach Cmax

WHO: World Health Organization

FIGURES

TABLES

1. INTRODUCTION

Tobacco smoking is the most widespread habit which risks human health, harms many organs and systems in human body, and also causes many other diseases [1]. Habit of smoking directly causes non-communicable diseases as well as harms human health indirectly by interacting with certain drugs.

1.1. Definition of Smoker and Smoking

Smoking is defined as the inhalation of the smoke of burning tobacco encased in cigarettes, pipes, and cigars. It is referred as cigarette smoking when the term of ‘’smoking’’ is used. Casual smoking is defined as the act of smoking only occasionally, usually in a social situation. Smoking habit is a physical addiction to tobacco products which is referred to cigarette in this study with serious health consequences.

Smoking is an addiction to nicotine that is defined as consuming 5 to 10 cigarettes or more per day [2]. A smoker is a person who has smoked 100 cigarettes in their lifetime and currently smokes cigarettes daily or nondaily [3].

In this study smokers are defined as individuals who smoked 7 or more cigarettes per day during the past year. Smokers are not classified as light, intermediate or as heavy smoker because in a study it is observed that smoking as few as 7 to 12 cigarettes daily, produced the same magnitude of induction on drug metabolism as smoking as 20 cigarettes daily [4]. Smokers, who smoke more than 20 cigarettes in a day, are considered as ‘’heavy smoker,’’ while other smokers who smoke 7 to 20 cigarettes, are referred to as ‘’smoker.’’

The term ‘’smoking-drug interactions’’ defines the changes in plasma-blood concentrations of the drugs that are caused by smoking.

1.2. Epidemiology of Smoking In Worldwide and Turkey

Smoking has been accepted as one of the leading causes of preventable death in worldwide that is practiced by 1.1 billion people and approximately 1/3 of the adult population in 2004 [5].

Smoking among men is highest in the WHO Western Pacific Region, with 51% of men aged 15 and above smoking some form of tobacco in 2009, according to WHO. Smoking among women is highest in the WHO European Region at 22% [6]. It is estimated that about one third of all adults worldwide are smokers although cigarette smoking rates could differ according to the gender and income levels of the countries [7].

Turkey is a tobacco-producing country and one of the top 10 tobacco-consuming countries in the world. (Figure 1) Turkey consumes about 2% of tobacco worldwide and 14% in the WHO European Region according to the WHO's statistical outcomes of 2009 [8].

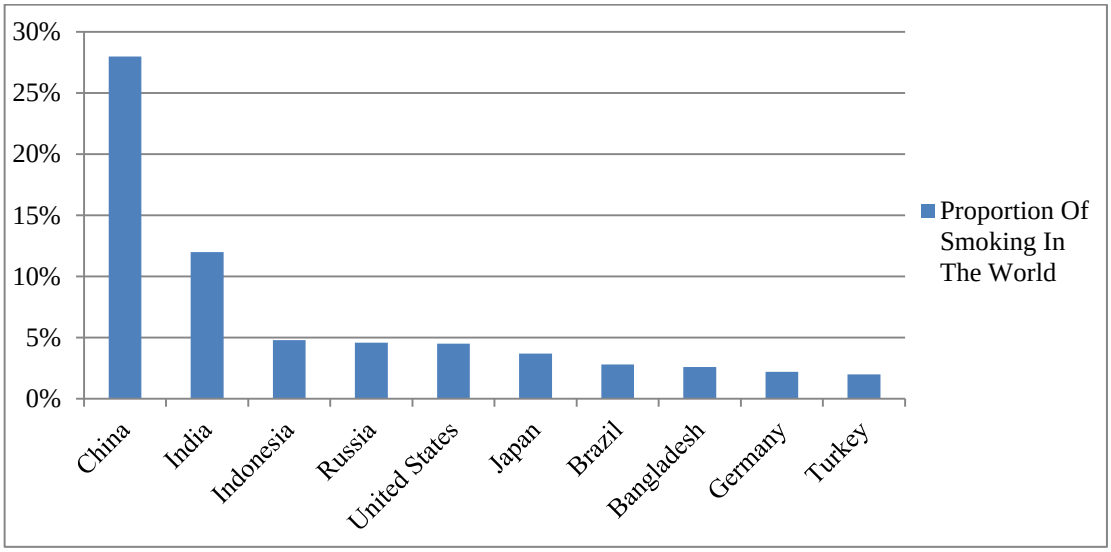

Figure 1 Top 10 Cigarette consuming countries in the world

In 2008, the number of Turkish adult smokers at the age of 15 and over, were 47.9% among males and 15.2% among females [9]. Based on its 2008 adult population of 55 million, it implies that about one-third of Turkish adults (17.3 million people) smoke, and 15.2 million are daily smokers. When the results are analyzed by age groups, it is observed that cigarette smoking is the highest among younger adult populations — 40% of those aged 25 through 44 currently smoke in 2010 [10]. In 2012, smoking rate of the adult population of Turkey regressed to 27.1% due to recent smoking legislations in Turkey [11]. (Figure 2)

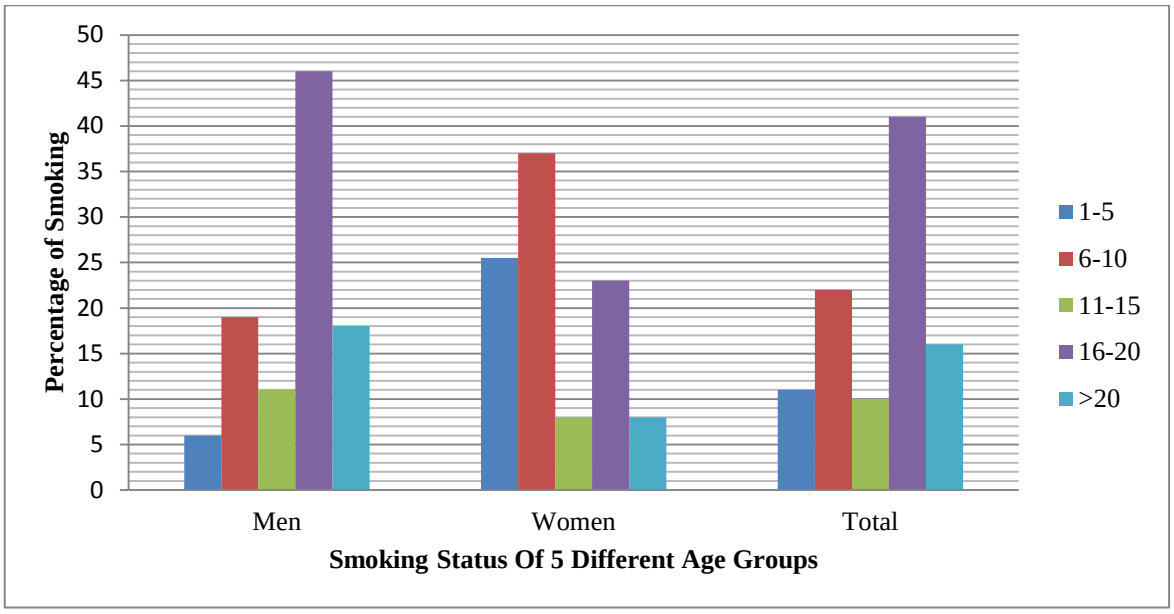

Figure 2 Percentage distribution of smoking status of adults 15 years and older who are current smokers, by number of cigarettes daily smoked. Turkey Global Adult Tobacco Survey (GATS), 2008

Daily smoking rates which refers to the number of tobacco product per day, increases until the age of 45, then shows a decreasing trend, both among men and women. (Table 1) Smoking habit is very uncommon among elderly women (1.6%), whereas one in five (17.9%) elderly men are smokers [1].

Table 1 Percentage distribution of adults 15 years and older who are currently daily, occasional (less than daily use) or non-smokers, by the age of the population. Turkey Global Adult Tobacco Survey (GATS), 2008

	Smoking Status			
Characteristics	**Daily**	**Occasional**	**Current Non-Smoker**	**Total**
	Percentage (95% GI)			
Age (Years)				
15-24	21.7 (18.7-24.7)	3.6 (2.4-4.8)	74.7 (71.6-77.9)	100,0
25-44	34.7 (32.9-36.6)	5.2 (4.4-6.0)	60.1 (58.1-62.0)	100,0
45-64	27.0 (24.9-29.0)	2.5 (1.8-3.3)	70.5 (68.4-72.6)	100,0
65+	8.7 (6.9-10.6)	1.6 (0.8-2.4)	89.7 (87.7-91.6)	100,0

1.3. Health Damages Caused By Smoking

Tobacco smoke contains more than 7,000 chemicals, at least 250 are known to be harmful including nicotine and the other smoke compounds that are carcinogens such as polycyclic aromates, hydrogen cyanide, carbon monoxide a combustion product, ammonia and trace amounts of heavy metals such as cadmium, nickel, chromium, lead and arsenic [12]. (Figure 3, Table 2, Table 3)

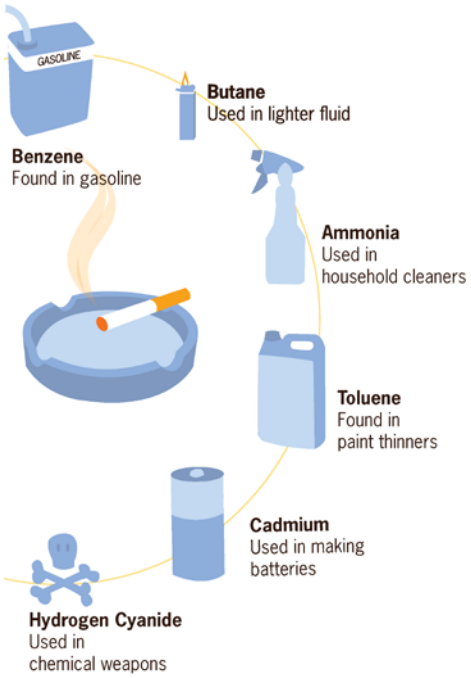

Figure 3 Some of the toxic chemicals in cigarette smoke.

Table 2 Some of the constituents in cigarette smoke.

Gaseous Portion	**Particulate Portion**	
Aldehydes	Acids	Insecticides
Ammonia	Alcohols	Lactams
Arsenic	Aldehydes	Lactones
Benzene	Amides	Nicotine
Carbon monoxide	Brown pigments	Nitrosamines
Hydrogen cyanide	Cadmium	Polycyclic aromatic
Nitric oxide	Carbohydrates	hydrocarbons
Nitrogen oxide	Esters	Polyphenols
Toluene	Imidazoles	Pyridines
Toluidine	Imides	Vinyl chloride

Table 3 Some of the polycyclic aromatic hydrocarbons found in cigarette smoke

Chrysene		Coronene
Fluoranthene		Benzofluoranthene
Napthalene		Dibenzenathracene
Pyrene		Ovalene
Benzoperylene		Phenanthrene
Benzpyrene		Anthracene
Benzfluoranthene		Benzanthracene

Nicotine, which is an alkaloid derived from the leaves of *Nicotiana tobacum* is the main constituent of cigarette. It is a strong psycho-stimulant that causes physical and psychological addiction [12]. It exerts cardiovascular effects like hypertension and increased heart rate.

Tobacco toxicity mainly occurs due to combustion products like carbon monoxide. Carbon monoxide limits the amount of oxygen so that red blood cells can not convey oxygen throughout the human body. Also, it may damage the inner walls of the arteries allowing fat to build up in them. Beside those toxic chemicals; tobacco also contains tar, which is a sticky substance that fills into deposits in lungs, causing lung cancer and respiratory distress.

In 1990s, 3 million deaths a year are caused by smoking worldwide, and this result is increasing. In 1997, tobacco use and secondhand exposure killed more than 6 million people (one death every six seconds). Tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and malaria combined killed less than tobacco. If this trend is not reversed, 10 million deaths will occur annually by the year 2020, 70% of which will be in the developing countries [6].

20% of 5 million patients hospitalized in 2000, suffered from a disease caused by tobacco, according to Turkish MoH. 23% of total patient days and 52% of total hospital deaths resulted from diseases caused by tobacco use [10].

1.3.1. Disease Burden from Tobacco

Tobacco smoking is often associated with ill-health, disability and death from non-communicable chronic diseases; it is also associated with an increased risk of death from communicable diseases. Exposure to tobacco smoking negatively impacts health throughout the course of a lifetime. The negative impact of tobacco use becomes particularly important about after the age of 30 and includes increased rates of cardiovascular death (ischemic heart diseases and stroke) in relatively young middle-aged adults, higher rates of cancers (especially lung cancer) particularly later in life, as well as death associated with diseases such as tuberculosis and infection of the lower respiratory tract [13]. (Table 4)

Table 4 Proportion of all deaths attributable to tobacco (%) [6]

WHO Region	**Proportion of all deaths attributable to tobacco (%)**		
	Men	**Women**	**All Adults**
African	5	1	3
Americas	17	15	16
Eastern Mediterannean	12	2	7
European	25	7	16
South East Asian	14	5	10
Western Pacific	14	11	13
Global	16	7	12

The principal non-communicable diseases caused by smoking include cancers (including lung, pancreas, mouth, pharynx, larynx, and bladder cancers), cardiovascular diseases (including ischemic heart disease, myocardial degeneration, pulmonary heart disease, and peripheral and cerebral vascular diseases), and respiratory diseases (including chronic bronchitis, emphysema, asthma, and chronic obstructive pulmonary disease). Smokers also are at higher risk of developing pneumonia and other airway infections [10]. (Figure 4)

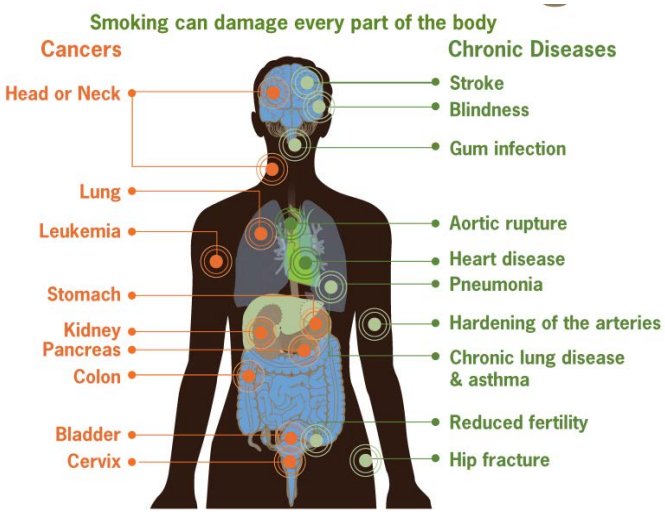

Figure 4 Risks of smoking

Turkish MoH estimates that smoking is responsible for 77% of tracheal, bronchus and lung cancers, 46% of upper aero-digestive system cancers, and 52% of chronic obstructive pulmonary diseases in Turkey in 2010 [10].

There are no nationwide morbidity figures in Turkey attributed to tobacco smoking specifically, nevertheless, disability-adjusted life years (DALY) were calculated for some diseases and some risk factors in 2000 [15]. Perinatal conditions take first place

with 8.9%, ischemic heart disease is in second place at 8.0%, and cerebrovascular diseases rank third with 5.9%, in all age groups [8].

1.4. Regulations For Smoking Control

Smoking is a harmful habit not only for the person who smokes but also for the people that are exposed to cigarette. WHO and national health authorities has been imposing restrictions on cigarette consumption at public places, schools, hospitals to minimize this habit which causes damages both to smokers and passive smokers.

1.4.1. WHO MPOWER

The World Health Organization has proposed recommendations for smoking cessation and treatment of tobacco dependence including behavioral and pharmacological interventions in 2003, called ‘’MPOWER’’ through the WHO Framework Convention on Tobacco Control (WHO FCTC) which is an evidence-based treaty that reaffirms the right of all people to the highest standard of health [15]. World Health Organization’s MPOWER strategy is an act against the smoking habit which includes specific steps through the smoking cessation process. The word of MPOWER is created by the initial letters of every step, that include **m**onitoring tobacco usage and prevention policies; **p**rotecting people from passive smoking; **o**ffering help to those who want to quit; **w**arning about the dangers of tobacco; **e**nforcing bans on tobacco advertising, promotion, and sponsorship; and **r**aising taxes on cigarettes. These are proven strategies that can help avert unnecessary illness and death [16].

1.4.2. Tobacco Control Legislation In Turkey

Smoking was responsible for 54,700 deaths in Turkey in 2003, 13% of total deaths, and 596,684 years of life lost. If the current smoking prevalence rates continue, tobacco will be responsible for over 127,000 deaths in 2050. Effective tobacco control and a reduction in prevalence to 10% by 2050 would save nearly 47,000 lives annually [10].

The only significant control policy was a ban on cigarette advertising on television, radio, and billboards before 1980s. Starting in 1981, cigarette warning labels that states "harmful to health" were required; this was strengthened to read "cigarette smoking is dangerous to health" in 1991.

In 1996, cigarette smoking was banned in some public places, including in the education, health, and cultural service locations, enclosed sports facilities, on public transportation, and in waiting areas. Public workplaces with five or more employees were required to create smoke-free areas. The ban on cigarette advertising was extended to other types of advertising, including magazine and newspaper advertising, and the use of tobacco brand names on non-tobacco products was prohibited. The sale of cigarettes to minors (under age 18) was prohibited. A stronger warning "Legal Warning: Harmful to Health" and was required on all imported and domestically produced cigarette packages. Finally, both public and private television and radio channels were required to broadcast at least 90 minutes per month of information about the consequences of tobacco use.

Turkey signed WHO's Framework Convention on Tobacco Control in 2004. Most recently, in January 2008, the Tobacco Control and Prevention of Hazards Caused by Tobacco Products Law has adopted. With this law, Turkey became the fifth country in Europe, and the first in Middle-East and Central Asia to become a smoke-free country.

The law strengthened restrictions on smoking in public places by making all public buildings, public transportation, taxis, and the inside and outside of all schools and health care facilities, sport facilities including soccer stadiums 100% smoke-free in April 2008. On July 19, 2009, the ban was extended to the hospitality sector, including restaurants, bars and Turkish coffee houses. Since July 2009, Turkey has been totally smoke-free in public places [10].

1.4.3. Smoking Cessation In Turkey

A recent survey, performed in 2008, shows that many adult smokers in Turkey want to quit; over half of the smokers who participated in the study said that they wanted to quit and 44.8 % had made a quit attempt, while 15.8 % had successfully quit. (Table 5, Figure 5) [8]

Table 5 Percentage of smokers 15 years and older who made a quit attempt and those who made a successful quit attempt, by age. Turkey Global Tobacco Survey (GATS), 2008

Characteristic	Smoking Cessation - made quit attempt			Smoking Cessation - successfully quit		
	Total	Men	Women	Total	Men	Women
	Percentage (95% CI)					
Overall	44.8 (42.5-47.0)	44.1 (41.5-46.6)	46.9 (42.6-51.1)	15.8 (13.5-18.0)	13.5 (11.1-16.0)	21.9 (16.5-27.4)
Age (Years)						
15-24	52.3 (46.3-58.4)	48.3 (40.8-55.9)	64.1 (54.2-73.9)	17.5 (10.9-24.0)	13.8 (6.6-21.1)	25.6 (13.1-38.0)
25-44	42.7 (39.7-45.7)	41.5 (38.2-44.9)	45.6 (40.2-51.1)	13.8 (11.0-16.7)	10.9 (7.9-13.9)	20.8 (14.4-27.3)
45-64	44.2 (40.0-48.4)	46.2 (41.5-51.0)	37.2 (28.4-46.0)	17.1 (12.3-21.9)	16.5 (11.4-21.7)	19.5 (6.1-32.9)
65+	40.6 (30.4-50.7)	43.1 (32.4-53.9)	-	26.1 (12.3-39.8)	25.4 (11.4-39.4)	-

One in four smokers (26.5%) had quit smoking in the past. The proportion of quitters increased by age; only 8.9% of smokers ages 15-24 quit smoking, compared to 68.7% for the 65 and over age group [8].

The quit rate did not differ for men (27.2%) and women (23.9%). The quit rate increased with age more than two-thirds (68.7%) of the elderly (65 years and over) had

quit. A little more than one fourth (26.5%) of the ever-daily smokers had quit smoking. (Table 6)

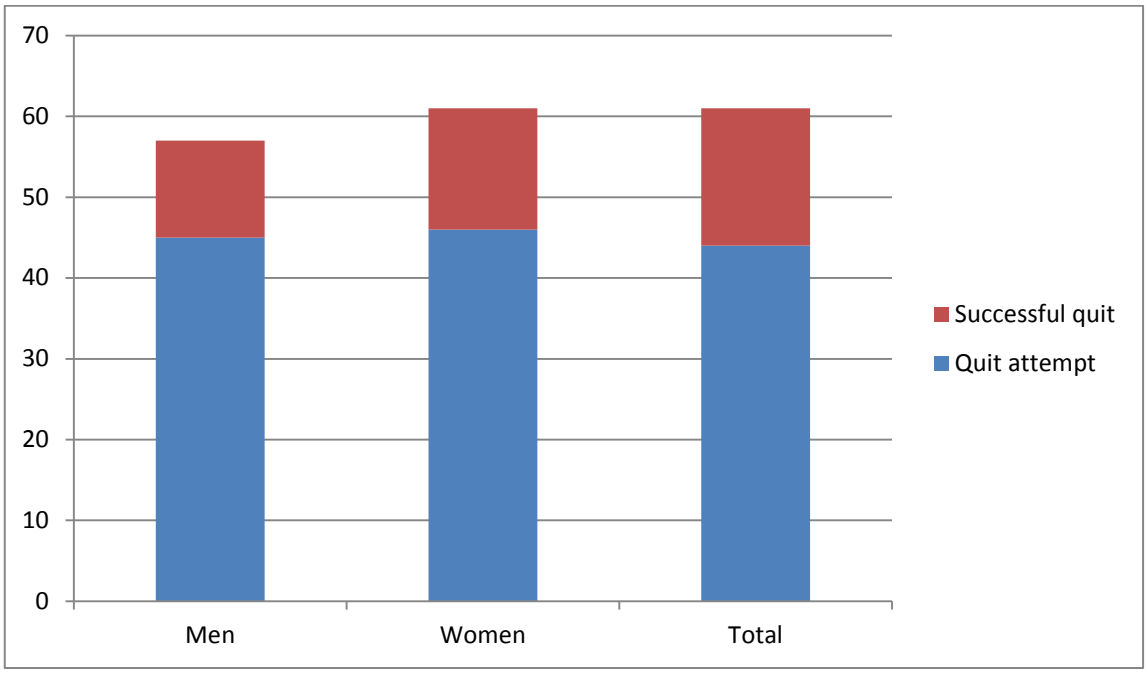

Figure 5 Percentage of quit attempt and successful quit among current and former smokers

Table 6 Percentage of ever daily smokers 15 years and older who have quit smoking (quit rate), by age group. Turkey Global Tobacco Survey (GATS), 2008

Characteristic	Former Daily Smokers (Among Ever Daily Smokers)		
	Total	Men	Women
	Percentage (95% CI)		
Overall	26.5 (24.7-28.2)	27.2 (25.2-29.2)	23.9 (20.5-27.2)
Age (Years)			
15-24	8.9 (5.1-12.7)	6.6 (2.3-10.9)	16.3 (7.4-25.2)
25-44	18.7 (16.5-20.9)	18.7 (16.0-21.4)	18.7 (14.9-22.6)
45-64	37.6 (34.4-40.8)	38.8 (35.2-42.3)	32.4 (25.8-39.0)
65+	68.7 (63.1-74.3)	68.4 (62.4-74.3)	70.9 (54.1-87.7)

1.5. Multiple Drug Usage And Smoking In Geriatry

Multiple drug usage is defined as the use of more than one medication and/or over-the-counter medications. Due to chronic health problems and illnesses, drug intake ranges from 3 to 8 medications taken concomitantly in elderly patients [17, 18].

1.5.1. Polypharmacy In Elderly

The risk of drug-drug and smoking-drug interaction and as well as adverse drug reactions increases relatively when the number of drugs given increases and patient compliance to medication regimens becomes more difficult [19].

The strongest risk factor for adverse drug-related events is the number of drugs prescribed, independent of age. Chronic administration of four drugs is associated with a risk of adverse effects of 50% to 60%; administration of eight or nine drugs increases the risk to almost 100%. Whereas the goal is to prescribe as few drugs as possible in the elderly, the presence of multiple diseases and multidrug regimens for common cardiovascular diseases often results in polypharmacy. Surveys estimate that about half of people older than 65 years use three or more medications prescribed on a daily basis, and 20% of patients 75 years and older have five drugs prescribed per outpatient encounter [20]. Even higher numbers of medications could be prescribed for nursing home patients, averaging six to eight medications per day.

In nursing home patients, drugs associated with adverse drug events are generally due to antibiotics, anticoagulants and antiplatelet drugs, atypical and typical antipsychotic drugs, antidepressants, antiseizure medications, or opioids [21]. Adverse drug effects may present with “atypical” symptoms in an older patient, such as mental status changes and impaired cognition. Therefore, strategies that minimize the chance of drug interactions and adverse drug effects are essential.

The alteration possibility of the concentration of concomitantly administered medications caused by pharmacokinetic interactions is more if the drugs that are used

together are metabolized by or inhibit the same pathway. Inducibility of hepatic enzyme activity can lower concentrations of medications and lead to ineffective therapy. Cigarette smoke is an inducer of CYP1A enzymes [22].

Age-related changes in cardiovascular physiology and dynamics affect pharmacodynamics. (Table 7) Greater age-related nervous system sensitivity to para-sympathetic stimulation may explain adverse effects such as urinary retention, constipation and fecal impaction, or worsened cognition in older patients who receive drugs with anticholinergic properties. Gastrointestinal transition time is generally increased in the elderly, and constipation is a frequent complaint of hospitalized elderly, less active elderly, and institutionalized elderly. Drug-induced constipation and bowel obstruction can occur in older patients receiving bile acid sequestrants, anticholinergic medications, opiates, and verapamil [23].

Table 7 Physiological changes that occur with aging and have the potential to influence drug disposition and metabolism

System	**Change**
General	Reduced total body mass Reduced basal metabolic rate Reduces proportion of body water Increased proportion of body fat
Circulatory	Decreased cardiac output Altered relative tissue perfusion Decreased plasma protein bingding
Gastrointestinal	Reduced gastric acid production Reduced gastric emptying rate Reduced gut mobility Reduced gut blood flow Reduced absorption surface
Hepatobiliary	Reduced liver mass Reduced liver blood flow Reduced albumin synthesis

A number of lists of medications considered “inappropriate” for routine use in the elderly because of adverse effects or lack of efficacy have been compiled. There are criteria that can help practitioners reduce the risk of patient harm by guiding more appropriate drug selection in the elderly commonly known as the Beers Criteria. The updated Beers Criteria list helps practitioners to prescribe more appropriate drugs for elderly people [24]. (Table 8)

Table 8 Abbreviated Beer’s List of Medications with Increased Risk of Adverse Drug Events in Patients Over 65

Medications	**Reason That Use Is A Problem**
Antidepressants	
amitryptline	Used to treat depression. These medications can cause sedation, weakness, blood pressure changes, dry mouth, problems with urination, and can lead to falls and fractures.
Sleeping Pills and Antianxiety Medications	
alprazolam	Used to treat insomnia. This medication produces prolonged sedation/sleepiness (often lasting for days and can worsen if taken daily) and can increase the risk of falls and fractures
lorazepam	
chlordiazepoxide	Used to treat insomnia and anxiety. Chlordiazepoxide and diazepam produce prolonged sedation (often lasting several days and worsen if taken daily) and can increase the risk of falls and fractures.
diazepam	
Heart Medications	
digoxin	Used to treat abnormal heart rhythms and heart failure. Because of decreased processing of digoxin by kidney, doses in older people should rarely exceed 0,125 mg daily. Except when treating certain types of abnormal heart rhythms.

Long-acting benzodiazepines, sedative and hypnotic agents, long-acting oral hypoglycemic agents, selected analgesics and NSAIDs, first-generation antihistamines, antiemetics, and gastrointestinal antispasmodics are usually considered inappropriate in the elderly. Amiodarone, clonidine, disopyramide, doxazosin, ethacrynic acid, guanethidine, and guanadrel have been classified as generally inappropriate in the elderly. More recent definitions of "inappropriate drug use" include failure to consider drug-disease interactions and failure to adjust drug dosages for age-related changes (e.g. digoxin at doses above 0.125 mg/day), drug duplication, drug-drug interactions, and duration of use. By use of these criteria, most drug use review studies concluded that inappropriate drug prescribing occurs in a significant fraction of older patients [21, 22]. Analyses suggest that inappropriate prescribing of medications to older patients in both the community and nursing homes has not decreased in recent years [22, 25].

1.5.2. Smoking And Geriatrics

Smoking is related to the main causes of death and it contributes to morbidity and disability associated with several chronic diseases among the elderly [26]. Smoking habit may contribute to the functional decline of the elderly and accelerate alterations in several systems and organic functions [27]. There are evidences [28, 29, 30] that smoking accelerates the aging process and consequently, reduces life expectancy. This is due to molecular alterations resulting from smoking habit that causes innumerable harmful modifications in several systems of the human body [29]. In the respiratory system there is a reduction of respiratory capacity and increased risk of chronic disease, bronchopneumonia and cancerogenous tumor [26, 30]. In the cardiovascular system, smoking is related to the pathogenesis of diseases such as myocardial infarction, coronary disease, diabetes mellitus type II, hypertension and intolerance to physical activity. In elderly smokers, the sensory organs are compromised and cognition is reduced, which considerably affects the quality of life in this age group [26, 30]. And also the correlation between BMI and duration of smoking time was observed; that is, the lower the BMI the longer the duration of smoking time [27]. This behavior may have keep elder people from gaining weight which is very important for the overall health conditions of the elderly.

It is acknowledged that tobacco smoking does not only affect the overall health of geriatric patients directly, but also it is linked to the handling of medications in the geriatric patients [31].

1.5.3. Clinical Risks During Smoking Cessation

Health care providers are urged to assess all patients for tobacco use, to strongly recommend tobacco cessation and to prescribe nicotine replacements or bupropion to help patients quit smoking [32].

However, it is not well recognized that the metabolism of many prescribed drugs are affected by tobacco smoking and that smoking cessation may necessitate dosage adjustment for these drugs. Smoking cessation reverses induced hepatic enzyme levels to normal [33] and also reverses other smoking-induced effects, markedly augmenting plasma drug concentrations in patients whose dose was established while smoking [34]. Nicotine replacement treatment to assist smoking cessation will not ameliorate this effect in most cases because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, but is related to aromatic hydrocarbons in tobacco smoke [35].

1.6. Smoking - Drug Interactions

Cigarette smoking is one of the environmental factors that contribute to interindividual variations in response to an administered drug. Polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke induce hepatic aryl hydrocarbon hydroxylases, thereby increasing metabolic clearance of drugs that are substrates for these enzymes. PAHs have been shown to induce 3 hepatic cytochrome P450 (CYP) isozymes, primarily CYP1A1, 1A2 and 2E1. Drug therapy can also be affected pharmacodynamically by nicotine [36].

Knowledge of the substrates, inhibitors, and inducers of these enzymes assists in predicting clinically significant drug interactions. In addition to inhibition and induction, microsomal drug metabolism is affected by genetic polymorphisms, age, nutrition, hepatic disease, and endogenous chemicals. Of more than 30 human isoenzymes identified to date, the major ones responsible for drug metabolism include CYP3A4, CYP2D6, CYP1A2, and the CYP2C subfamily [37]. (Table 9)

Table 9 Human cytochrome P450 (CYP450) superfamily.

Most important CYP-isoforms	Abundance in liver (%)	% of drugs metabolized
CYP3A4	30	52
CYP2C proteins	20	20
CYP1A2	13	11
CYP2E1	7	7,5
CYP2A6	4	1,2
CYP2D6	2	25
Other CYPs	ca. 25	2,5

Cigarette smoking might cause variations on the effects of prescribed medications. It might cause induction on the drugs both in pharmacokinetic and pharmacodynamic pathways. Long term smoking habit might change the enzyme levels which perform drug metabolism. Induction of those specific enzymes causes reduction on their

substrates plasma levels and thus their pharmalogical effects. Pharmacodynamic interactions are associated with diminished effects of the drugs due to controversial effects of smoking.

Various physiological and pathological factors can also affect drug metabolism. Physiological factors that can influence drug metabolism include age, individual variation (e.g. pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, or sex differences. Drugs are metabolized more slowly in fetal, neonatal and elderly human than in adults [38].

1.6.1. Pharmacokinetic Interactions

Older adults are generally more susceptible to drug effects, with adverse drug reactions occurring 2–3 times more frequently in persons over age 65. Reduced renal drug elimination (about 50%), decreased hepatic drug clearance, changes in body water content and changes in body fat content also increase risks of adverse drug effects in older adults [39].

Pharmacokinetic interactions are associated with enzyme induction. During the metabolisation step of certain substrates, level of metabolising enzyme increases, and biodegradation of the enzyme might also delay. Although activities of cytochrome P450 enzymes are reduced in older adults, conjugation mechanisms are maintained [40].

1.6.1.1. Mechanism Of Induction

Five different main mechanisms of induction are distinguished for drug-metabolising enzymes currently. Ethanol type of induction is mediated by ligand stabilisation of the enzyme, but the others appear to be mediated by intracellular ‘receptors’ namely aryl hydrocarbon (Ah) receptor, peroxisome proliferator activated receptor (PPAR), constitutive androstane receptor (CAR, phenobarbital induction) and pregnane X receptor [PXR, rifampicin (rifampin) induction]. [41]. (Table 10)

Table 10 Substrates of some CYP enzymes

	Examples of model drugs
1A2	Caffeine, theophylline
2C9	Diclofenac, ibuprofen, phenytoin, tolbutamide, S-warfarin
2C19	Mephenytoin, omeprazole (+3A4), diazepam (+3A4)
2D6	Debrisoquine, sparteine, dextromethorphane, amitriptyline, codeine propafenone (+3A, 1A2 and phase II)
2E1	Chlorzoxazone, halothane, paracetamol (+conjugation)
3A3/4	Cyclosporine, erythromycine, lidocaine, midazolam, nifedipine verapamil (+1A2, 2C)

The mechanism of interaction between smoking and drugs is usually the induction of the metabolizing enzymes. Enzyme induction could occur in the amount of the enzyme or at the activity of the enzyme [42]. As the metabolism of the drugs increase, the efficacy of those drugs decreases.

The polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke bind to the aryl hydrocarbon (Ah) receptor in the cell. This PAH-Ah receptor complex depart into the nucleus and stimulate the ARE (Ah responsive element). Thus CYP gene's transcription activities increase and amount of mRNA increases as well. Relatively amino acids turn into proteins on the rough ER (Endoplasmic reticulum) by the lead of mRNA and the enzyme production process is completed by the participation of haem to the protein [42].

The onset of the induction time and the amount of enzymes will be produced as a result of the interaction is not clear. The induction of the enzymes can begin among 3 to 6 hours and the maximum effect is observed in 24 hours [13, 43]. The induction degree of those enzymes can vary with age, sex, race and other genetic factors [44, 45]

The induction degree also can vary with the quantity of smoked cigarettes, the bioavailability of the components in inhaled cigarette smoke, and inhalation rate of the individual [42].

The number of cigarettes that a person smokes changes the clearance rates of the drugs because the induction rates of specific hepatic enzymes also changes. A heavy smoker who smoke more than 20 or more cigarettes in a daily basis would encounter a higher enhancement in drug clearance than a person who smoke fewer cigarettes (6 or less) in a non-daily basis [42, 46].

1.6.1.2. The Constituents Of Cigarette That Cause Induction

It is shown that smoke hepatic cytochrome P450 isoenzymes are induced by cigarette smoke. One of the constituents of cigarette smoke is polycyclic aromatic hydrocarbons (PAHs) that are products of incomplete combustion. They are mainly responsible for this effect on drug metabolism. PAHs have been shown to induce primarily 3 isozymes, CYP1A1, CYP1A2 and CYP2E1 and it is also known that they induce CYP2A6, CYP2B6 and CYP2D6 [42, 47, 48].

Not only the PAHs but also the other constituents in cigarettes involved in enzyme induction; namely nicotine, carbon monoxide and cadmium may also play a role. It is known that nicotine activates the mesolimbic pathway which is also known as the reward pathway. It is studied that nicotine might induce CYP2B1 and CYP2B2 in rat brains [49].

In another study [50] it is observed that nicotine increases the content and the activity of CYP2A1/2A2/2E1 in specific regions of rat brains. Absence of the hepatic activity allows neglecting the effect of nicotine on drug metabolism. Nicotine also involves in the induction of CYP2E1, CYP2A1/2A2 and CYP2B1/2B2 in some regions of rat brains [51].

It is shown that carbon monoxide inhibits drug metabolism in animal studies depending to the given dose [2]. Higher CO concentrations cause stronger inhibition on CYP enzymes at *in vitro* studies [52, 53]. It is shown that even exposure to cigarette smoke can cause inhibition of clearance on specific drugs [54]. Cadmium involves in the inhibition of CYP2E1 in animal studies, but it is also dose dependent. High doses of cadmium are required to achieve its inhibitory effect which is not possible to be exposed only with smoking [55].

The relevance of these data from animal models to human drug metabolism has not been established. Smoking was shown not to significantly affect other CYP isozymes, such as 2C19, 2C9 and 2D6 [56, 57].

1.6.1.3. The Enzymes Induced By Smoking

CYP1A1 is an extrahepatic CYP enzyme that activates carcinogenic compounds. It is thought that chronic exposure to chemicals and environmental carcinogens by inhalation might induce the level of CYP1A1 extrahepatic tissues especially in lung, through the aryl hydrocarbon receptor (AhR) [58]. The induction of CYP1A1 is thought to be a major mechanism leading to the development of lung cancer [59]. Thus risk of lung cancer and high levels of activity of CYP1A1 are strongly associated [54]. CYP1A1 is readily detectable in human lung, intestine, skin, lymphocytes and placenta, particularly from cigarette smokers [60]. CYP1A1 is not important for human drug metabolism; it has been mostly implicated in carcinogenesis and cancer progression [61].

An induction might occur through the metabolism of the drugs that are the substrates for CYP1A2 due to cigarette smoking. The most consistently observed effect is an increase in the clearance of those drugs. Selected drugs that interact with smoking are caffeine, clozapine, fluvoxamine, mexiletine, olanzapine, tacrine, and theophylline. Other common drugs metabolized by CYP1A2 are duloxetine, erlotinib, frovatriptan, melatonin, mirtazapine, ondansetron, ramelteon, tizanidine, triamterene, warfarin, imipramine, haloperidol, pentazocine, propranolol, flecainide and estradiol [63].

Cigarette smoking also results in faster clearance of heparin, possibly related to smoking-related activation of thrombosis with enhanced heparin binding to antithrombin III. Cutaneous vasoconstriction by nicotine may slow the rate of insulin absorption after subcutaneous administration [54].

CYP2E1 accounts for approximately 7 to 10% of the total CYP content in human liver [64, 65]. Lung, kidney, lymphocytes and placenta are also additional locations for this enzyme. Paracetamol, alcohol, chlorzoxazone, dapsone, disulfiram and enflurane are common substrates. CYP2E1 is also associated with the activation of procarcinogens. Genetic polymorphism, alcohol and isoniazid are associated with induction of CYP2E1 [64].

Smoking is shown not to significantly affect other CYP isozymes, such as 2C19, 2C9 and 2D6 [56].

1.6.1.4. The Drugs Induced By Smoking

Caffeine is mainly metabolized by CYP1A2 and often used in studies as a marker for CYP1A2 activity [66]. Its clearance is increased by 56% in smokers [31]. When a patient quits smoking, the patient's caffeine intake should be reduced by half to avoid excessive caffeine levels. Careful evaluation of a patient's total daily caffeine intake is important, so all sources of caffeine, such as nonprescription drugs and dietary supplements, should be examined [67].

Theophylline is a xanthine derivative that is indicated for asthma and bronchospasm treatment by oral and i.v. route especially in patient setting. Theophylline is metabolised mainly (app. %70) in the liver by CYP1A2. It has a narrow therapeutic index and small dose fluctations may cause disproportional alterations in serum concentration. In a study, it is observed that theophylline's clearance is faster and half-life is shorter in smokers compared to nonsmokers [31]. One week after cigarette

cessation enzyme induction reverts [68]. Plasma theophylline levels should routinely be monitored in smokers, and dosages should be adjusted properly [67].

A study which observes a 36,6% decrease in clearance of theophylline after smoking cessation, recommends that theophylline dose might be decreased by 25–33% after smoking cessation to maintain therapeutic drug levels in the narrow range of 10–20 l/ml [69].

Clozapine, an atypical antipsychotic drug with a narrow therapeutic range, is metabolized primarily by CYP1A2 but also by CYP2C19 and possibly CYP3A4 [66,70]. A study shows that nonsmokers had 3.2-fold higher plasma clozapine levels compared with smokers [66]. Consumption of 30 or more cigarettes daily, significantly affect mean intraindividual variation in plasma clozapine concentrations at low doses (100mg) [67].

It is observed that smokers have significantly lower mean plasma clozapine concentrations than nonsmokers in another study which is conducted with clozapine [71]. In another study [72], plasma clozapine concentration of smokers is found to be lower than the amount of plasma clozapine concentration that is found in nonsmokers, and the difference between two groups is statistically significant [42]. These studies indicate that plasma clozapine concentrations are generally lower in smokers compared to nonsmokers; therefore smokers may need higher drug dosages to achieve its minimum effective concentration (350 micrograms/L) [73].

Clozapine’s effective dose varies according to every individual. The effective dose is; to achieve symptom control without toxic side effects. Toxic side effects such as sedation, hypotension, and seizures may be observed in high plasma concentrations [74].

Olanzapine, a widely used atypical antipsychotic, is extensively metabolized CYP1A2 and partially CYP2D6, being minor metabolic pathway [75, 76].

Tobacco smoke, an inducer of CYP1A2, decreases plasma concentrations of olanzapine. In a study Tmax of olanzapine in smokers is found to be shorter and the oral clearance of olanzapine in smokers is higher than in nonsmokers due to induction of the CYP1A2 metabolic pathway by cigarette smoking. Dosage modification should be considered for patients with factors that are associated with variation of drug's metabolism [77].

Another study finds the plasma concentrations of olanzapine are lower in patients with cigarette smoking. Smoking increases olanzapin metabolism by 98% [78]. A study recommends an average dosage-correction of 1.5 fold for clozapine and olanzapine in smokers [79].

Smoking rate of the schizophrenia or bipolar disorder patients is very high [80, 81] and that emphasises the clinical importance of paying attention to the effects of cigarette consumption on the pharmacokinetics of various psychotropic drugs.

Chlorpromazine is an antipsychotic drug which is metabolized by CYP1A2 and CYP2D6. Smoking is related with varied plasma chlorpromazine concentration. It seems to be involved with both pharmacodynamic and pharmacokinetic interactions [82].

A case report of a patient who uses chlorpromazine for controlling the symptoms of schizophrenia shows that more severe adverse effects might be observed following a sudden cessation of cigarette smoking, which was correlated with an increase in plasma chlorpromazine concentration [83]. Another study [84] shows that the clearance of chlorpromazine is faster in the chronic schizophrenia patients with smoking habit. Those studies present that heavy smoking is associated with a decrease in the plasma concentrations of chlorpromazine due to enzyme induction, and a higher dosage may be required in patients who smoke cigarette.

Less drowsiness and orthostatic hypotension is observed in smokers compared with nonsmokers [82]. In another case report, a patient with schizophrenia develops severe

drowsiness on the same dose of chlorpromazine treatment regime after smoking cessation, when he starts to smoke again symptoms relieves. Plasma concentrations are 3 times higher after quitting smoking compared with those while smoking [83].

Another study shows that chlorpromazine‘s frequency of drowsiness is higher in nonsmokers than that is of smokers. It is hypothesized that these findings are a result of induction of liver microsomal enzymes and more rapid metabolism of chlorpromazine in smokers. Another possibility is that nicotine could produce ‘activation’ effects, thereby partially accounting for less sedation found in the heavy use group [42].

Propranolol is a beta blocker drug which is metabolised by mainly CYP1A2, CYP2C19. Beta- blockers interactions with smoking are based on both pharmacodynamic and pharmacokinetic pathways. In the case of concomitant usage of cigarette and beta blockers, smoking can reduce the beneficial effect of beta-blockers on blood pressure and heart rate [54]. The oral clearance of propranolol is increased by 77% in smokers compared with nonsmokers. The study shows that, there is a selective effect of smoking on propranolol metabolism and suggests that side-chain oxidation and glucuronidation are mediated by isoenzymes inducible by aromatic hydrocarbons [54, 85, 86].

Clinical effects are difficult to predict since propanolol dosage varies from 80–640 mg daily. It may be crucial to observe for signs and symptoms of overdose. For example, bradycardia, fatigue, dizziness and other symptoms of overdose suggest a need to decrease doses of propanolol and verapamil [35]. Smokers may need larger doses due to increased clearance [54].

Verapamil is a calcium channel blocker which is metabolised by 3A4 mainly and 1A2, 2A6, 2C8/9, 2E1 partly, is used for angina pektoris, hypertension and supraventricular tachyarrhythmia. Smoking cessation decreases verapamil clearance by eight fold [87].

Warfarin is an oral anticoagulant which is metabolised by CYP2C8/9 mainly and 1A2, 2C19, 3A4 partly.

In a crossover study; it is observed that there is an increase in warfarin's steady state level, t1/2, and apparent volume of distribution (Vd); and a decrease in clearance rate when patients stop smoking. There is not an alteration in its prothrombin time. It shows that cigarette smoking does affect warfarin clearance, t 1/2, and apparent volume of distribution, though the net effect on warfarin's pharmacodynamic activity is negligible, at least at doses which are ineffective therapeutically [88].

A prospective study [89] reports a 13% increase in average study-state warfarin level and a 13% decrease in warfarin clearance rate when smokers stop smoking. Two case reports document the effects of smoking cessation on warfarin requirements [90, 91]: report an INR prolongation and the need to reduce warfarin dose 14–23% in individuals who stops smoking after achieving a stable warfarin dose [35].

Alprazolam is an oral benzodiazepine derivative which is metabolised by CYP3A4. In a study [92] it is observed that Alprazolam's mean elimination half-life is significantly shorter in the smokers than nonsmokers. CYP1A2 might be involved in the metabolism of alprazolam [42].

Lorazepam is a benzodiazepine which is not a substrate of CYP enzyme system and metabolized by glucuronic acide conjugation. A study which assesses the kinetic properties of lorazepam suggests that cigarette smoking enhance the clearance of lorazepam [93]. In another study, 10 healthy cigarette smokers and a control group with 10 nonsmoking individual are matched according to their age, bodyweight and gender; and receive same dose of lorazepam [94]. Elimination half-life is significantly shorter in smokers compared with controls. In smokers, there is a slight increase in total lorazepam clearance compared with nonsmokers. Observations of a study [95] about lorazepam show that higher clearance is also associated with heavy cigarette smoking.

Haloperidol is an antipyschotic active ingredient which is metabolised by CYP2D6 and 3A4 mainly and CYP1A2 partially. In a study, the clearance and Css of Haloperidol are compared for 23 smokers and 27 nonsmokers; and the results show that smokers has significantly lower Css and higher haloperidol clearance [96]. The clinical significance is unclear, since haloperidol concentration in all patients was within the therapeutic limits [54].

It is assumed that in smokers, plasma concentrations of haloperidol and reduced haloperidol are significantly lower than in nonsmokers. The clearance of haloperidol was significantly greater in smokers compared with nonsmokers. It may be suggested that plasma concentrations of haloperidol should be carefully monitored when patients either start or stop smoking [42].

In a study with single dose haloperidol [97], it is observed that the elimination half-life of haloperidol in smokers is significantly shorter than in nonsmokers. Another study [98] with steady state concentrations of haloperidol shows that total plasma clearance at steady state is significantly higher in the smoking than in the nonsmoking group. Those studies suggest that smokers may require slightly higher dosages of haloperidol to maintain similar plasma concentrations-theoretically.

A study [99] which is conducted with the patients with schizophrenia shows that the nonsmokers have higher steady-state haloperidol concentrations than smokers at low dosages (<0.5 mg/kg/day). At higher doses, greater than 0.5 mg/kg/day, the difference between the steady-state concentration of haloperidol in smokers and nonsmokers is insignificant. The reason for this finding may be that high serum concentrations of reduced haloperidol saturate its back conversion to haloperidol. Smokers receiving lower dosages might convert reduced haloperidol to haloperidol faster, and thereby serum haloperidol concentrations would become undistinguishable from those in nonsmokers. This finding could imply that other CYP isozymes not induced by smoking may be involved in haloperidol disposition [42].

Results indicate that smoking may induce the enzyme(s) metabolizing haloperidol, which results in lower plasma haloperidol concentrations in smokers than in nonsmokers, particularly at low doses of haloperidol [100].

Rivastigmine is a cholinesterase inhibitor which is metabolized by cholinesterase via hydrolysis. CYP enzymes have a minor role on its metabolization. Clearance of rivastigmine is decreased by 23% after smoking cessation, so monitoring for GI (gastrointestinal) problems, dizziness and cholinergic effects is recommended after smoking cessation [101].

Risperidone is an oral atypical antipsychotic which is metabolised by CYP2D6 mainly and 3A4 partially.

Duloxetine is an SSNRI (Selective seratonine noradrenaline reuptake inhibitor) which is metabolised by CYP1A2 and 2D6 mainly.

Venlafaxine is an SNRI which is metabolised by CYP2D6, 3A4 mainly and 2C8/9, 2C19 partially.

Tramadol is an opiate agonist which is metabolised by CYP2D6 mainly, 3A4 partially. This opiate analgesic is bioactivated *in vivo* via CYP2D6. Inhibiting this enzyme would decrease the effects of analgesic. The active metabolite might also affected by, CYP enzymes.

Tizanidine is a centrally acting miyorelaxant which is metabolised by CYP1A2. The sensitivity of tizanidine to CYP1A2 inhibitors is a known interaction [102]. The CYP1A2 inhibitor ciprofloxacin recently was noted to interact with tizanidine [6]. One would expect the metabolism of tizanidine (and the metabolism of other CYP1A2 substrates) to be increased by smoking.

Table 11 Pharmacodynamic interactions between smoking and drugs [54]

Drug	Interaction	Mechanism
Benzodiazepines (Diazepam, Chlordiazepoxide)	Decreased sedation and drowsiness	Probably CNS stimulation
Beta-Blockers	Less effective for blood pressure and heart rate reduction in smokers.	Probably decreased end-organ responsiveness resulting from sympathetic activation by nicotine
Opioids (Dextropropoxyphene, pentazocine)	Decreased analgesic effect in smokers; higher doses needed to achieve analgesia.	Unknown

1.6.2. Pharmacodynamic Interactions

As smoking increases drug clearance through hepatic enzymatic stimulation, nicotinic actions may also potentiate dopaminergic and other pharmacological mechanisms. Changes in pharmacodynamic effects of drugs especially in older adults may result in increased activity of drug concentration [103].

Pharmacodynamic interactions are associated with a lesser magnitude of blood pressure and heart rate lowering during treatment with beta-blockers, less sedation from benzodiazepines and less analgesia from some opioids, most likely reflecting the effects of the stimulant actions of nicotine. Because it activates the sympathetic nervous system, nicotine can counter the pharmacologic actions of certain drugs [46, 67]. In addition to its actions on nicotinic receptors, thus modulating cholinergic activity, nicotine has been extensively evaluated for its effects upon the dopaminergic system. Nicotine has high affinity agonist binding for the nicotinic receptors on dopaminergic

neurons. In addition to many CNS functions, these neurons could be involved in the basic reward mechanism found in drug dependence. This agonistic effect results in a variety of pharmacological activities, including stimulation of dopamine release in a dose-dependent manner, development of acute and chronic tolerance and increased dopamine utilisation [104].

Insulin

Tobacco smoking may reduce blood flow to the skin and subcutaneous tissue, slowing the absorption of injected medications such as insulin. Tobacco smoking results in faster clearance of heparin, possibly related to activation of thrombosis with enhanced heparin binding to antithrombin III [54].

Antipsychotics

The interaction between antipsychotics and nicotine exposure from smoking is very complex, involving both pharmacokinetic and pharmacodynamic mechanisms, and the details remain to be elucidated. Clinicians need to be aware that smoking is a major factor that can affect the pharmacodynamics of antipsychotic drugs [42].

Oral Contraceptive Pills (OCPs)

Some of the pharmacodynamic interactions are relevant with nicotine, the main content of cigarette. The most clinically significant pharmacodynamic interaction with smoking is with combined hormonal contraceptives. The use of oral contraceptives is contraindicated in women age 35 years or older who smoke 15 or more cigarettes daily [105, 106]. The concomitant use of cigarette and oral contraceptives increases the risk of arterial adverse events such as ischemic stroke, and myocardial infarction (MI). But the clinical efficacy of hormonal contraceptives is not changed in smokers.

The interaction between smoking and oral contraceptives is a complex and deadly one; women older than 35 years old who smoke more than 15 cigarettes a day are clearly at increased risk of myocardial infarction [107].

The most clinically significant interaction of smoking occurs with **combined hormonal contraceptives.** The use of oral contraceptives increases the risk of cardiovascular adverse effects, specifically thromboembolism (e.g.,venous thrombosis, pulmonary embolism), ischemic stroke, and myocardial infarction (MI), but the risk is lower than that associated with the higher-dose oral contraceptives used in the past [108,109]. The use of oral contraceptives is contraindicated in women age 35 years or older who smoke 15 or more cigarettes daily [110,111]. Of note, the clinical efficacy of hormonal contraceptives is not reduced in smokers [67].

The efficacy of **inhaled corticosteroids** may be reduced in patients with asthma who smoke. In patients with mild asthma receiving 1000 microgram daily of inhaled fluticasone (as two puffs twice daily with a metered-dose inhaler), the increase in peak expiratory flow at three months was significantly greater in nonsmokers (27 L/ min), compared with a decrease of 5 L/min in smokers [112]. Another study of patients with mild, persistent asthma demonstrated significantly less improvement in morning peak expiratory function in smokers taking low-dose inhaled beclomethasone (400 microgram daily) than in nonsmokers (p = 0.019) [113]. These differences however were not significant in patients receiving 2000 microgram daily of inhaled beclomethasone. Practitioners should be aware that patients with chronic asthma may be less responsive to inhaled corticosteroids and should be a targeted priority for smoking cessation interventions.

Beta-blockers are shown to be less effective for blood pressure and heart rate reduction in smokers compared to nonsmokers in 2 large trials of hypertension, as well as being less effective in preventing end-organ damage [114,115]. However, in another study no difference is found of beta blocker’s benefit on myocardial infarctions prevention between the smokers and nonsmokers [116]. Since nicotine causes

catecholamine release and increases blood pressure and heart rate, this interaction is interpreted as a pharmacodynamic interaction.

Factors such as age, ethnicity, gender, concurrent use of other substances commonly abused with tobacco dependence and amount of smoking (light *vs* heavy) can also contribute towards the wide interpatient variability found between smoking and drug disposition. One of the main ingredients of tobacco – nicotine – could have additional pharmacodynamic effects. Therefore, smoking creates complex interactions with psychotropic drugs [42].

1.7. Kayışdağı Darülaceze

Kayışdağı Darülaceze is a nursing home for elderly people who are deprived socially and economically. Kayışdağı Darülaceze is a government institution which provides nursing services for elderly in need and ensures them to taking part in social life. The management of Darülaceze implements the legislation on smoking habit carefully in their facility, but taking one step forward this institution is planning to turn into a total smoking-free facilty due to its institutional structure and identity as health services providers. The management intends to facilitate the transition within two steps. Initially, the management will provide a smoking cessation program to the staff. After maintaining a decline in the number of smoking staff, management will provide the same opportunity for the patients. Through that program, the management targets to inform all smokers in the facility about the harms of smoking and support them to quit smoking.

Harms of cigarette smoking are widely established and well-known in the recent years, and that motivates people for quitting. But cigarette smoking may cause harm even in the period of cessation. Starting and quitting smoking alters the CYP enzyme levels in liver that affects the clearance of routinely used drugs. Physicians should monitor their patients whether they need a dose adjustment in case of the change on their smoking habits [117].

Increased plasma concentrations after smoking cessation may cause serious clinical consequences, particularly in the drugs with narrow therapeutic ratios. Narrow therapeutic ratio is defined according to 21 CFR 320·33(c) (United States Code of Federal Regulations) [118] as drugs having a less than two fold difference between the median lethal (LD50) and median effective dose (ED50) or a less than two-fold difference between the minimum toxic and minimum effective concentration in the blood. Examples of drugs with narrow therapeutic ratios include warfarin, clozapine, olanzapine and theophylline [34, 119].

Cigarette smoking causes pharmacokinetic alterations at different phases of drug metabolism. Vasoconstrictor effect of smoking might cause a secondary change in the absorption of drugs whereas smoking directly alters the levels of hepatic enzymes like CYP1A2 and it causes pharmacokinetic changes. Geriatric population is already under a great risk due to polypharmacy and smoking increase this risk further.

It is clear that smoking cessation can have an effect on the drugs metabolized by CYP1A2 as well as other drugs. Although no randomized controlled trials were found to document increased plasma concentrations due to smoking cessation, or the absence of researches that document appropriate post-smoking dose changes for many of these drugs there are available studies (eg. case studies, quasi-experimental studies) that provide some important evidence.

It is observed that serum concentrations of some of the interacted drugs may increase up to 40% after smoking cessation, which is particularly significant for drugs with a narrow therapeutic ratio [34]. Also propoxyphene, mexilitine, amitriptyline and diazepam have been identified as drugs that should be avoided in older adults because they pose unnecessarily high risks according to Beers criteria [120]. It is necessary to be cautious for the risks while prescribing them for older adults who quit smoking [35].

This cessation period especially important for the elderly people who are more vulnerable for the side effects of the medicines due to decline of their drug elimination related to their decreased renal functions, and the risks for this period for elderly

population should be highlighted. It is difficult to monitor all clinical changes related to drug elimination and link those alterations to changing smoking habit because of the higher numbers of patients that are living in the nursing home and only a few numbers of doctors that take care for those patients. The impact of cigarette smoking needs to be considered in planning and assessing responses to drug therapy.

The pharmacist is a health care provider who can actively participate in illness prevention and health promotion along with other members of the health care team. One of the roles of pharmacists is to provide pharmaceutical care in collaboration with patients, physicians, nurses and other healthcare providers.

Pharmaceutical care is a philosophy of practice in which the patient is the primary beneficiary of pharmacist's actions. Pharmaceutical care focuses on the attitudes, behaviors, commitments, concerns, ethics, functions, knowledge, responsibilities and skills of the pharmacist on the provision of drug therapy with the goal of achieving definite therapeutic outcomes toward patient health and quality of life [121, 122].

Clinical pharmacy is a health specialty, which describes the activities and services of clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices. It includes all the services performed by pharmacists practicing in hospitals, community pharmacies, nursing homes, home-based care services, clinics and any other setting where medicines are prescribed and used.

The term "clinical" does not necessarily imply an activity implemented in a hospital setting. It describes that the type of activity is related to the health of the patients. This implies that community pharmacists and hospital pharmacists both can perform clinical pharmacy activities.

The overall goal of clinical pharmacy activities is to promote the correct and appropriate use of medicinal products and devices. These activities aim at:

- Maximizing the clinical effect of medicines, i.e., using the most effective treatment for each type of patient

- Minimizing the risk of treatment-induced adverse events, i.e., monitoring the therapy course and the patient's compliance with therapy
- Minimizing the expenditures for pharmacological treatments born by national health systems and by the patients, i.e., trying to provide the best treatment alternative for the greatest number of patients. [123]

An extensive pharmaceutical care and plan should be applied to those elderly patients in Darülaceze who tend to quit smoking by clinical pharmacist. This pharmaceutal care and plan would save patients from the risks of undesirable effects of drugs and help the patients to maintain their compliance to the drug therapy.

2. AIM AND OBJECTIVES

Limited resources for extensive pharmaceutical care upon patients require personnel pharmaceutical care for each patient. Monitorisation of the patients' overall medical situation by clinical pharmacists would not only aid patients' pharmaceutical therapy and quality of life but also would ease the burden of other health care providers.

This study is performed to attract attention to possible smoking-drug interactions that might affect the health of the elderly people that would quit smoking during the implementation of smoking legislation in the facility and receiving more than one medication in Darülaceze.

The main aim of the present study is to investigate the potential risks of smoking-drug interactions in elderly population that will quit smoking in a pilot area (Kayışdağı Darülaceze).

In order to attain this basic objective, additional specific aims are:

-To assess the interactions between smoking and the pharmacologic groups of the drugs mostly used by the residents in Darülaceze.

-To assess the studies report the effect of smoking cessation on the metabolism of the medications currently used by Darülaceze residents.

-To highlight the potential interactions between smoking or smoking cessation and medications that should be considered in clinical and prescribing decisions [3].

-To observe the correlation between multiple drug usage and drug-smoking interactions.

-To aid the implementation of the rational patient therapy ideally.

3. MATERIALS AND METHODS

The study was conducted at the Institution of Kayışdağı Darülaceze, a government organization for elderly as a nursing home, in Istanbul, Turkey. The routinely smoking residents with multiple drug usage are evaluated in our study.

This study is approved by the Ethics Committee of Yeditepe University at 13.11.2012 with the confirmation number of 251. (Research Ethics Committee of Ministry of Health Yeditepe Research and Teaching Hospital in Istanbul, Turkey) (APPENDIX A)

3.1. Background

Kayışdağı Darülazece is the pilot area of the present study that would be a smoke-free facility in order to meet the recent smoking legislations in public buildings, hospitals and schools. The residents who are older than 55 years old with smoking habit and have one or more chronical diseases, took part in the study.

Studies that evaluate smoking-drug interactions discuss that beginning and quitting smoking may alter the metabolism of some drugs. In light of those studies and case reports, it could be said that plasma concentrations of specific drugs may alter due to cigarette smoking.

This study evaluates the medicines of 226 residents of Darülaceze and investigates any possible interactions between their drugs and cigarette smoking, and the potential risks during the period of smoking cessation.

The subjects of the present study are 226 residents of Kayışdağı Darülaceze with long term smoking habit with multiple drug usage. Those patients are expected to quit smoking via the smoking cessation program organized by the administration of the

nursing home due to its upcoming rule of being a smoke-free facility. A possible change in smoking habits of the patients might alter the pharmacokinetics of the drugs, in this case an enhancement on the effects of the drugs that the patients receive.

3.2. Study Population And Study Center

Kayışdağı Darülece has 10 living complexes in the interior units and 3 exterior units each are categorised according to the medical profiles of the patients. The present study is conducted at the living complexes named as: Güven, Papatya, Sevgi, Dolunay, Zümrüt, Çınar, Umut, Huzur and Dr. Beşir Akınal.

This work carried out over a period of the time between February 1, 2012 and May 31, 2013 with the data that was collected at February 2012.

226 patients were included and all the patients were smoking and receiving more than one medicine for a chronic disease.

3.2.1. Inclusion Criteria

-Being over 55 years old
-Being a regular smoker
-Receiving a regular pharmacotherapy.

3.2.2. Exclusion Criteria

-Being younger than 55 years old
-Being a non-smoker
-Not receiving any medical therapy.

3.3. Data Collection

Collection of the medical records and their analysis is conducted in a period of 30 days from the database of a specific patient record program of Darülaceze.

Patients' medical records were collected from the facility's database that is a special patient organizing program in a hardcopy form. The medical records include number of daily cigarette, number of years patients have been smoking, drugs currently in use, and the diseases of patients. Medical records of patients were received from the facility in the beginning of this study (February 2012) as a hardcopy and converted the records into a softcopy form using MS Excel.

3.4. Study Design

A descriptive study was performed by assessment of retrospective data that is collected from Kayışdağı Darülaceze. The potential risk of smoking cessation in elderly patients with long-time drug usage due to their chronic conditions was studied.

Medical records of patients were collected as hard copy forms and processed on Microsoft Office Excel 2007. Patient profile forms which was composed on MS Excel, contain the name of the patients, the site of Darülaceze that patient lives, number of cigarettes that patient smokes, the period of the year that patient smoke and names of patient's diseases. (Table 12)

Table 12 Appearance of MS Excel Workbook that contain patients' medical records

Patient Code	Patient Name	Name of Complex	Cigarette /Day	Year	DISEASE
80	H.GÖK.	UMUT	4		HYPERTENSION, DEMENTIA, PSYCHOSIS
111	İ.SAND.	UMUT	4		DEMETIA, DIABETES MELLITUS, PERIPHERAL VASCULAR DISEASE, HYPERTENSION
155	M.YILD	UMUT	4		HYPERTENSION
220	Y.KAR	UMUT	4		PSYCHOSIS, DEMENTIA, VENOUS INSUFFICIENCY
75	H.D.ÖZO	PAPATYA	8	20	DIABETES MELLITUS, DEPRESSION
94	H.ARS.	PAPATYA	8	15	DIABETES MELLITUS
8	A.GÜL.	ZÜMRÜT	15	50	HYPERLIPIDEMIA
32	A.GÜM.	UMUT	15		DEMENTIA, PSYCHOTIC DISORDER
42	C.ÖZT.	DOLUNAY	15		CHRONIC SCHIZOPHRENIA, MENTAL RETARDATION, HYPERTHYROID
55	E.KIL.	DOLUNAY	15		CHRONIC SCHIZOPHRENIA, PARKINSON, CHRONICAL PSYCHOSIS, PERIPHERAL ARTHERIAL DISEASE
72	G.PEVL.	HUZUR	15	30	CHRONICAL CARDIAC INSUFFICIENCY, PARKINSON, PSYCHOSIS, VENOUS INSUFFICIENCY
144	M.ÇIN	DOLUNAY	15		MENTAL RETARDATION, PSYCHOTIC DISORDER
212	V.ERD.	DOLUNAY	15		MENTAL RETARDATION, DIABETES MELLITUS

Macros and formulas were designed via Microsoft Visual Basic (version 2010) that analyses the data and evaluates the statistical outcomes. This provides a classification according to pharmacological classification of the applied medical therapies, smoking-drug interactions and number of interacted drugs. (Table 13, 14, 15, 16)

Table 13 Pharmacological groups of the patients' drugs

Drug Code	Name of Drug	Pharmacological Group
1	ABIZOL	ANTIPSYCHOTIC
2	ACTONEL	TREATMENT OF OSTEOPOROSIS
3	ADALAT CRONO	CALCIUM CHANNEL BLOCKER
4	AKINETON	ANTI-PARKINSON
5	ALDACTAZIDE	THIAZIDE DIURETIC
6	ALDACTONE	K SPARING DIURETIC
7	ALVASTIN	ANTI-HYPERLIPIDEMIC
8	ALZANT	TREATMENT OF ALZHEIMER
9	AMARYL	ANTIDIABETIC

Table 14 Interaction status of patients' drugs

Patient Code	Code of Drug	Interaction Status
1	36	NO
1	87	NO
1	143	NO
1	204	NO
1	227	NO
1	261	NO
25	225	NO
25	288	YES
26	4	NO
26	194	YES
26	243	NO

Table 15 Number of patients using drugs with smoking interaction

Name of Drug	Number of Patient
REXAPIN	31
TEOKAP	14
BRONKOLIN	13
LARGACTIL	11
NORODOL	8
RISPERDAL	7
EXELON	6
ZYPREXA	6
OLFREX	6
RILEPTID	5
ATIVAN	4
COUMADIN	4
SIRDALUD MR	4
XANAX	3

Table 16 Percentage of the drugs' pharmacological groups

Pharmacological Group	Percentage of Patient
ANTIPSYCHOTIC	54,30%
XANTHINES	19,21%
ANXIOLYTIC	5,96%
ANTIDEPRESSANT	5,96%
ALZHEIMER TREATMENT	3,97%
ANTICOAGULANT	2,65%
MYORELAXANT	2,65%
ANALGESIC	1,99%
BETA BLOCKER	1,99%
CALCIUM CHANNEL BLOCKER	0,66%
ANTIDIABETIC	0,66%

The sources which were researched about the topic of smoking-drug interactions were searched on the databases of Science Direct, Medscape, and PubMED. Keywords used were: *smoking-drug interactions, pharmacokinetics, smoking cessation, antipsychotic agents, CYP1A2, adverse effects, contraceptives, dosage, insulin* and *enzyme induction.* Micromedex, which is an online, evidence-based clinical reference program, used by terms of which further research was conducted.

3.5. Data Analysis

A list of active ingredients which are known to have a potential for smoking-drug interactions were created on MS Excel, and the active ingredients which do not have license in Turkey were excluded from the list. A list of active ingredients that are composed according to the publication searches from the scientific databases, and these two documents were compared to analyze whether there is an interaction with smoking on the medications of the smoking patients in Darülaceze. (Table 17)

Table 17 An example of the data sheet of MS excel that contains interaction results of the drugs

Patient Code	**Number of Patient's Drugs**	**Number of Interac-ting Drugs**	**Name of Drugs**				
1	24	2	DİLATREND (carvedilol)	FORADIL COMBI (formeterol fumerate + budesonide)			
2	19	3	LEVEMIR (insulin)	FORADIL COMBİ (formeterol fumerate + budesonide)	NOVORA-PID (insulin)		
3	19	5	HUMULIN R (insulin)	LANTUS (insulin)	GLUCO-BAY (acarbose)	LEVE-MIR (insulin)	COSOPT (dorsilamide + timolol)
4	18	3	VASOXEN (nebivolol)	FOSTER (beklametasone + formeterol fumerate)	COMBIGAN (timolol + brimonidine)		
5	17	3	FORADIL COMBI (formeterol fumerate + budesonide)	TEOKAP (theophylline)	FLIXOTIDE (fluticasone)		
6	17	5	LEVEMIR (insulin)	GLUCOBAY (acarbose)	LANTUS (insulin)	NOVO-MİX (insulin)	GLİFOR (metformin)
7	17	3	VASOXEN (nebivolol)	FORADIL COMBI (formeterol fumerate+budesonide)	TALOTREN (theophylline)		

An algorithm was created by assigning interaction levels for each active ingredient to make it more comprehensible and to highlight the active ingredients which bear more clinical significance where interactions occur. According to the algorithm, active ingredients were evaluated according to three different criteria. If number of publications in which the active ingredient studied was higher than 2, the score of the active ingredient was counted as 1. If any interruption occurs during routine medicine intake cause any vital risk or critical consequences like shortness in breathing (eg. theophylline), epilepsy seizure (eg. benzodiazepine) causes adverse reactions that affect overall health condition and quality of life seriously (eg. emerging symptoms of schizophrenia), and the drug has a narrow therapeutic index; another point would be added to the score of the active ingredient. And finally if all the studies claim similar data for the interaction ratios or effects of the active ingredient and the results of different studies do not conflict, a final point would be added to the active ingredient. Thus a rough classification for the clinically more important drugs that might interact with smoking, of Darülaceze patients would be presented. (Table 18, 19)

Table 18 Interaction degrees of drugs

INTERACTION DEGREES	NAME OF DRUGS
GROUP1	CHLORPROMAZINE, CLOZAPINE, HALOPERIDOL, OLANZAPINE, THEOPHYLLINE, WARFARIN
GROUP2	ALPRAZOLAM, LORAZEPAM, PROPRANOLOL, VERAPAMIL
GROUP3	AMITRYPTILINE, CLONAZEPAM, DULOXETINE, RISPERIDONE, RIVASTIGMINE, TIZANIDINE, TRAMADOL, VENLAFAXINE

Table 19 Number of patients in each interaction degree

	NUMBER OF PATIENTS WITH INTERACTION
GROUP1	103
GROUP2	11
GROUP3	40

Many researches have been conducted by several publications, concerning whether changes in the dosing regime or in the blood-plasma levels negatively affect one's health seriously. If most of the studies have reached consensus on the effects of drugs while quitting smoking, those active ingredients would be included in the group of drugs which has severe interaction degree with smoking according to this algorithm. Those drugs with severe interaction degree were analyzed in this study widely among the other groups and in the first order in the chapter of pharmacokinetic interactions (1.6.1. Pharmacokinetic Interactions). The drugs which maintain 2 criteria out of 3 were accepted in the group of drugs with moderate interaction degree with 2 points. Drugs which supply only 1 point would be accepted in the group of drugs with mild interaction degrees. The last group was not explained widely, only their possible interaction mechanism was studied.

3.6. Statistical Analysis

The correlation between multiple drug usage and smoking-drug interactions in elderly patients (age > 55 years) were investigated by using the statistical analysis program SPSS (PASW Statisticals 18) using chi square analysis. Number of drugs that patients used and number of drugs which are interacted with smoking were obtained from the patient profile forms that are composed on MS Excel formerly. (Table 12) P-

values less than 0.05 (95% confidence intervals) were regarded as statistically significant.

Correlation coefficients between smoking-drug interactions and multiple drug usage were calculated by using Pearson correlation analysis. A value of $p < 0.05$ in a two-tailed distribution was considered statistically significant.

3.7. Limitations

The nursing system is based on receiving voluntary services and since the number of residents is high, every volunteer's help is welcomed whether one has a history of any medical education or not. This situation has occasionally caused inadequate or misrecorded information in the medical records of the patients. Brand name of some drugs were recorded incorrectly, some patients' information of cigarette/day and years of smoking, diseases and drugs are not applied. Those patients with no information had to be excluded and thus might cause an incomplete assessment over the smoking patients.

4. RESULTS

The basic characteristics of 226 elderly patients that were included in the study are summarized in Table 20 and Table 21.

Table 20 Basic characteristics of the pilot population

	TOTAL	MALE	FEMALE
AGE (YEARS)	62,54	63,33	54,5
MULTIPLE DRUG USAGE	203	184	19
SMOKING DRUG INTERACTIONS	175	159	16
MEAN NUMBER OF DISEASES	2,8	2,99	1,3

Table 21 Number of Diseases of Patients

Number Of Diseases	Percentage Of Diseases
3 Diseases	30,51%
2 Diseases	22,89%
1 Diseases	18,64%
4 Diseases	16,11%
5 Diseases	9,33%
6 Diseases	1,69%
7 Diseases	0,84%

Of the 1000 residents of Kayışdağı Darülaceze, 226 (%22,6) were routine smokers. Of the 226 smokers, 19 (%8,40) patients were female, and 207 (%91,60) were male.

Out of 226 residents 51 of the patients' information regarding date of birth was not available. The mean age of 175 patients was 62,54. Out of 207 male patients, information about the date of birth was available for 159 patients, and the mean age of the males was 63,33. Out of 19 female patients, the information about the date of birth was available for 16 patients, and the mean age of the females was 54,50.

All of the 226 patients, smoking status of 140 patients were available. Those 140 patients were regular smokers and mean smoking year of the patients were 26,18 in which the longest smoking period was 65 and shortest period was 2. Information of daily smoking rate was available for 138 patients out of 226, and their mean daily smoking rate is 17,13 in the group. Maximum daily smoking rate was 40 and minimum daily smoking rate was 2.

210 patients' medication informations were available out of 226 patients. 203 out of 210 (%96,6) of the patients use more than one medication and the maximum number of drugs used were 24. Distribution of the chronic diseases is shown in Table 22. (Respiratory diseases, cardiovascular, cognitive diseases etc.)

Table 22 Classification of Patients' Diseases

Classification Of Diseases	**Percent of Patient**
CARDIOVASCULAR DISEASES	27,25%
PSYCHIATRIC DISEASES	25,45%
ENDOCRINOLOGIC DISEASES	14,07%
RESPIRATORY DISEASES	10,78%
COGNITIVE DISEASES	5,69%
VENOUS DISEASES	4,79%
NEUROLOGICAL DISEASES	4,79%
INFECTIOUS DISEASES	1,80%
UROLOGICAL DISEASES	1,50%
CEREBROVASCULAR DISEASES	1,20%
RENAL DISEASES	1,20%
HEMATOLOGICAL DISEASES	0,60%
OPHTHALMOLOGICAL DISEASES	0,30%
ONCOLOGICAL DISEASES	0,30%
DERMATOLOGICAL DISEASES	0,30%

93 (%78.8) of those 118 smoking patients had more than one chronical diseases and (% 21.2) 31 of those patients suffer from respiratory diseases.

Due to limited information, educational status and professions of the patients were not available.

The correlation between multiple drug usage and smoking-drug interactions in elderly patients which was performed with Pearson Correlation analysis in statistical analysis program SPSS, were found moderately significant through positive direction. P value was smaller than 0.05 and r value was 0.545.

Table 23 Descriptive Statistics of SPSS analysis

	Mean	Std. Deviation	N
Number of Used Drugs	7,68	4,057	210
Number of Interacted Drugs	1,18	1,147	210

Table 24 Correlation analysis of multiple drug usage and smoking-drug interactions

		Number of Used Drugs	Number of Interacted Drugs
Number of Used Drugs	Pearson Correlation	1	,545**
	Sig. (1-tailed)		,000
	N	210	210
Number of Interacted Drugs	Pearson Correlation	,545**	1
	Sig. (1-tailed)	,000	
	N	210	210

**Correlation is significant at the 0,01 level (1-tailed).

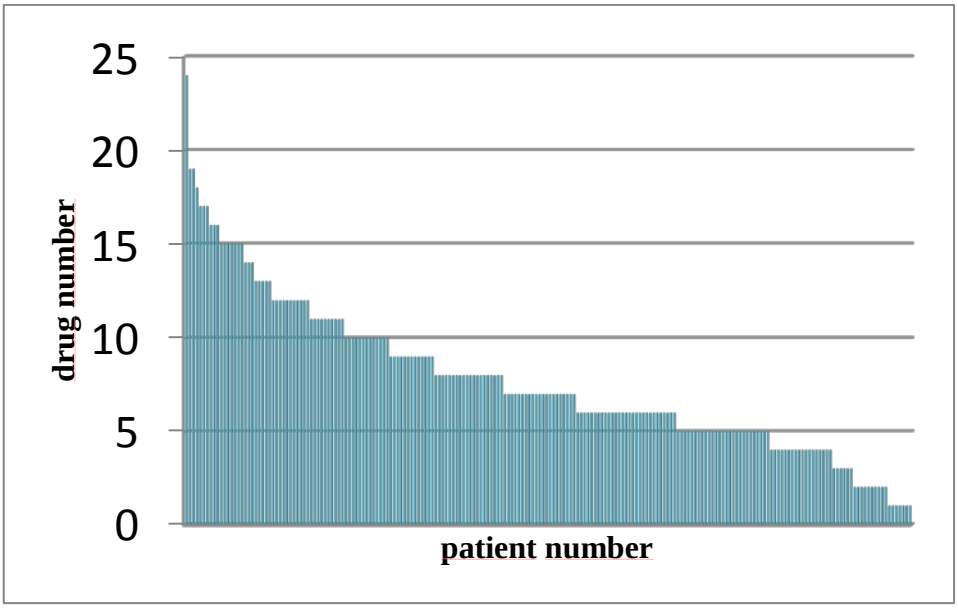

Figure 6 Total number of drugs used by patients

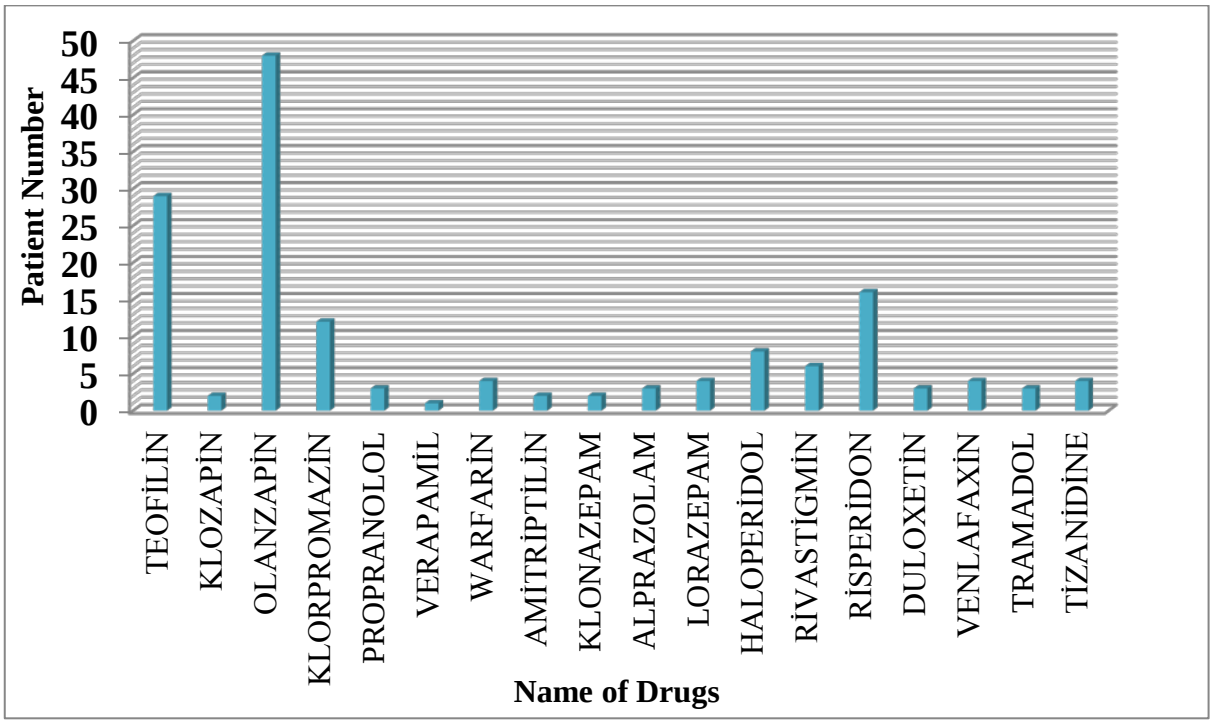

Figure 7 Number of patients according to the active ingredients that interact with smoking

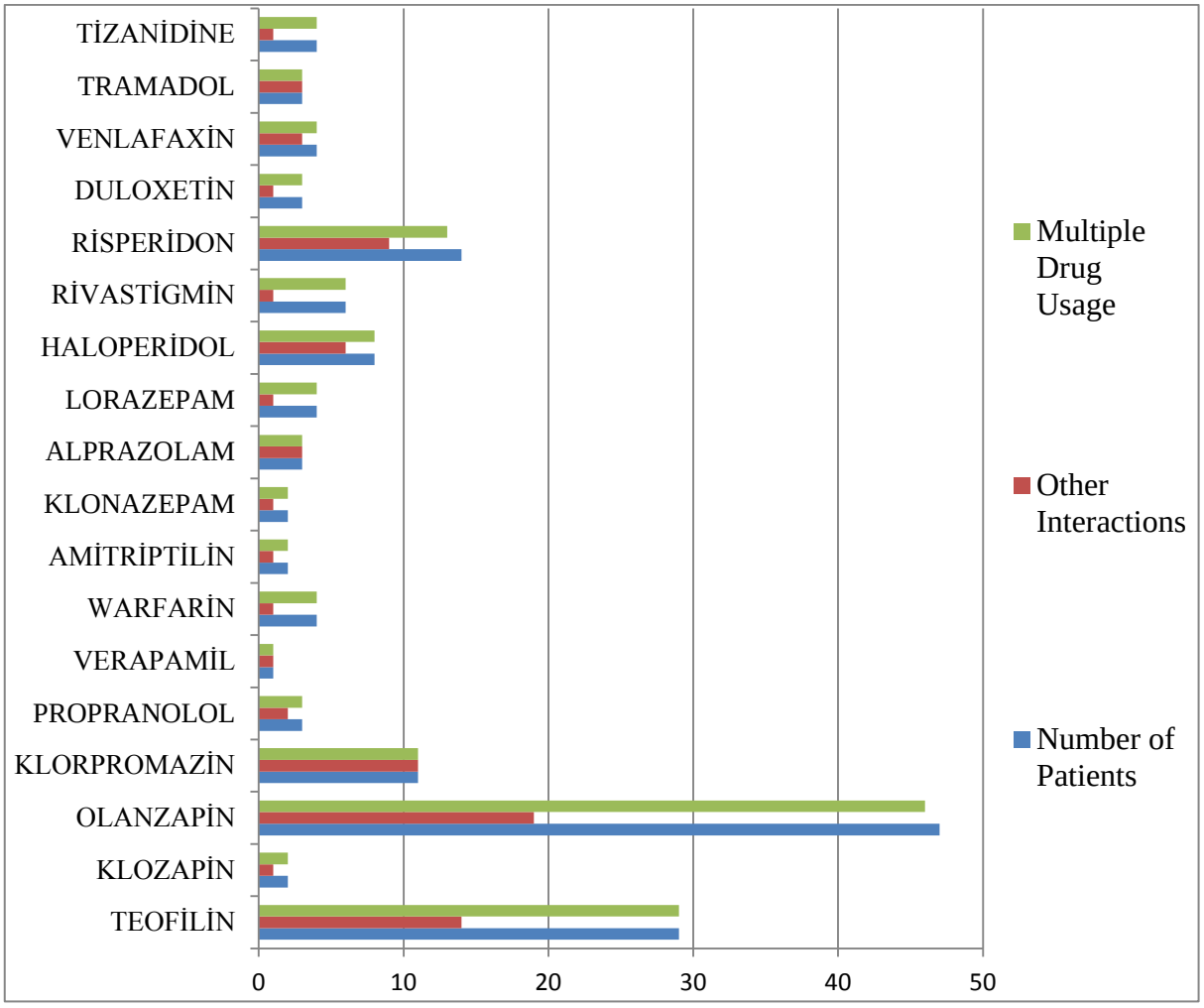

Figure 8 Analysis of multiple drug usage and number of drugs that interact with smoking

5. DISCUSSION

Importance of drug dosage adjustment on patients with smoking habit is studied several times even as cases or evidence based studies. Although variations in plasma concentrations of drugs cannot be documented with randomized controlled trials, other available studies maintain information on the variation of blood levels of drugs after smoking cessation. A change in blood plasma concentration is particularly significant for drugs with a narrow therapeutic ratio.

Interactions are caused by components of tobacco smoke – not nicotine – and nicotine replacement therapy will not affect changes in medication levels caused by smoking cessation [2]. Cigarette smoking should be specifically studied in clinical trials of new drugs [54]. It appears that every inducer has its own pattern of induction; knowledge of the main mechanism is often not sufficient to predict the extent and time course of induction, but may serve to make the clinician aware of potential dangers.

It can be understood that smoking has incontrovertible effects on the metabolism of drugs by reviewing studies up to date. It is observed that PAHs in the cigarette smoke induce enzymes like CYP1A2 that plays an important role in the drug metabolism. Alteration in pharmacokinetics may change blood-plasma concentrations of drugs. It is vital to maintain a balanced and stable plasma concentration of drugs especially with chronical diseases like diabetes, schizophrenia, and cardiac arrhytmies. Risk of alteration of those drugs' plasma concentration should be evaluated in case of smoking cessation.

The effect of smoking cessation on drug metabolism by controlled studies has been tried to be interpreted practically via theories on pharmacokinetics of drug metabolism. The data related to smoking-drug interactions which is used in the present study is obtained from the case studies and the limited controlled studies that involve small number of subjects instead of comprehensive controlled studies with sufficient number of subjects. Noteworthy studies attract attention about the effects of smoking cessation

of patients on antipsychotics due to important side effects of the drugs and/or recurrence of the psychotic conditions symptoms, nevertheless any agreed quantitative data is not available about the effect of smoking cessation on plasma concentrations of the antipsychotics. Although there are some available results on plasma concentrations of drugs or drug metabolism rates, it is still harder to get a clear output due to the variety of genetic factors, quantity of the number of subjects, and applying the right drug dosage.

It is clear that smoking cessation can have an effect on drugs metabolized by CYP 1A2 as well as some other drugs. Although researches have not documented appropriate post-smoking dose changes for many of these drugs, clinically significant drug interactions should be beared in mind, because lack of adequate studies does not make the hypothesis less noteworthy. This study is performed to highlight those interactions. Drug metabolism changes related to smoking cessation could be particularly important in diabetics who are maintaining tight control, patients with anticoagulant therapy or antipsychotic therapy or in older adults, whose drug metabolism is affected by aging and who are more likely to be taking multiple drugs.

Although no evidence of clinical problems and no dosage recommendations were found for propoxyphene, mexilitine, amitriptyline and diazepam, these have been identified as drugs that should be avoided in older adults because they pose unnecessarily high risks according to Beers criteria, supporting the need for caution when prescribing them for older adults who quit smoking [35].

Considering all those factors that are mentioned above it should be emphasized that the population in nursing homes are much more vulnerable and susceptible to smoking-drug interactions. This interpretation was verified by scanning the medicine regimes of Darülaceze residents which included usually multiple drug usage. Metabolism rates of elderly population slow down gradually through aging process. Therefore, presence of a clinical pharmacist is necessary to take care of the patients, to assess overall medical profile and drug therapy bearing in mind the patients' physiological capacity.

Studies that analyze the risks of smoking-drug interactions, point to importance of the smoking habit of patients, and physicians should bear in mind the possible risks for a patient quitting smoking with a routine medical therapy. Patients in Darülaceze have private examination routines with doctors. Volunteer doctors visit and examine the patients in their specialty and the patients' routine medicines and physical conditions might not play a big role in treatment plan due to high number of the residents and limited number of doctors. Thus it would be a heavy load for doctors to keep in mind of all routine drugs of the patients (drug-drug interactions), smoking habits (smoking-drug interactions), consumption of herbal products (drug-herb interactions), while examining the patients and prescribing medications during a limited examination period.

5.1. Relevance to clinical practice

Since smoking rates of population remain high worldwide, it is important for health care providers in community and in acute care settings to determine a patient's smoking status and to obtain a list of all current medications. Immediate dose reductions should be applied whenever patients cease smoking under treatment with CYP1A2 metabolised drugs with a narrow therapeutic ratio such as olanzapine, clozapine and theophylline. Although an early warfarin study failed to document changes in prothrombin time, this study did find increased serum levels and decreased warfarin clearance rates of 13%, consistent with later case studies documenting increased INR and an adjustment for doses is needed by the amount of %14 and 23%. Based on this evidence, health care providers should anticipate the need to decrease warfarin dose by 13–23% in people who stop smoking. Careful monitoring for signs of overdose or increased adverse drug effects should be instituted for other drugs listed in this article, especially for older adults who use multiple medications. This recommendation has particular relevance for hospitalized patients who are abruptly subjected to involuntary smoking cessation due to the speed at which the induction of CYP1A2 dissipates [35].

6. CONCLUSION

Potential risks of the smoking-drug interactions in elderly population are investigated in this study. In addition to those risks it must also considered that usage of more than one medication at the same time increases the risks. Beers criteria studies assess the data about concomitant drug usage. All these factors emphasize the vulnerability and susceptibility of the population.

When all of these health risks are assessed, there needs to be other health professions to manage the clinical problems of elderly patients living in nursing home such as Darülaceze, where population of the patients is high and doctors may not be able to take care of the patients' whole medical profile apart from the treatment of their specialty. So, a clinical pharmacist could be employed to take care of the patients overall health issues while taking into consideration drug-drug interactions, drug-food interactions, drug-smoking interactions and to control the risk assessments of the patients.

As clear guidelines for clinical practice are not available, a general approach for smoking-drug interactions should be taken. On starting CYP1A2 substrates; the patient's smoking status should be obtained, efficacy and possible adverse effects of the drugs should be monitored closely, dose adjustment should be assessed if necessary, and smoking status of the patient should be monitored routinely.

In case of smoking cessation of patients who are at risk for smoking- drug interactions of their drugs that are used routinely; interaction status of drugs should be investigated, clinical significance of any potential interaction should be determined, possible adverse effects of drugs should be monitored closely, and dose adjustment should be applied if necessary.

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APPENDIX A: Ethics Committe Approval Document

Approval document of Research Ethics Committee of Ministry of Health Yeditepe Research And Teaching Hospital in Istanbul, Turkey. Approval date is 13.11.2012 with the confirmation number of 251.

YEDİTEPE ÜNİVERSİTESİ HASTANESİ

YEDİTEPE ÜNİVERSİTESİ KLİNİK ARAŞTIRMALAR ETİK KURULU KARAR FORMU

KURUL ADI	**YEDİTEPE ÜNİVERSİTESİ KLİNİK ARAŞTIRMALAR ETİK KURULU**
AÇIK ADRES	YEDİTEPE ÜNİVERSİTESİ HASTANESİ Devlet Yolu Ankara Cad. No: 102-104, 34752 Kozyatağı, İstanbul
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BAŞVURU BİLGİLERİ	ARAŞTIRMANIN AÇIK ADI	Smoking Cessation :Potential Smoking-Drug Interactions In Elderly Patients With Polypharmacy		
	ARAŞTIRMA PROTOKOLÜNÜN KODU			
	EUDRACT NUMARASI			
	SORUMLU ARAŞTIRMACI ÜNVANI/ADI/SOYADI	Yrd.Doç.Dr.Philips Martin Clark Ecz.Gözde Kaftan		
	SORUMLU ARAŞTIRMACININ UZMANLIK ALANI	Klinik Eczacılık		
	KOORDİNATÖRÜN ÜNVANI/ADI/SOYADI			
	KOORDİNATÖRÜN UZMANLIK ALANI			
	ARAŞTIRMA MERKEZİ	Darülaceze Müessese Müdürlüğü		
	ARAŞTIRMA MERKEZİNİN AÇIK ADRESİ	Darülaceze Müessese Müdürlüğü		
	DESTEKLEYİCİ VE AÇIK ADRESİ			
	DESTEKLEYİCİNİN YASAL TEMSİLCİSİ VE ADRESİ			
	UZMANLIK TEZİ/AKADEMİK AMAÇLI	UZMANLIK TEZİ ☒	AKADEMİK AMAÇLI ☐	
	ARAŞTIRMANIN FAZI VE TÜRÜ	FAZ 1	☐	
		FAZ 2	☐	
		FAZ 3	☐	
		FAZ 4	☐	
		BE/BY	☐	
		DİĞER	☒	Diğer ise belirtiniz:Gözlemsel Araştırma
		İLAÇ DIŞI ARAŞTIRMA	☐	Belirtiniz:
	ARAŞTIRMAYA KATILAN MERKEZLER	TEK MERKEZ ☒	ÇOK MERKEZLİ ☐	ULUSAL ☒ / ULUSLARARASI ☐

	Belge Adı	Tarihi	Versiyon Numarası	Dili
DEĞERLENDİRİLEN BELGELER	ARAŞTIRMA PROTOKOLÜ	23.10.2012		Türkçe ☒ İngilizce ☐ Diğer ☐
	ARAŞTIRMA BROŞÜRÜ			Türkçe ☐ İngilizce ☐ Diğer ☑
	BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU			Türkçe ☐ İngilizce ☐ Diğer ☐
	OLGU RAPOR FORMU			Türkçe ☒ İngilizce ☐ Diğer ☐

	Belge Adı		Açıklama
DEĞERLENDİRİLEN DİĞER BELGELER	ARAŞTIRMA BÜTÇESİ	☐	
	SİGORTA	☐	
	HASTA KARTI/GÜNLÜKLERİ	☐	
	İLAN	☐	
	YILLIK BİLDİRİM	☐	

YEDİTEPE ÜNİVERSİTESİ HASTANESİ

YEDİTEPE ÜNİVERSİTESİ KLİNİK ARAŞTIRMALAR ETİK KURULU KARAR FORMU

	SONUÇ RAPORU	☐	
	GÜVENLİLİK BİLDİRİMLERİ	☐	
	DİĞER	☐	

KARAR BİLGİLERİ	**Karar No:** 251	**Tarih:13.11.2012**
	Yrd.Doç.Dr.Phılıps Martın Clark ve Ecz.Gözde Kaftan sorumluluğunda yapılması tasarlanan ve yukarıda başvuru bilgileri verilen klinik araştırma başvuru dosyası ve ilgili belgeler araştırmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş, gerçekleştirilmesinde etik bir sakınca bulunmadığına toplantıya katılan etik kurulu üyelerinin oy çokluğu ile karar verilmiştir.	

ETİK KURULU BİLGİLERİ

ÇALIŞMA ESASI	Klinik Araştırmalar Hakkında Yönetmelik, İyi Klinik Uygulamaları Kılavuzu, Yeditepe Üniversitesi Tıp Fakültesi, Klinik Araştırmalar Etik Kurulu Kuruluş ve Çalışma Esasları.

ETİK KURUL BAŞKANI UNVANI/ADI/SOYADI: Prof. Dr. R. Serdar ALPAN

ETİK KURULU ÜYELERİ

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Cinsiyet		İlişki *		Katılım **		İmza
Prof. Dr. R. Serdar Alpan	Farmakoloji	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. M. Reha Cengizlier	Pediatri	YÜTF	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	MAZERETLİ
Prof. Dr. S. Sami Kartı	Hematoloji	YÜTF	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	
Prof. Dr. Serdar Öztezcan	Biyokimya	YÜTF	E ☒	K ☐	E ☐	H ☐	E ☐	H ☐	MAZERETLİ
Doç. Dr. Baki Ekçi	Genel Cerrahi	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Ferda Özkan	Patoloji	YÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Prof.Dr. Dr. Nural Bekiroğlu	Biyoistatistik	MÜTF	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	MAZERETLİ
Doç. Dr. Esra Can Say	Diş Has. Ted.	YÜDF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Doç. Dr. Meriç Köksal	Eczacılık	YÜEF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Ali Rıza Okur	Hukuk	YÜHF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof. Dr. Başar Atalay	Beyin Cerrahi	YÜTF	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Yrd.Doç.Dr.Nesrin Sarıman	Göğüs Hastalıkları	MÜTF	E ☐	K ☒	E ☐	H ☐	E ☐	H ☐	MAZERETLİ
Yrd.Doç.Dr.Esin Öztürk Işık	Biyomedikal Mühendisi	YÜTF	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Bilge Firuzbay	Sivil Üye/Emekli		E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	

* : Araştırma ile İlişki
** : Toplantıda Bulunma

Önemli Not: Çalışmanızın Klinik Araştırmalar Etik Kurulu tarafından onaylanan protokole göre yürütülmesi ve çalışma protokolündeki değişiklilerin kurulumuza bildirilmesi gerekmektedir.

T.C.
İSTANBUL BÜYÜKŞEHİR BELEDİYE BAŞKANLIĞI
Sağlık ve Sosyal Hizmetler Daire Başkanlığı İstanbul Darülaceze Müdürlüğü

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Konu :Sigara Kullanımı ve Polifarmisi

Sayın Philip Martin Clark

Yeditepe Üniversitesi Eczacılık Fakültesi
Klinik Eczacılık Anabilim Dalı Başkanı

İlgi:26.01.2012 tarihli dilekçeniz

İlgi dilekçede Yeditepe Üniversitesi Klinik Eczacılık Anabilim dalı olarak "Darülaceze Sakinlerinin Sigara Kullanımı ve Polifarmisi " konulu nikotinin hastaların kullandıkları ilaçlar üzerine ve hastaların mevcut hastalıklarına etkisini inceleyen bir çalışma yapmak istediğinizi belirterek bu çalışma kapsamında hastaların kullandığı ilaçlar, hasta hikayesi, hasta ve personelle görüşme talebinde bulunmaktasınız.

Söz konusu talebiniz Müdürlüğümüz tarafından uygun bulunmuştur.

Gereğini rica ederim.

İsrafil AYDIN
İstanbul Darülaceze Müdürü

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CURRICULUM VITAE
GOZDE KAFTAN

Gozde Kaftan was born on 16.03.1986 in Canakkale, Turkey. She graduated with a B.Sc. (Pharmacy) degree in 2009 from Yeditepe University, Faculty of Pharmacy. She started to work as a Pharmacy Manager in the Pharmacy For Practice in Yeditepe University Faculty of Pharmacy in 2010. In the same year, she started her M.Sc. degree in Clinical Pharmacy Programme and her M.Sc. thesis entitled "Smoking-Drug Interactions With Multiple Drug Usage In Elderly People'' under the supervision of Assist. Prof. Dr. Philip Martin Clark in the Department of Clinical Pharmacy in Yeditepe University. Gozde Kaftan is currently employed as Drug Safety Officer in **Bilim Pharmaceuticals in Istanbul, Turkey.**