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THE EVALUATION OF HEALTH CARE PRACTITIONERS' PERSPECTIVES BY DRUG BURDEN INDEX ON PERSCRIBED MEDICATIONS FOR OLDER TURKISH ADULTS

MASTER THESIS

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ONAY

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

/ / 2018

Abdelrahman SALHIN ABDELBARY

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LIST OF SYMBOLS AND ABBREVIATIONS

ACB	Anticholinergic Cognitive Burden scale
Ach-DBI	Anticholinergic Drug Burden Index
ACTH	Adrenocorticotropic Hormone
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ANOVA	Analysis of Variance
BUN	Blood Urea Nitrogen
CYP450	Cytochrome P450
DBI	Drug Burden Index
DDI	Drug-Drug Interactions
DLB	Dementia with Lewy Bodies
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GIT	Gastrointestinal Tract
HgbA1C	Hemoglobin A1C
IP	Inappropriate Prescribing
MCI	Mild Cognitive Impairment
MRDD	Minimum Recommended Daily Dose
OAB	Overactive Bladder
OTC	Over the Counter drugs
PIM	Potentially Inappropriate Medications
Sed-DBI	Sedative Drug Burden Index
START	Screening Tool to Alert doctors to the Right Treatment
STOPP	Screening Tool of Older Persons Prescriptions
UI	Urinary Incontinence
WHO	World Health Organization

ABSTRACT

Salhin, A. (2018). The Evaluation of Health Care Practitioners' Perspectives by Drug Burden Index on Prescribed Medications for Older Turkish Adults. Yeditepe University, Institute of Health Science, Department of Clinical Pharmacy, MSc thesis, Istanbul.

The aim of the study is to determine the value of the Drug Burden Index (DBI), the demographic and clinical factors that may affect the DBI and evaluate the health care practitioners practice according to the DBI in Turkey. 520 Prescriptions of male and female patients 40 years old or more was randomly extracted from 11 pharmacies from six different cities in Turkey. The Drug Burden Index was then calculated for each prescription and a retrospective analysis was performed according to patient's age, gender, number of drugs, number of morbidities, diagnosis and physician's specialty. The mean age for all patients was 62.43 ± 0.57 (Mean ± SEM) and 52.3% were female. 1412 drug was prescribed with a total mean of 2.72 ± 0.065 drug per prescription. The number of drug consumption increased significantly with age ($p = 0.007$). 221 prescriptions (42.5%) were written by general practitioners and family doctors, while 299 prescriptions (57.5%) were written by specialist physicians. The mean DBI was found to be 0.206 ± 0.017, the Anticholinergic Drug Burden Index (Ach-DBI) was found to be 0.196 ± .016 and Sedative Drug Burden Index (Sed-DBI) was found to be 0.01 ± 0.004. 156 prescription included at least one drug with anticholinergic or sedative effect, with prevalence percentage of DBI > 0 of 30% and prevalence percentage of DBI ≥ 1 of 5.8% of total prescriptions. The DBI increased significantly with the increase in number of drugs consumed and the number of disease diagnosed per patient ($p < 0.0001$). As a conclusion, Health care practitioners need to pay more attention to the DBI when prescribing for elderly patients, in order to reduce the risk of anticholinergic and sedative adverse events.

Key Words: Drug Burden Index, Anticholinergics, Sedatives, Aging, Elderly, Turkey.

Özet

Salhin, A. (2018). İlaç Yükü Endeksine göre, yaşlı erişkinlerin reçetelerinin ve Sağlık hizmeti uygulayıcılarının durumunun değerlendirilmesi. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Klinik Eczacılık AD, Master tezi, İstanbul.

Bu çalışmanın amacı, İlaç Yükü Endeksinin değerini ve İlaç Yükü Endeksini etkileyebilecek demografik ve klinik faktörleri belirlemek ve Türkiye'deki Sağlık Hizmeti uygulayıcılarının İlaç Yükü Endeksine göre değerlendirmektir. 40 yaş ve üzeri 520 kadın ve erkek hastanın reçeteleri, Türkiye'nin altı farklı şehrinden ve 11 farklı eczaneden, rasgele olarak toplanmıştır. Daha sonra her bir reçete için İlaç Yükü Endeksi hesaplanarak hastanın yaşına, cinsiyetine, ilaç sayısına, hastalık sayısına, tanılara ve hekimlerin uzmanlık alanına göre retrospektif bir analiz yapılmıştır. Tüm hastaların ortalama yaşı 62.43 ± 0.57 ve % 52.3'ü kadındır. Reçetelerindeki toplam ilaç sayısı 1412 ve reçete başına ortalama 2.72 ± 0.065'tir. İlaç tüketimi sayısı yaşla birlikte istatistiksel olarak anlamlı biçimde artmıştır ($p = 0.007$). Pratisyen hekimleri ve aile hekimleri tarafından 221 (% 42.5), uzman hekimleri tarafından 299 reçete (% 57.5) yazılmıştır. Ortalama İlaç Yükü Endeksi 0.206 ± 0.017, Antikolinerjik İlaç Yük Endeksi 0.196 ± 0.016, Sedatif İlaç Yük Endeksi ise 0.01 ± 0.004 olarak bulunmuştur. 156 reçete en az bir antikolinerjik veya sedatif etkisi olan ilacı kapsamaktadır. Bununla birlikte, İlaç Yükü Endeksi sıfırdan fazla olan reçetelerin yaygınlığı % 30 ve İlaç Yükü Endeksi birden fazla olan reçetelerin yaygınlığı % 5.8'dir. İlaç Yükü Endeksi, hem hasta başına tüketilen ilaç sayısı hem de teşhis edilen hastalık sayısı ile önemli ölçüde artmıştır ($p < 0.0001$). Sonuç olarak, antikolinerjik ve sedatif yan etki riskini azaltmak için, sağlık hizmeti uygulayıcılarının yaşlı hastalar için reçete yazarken İlaç Yükü Endeksine daha fazla dikkat etmeleri gerekmektedir.

Anahtar Kelimeler: İlaç Yükü Endeksi, Antikolinerjikler, Sedatifler, Yaşlanma, Yaşlılık, Türkiye.

1. INTRODUCTION

The proportion of older people in the population is increasing globally. It is estimated that 22% of the world's total population will be over 60 years of age by 2050 (1). In Turkey, the number of elderly people (those above 65 years) has been increased between 2012 – 2106 by 17.1%, to reach 8.3% of the whole population in 2016 (2). Furthermore, other evidence shows that the largest per person consumption of medicines is by older people, especially the oldest old (aged over 84 years) (3). This age group is usually associated with physiological changes that affect both Pharmacokinetics (absorption, distribution, metabolism and elimination) and Pharmacodynamics properties (4). These changes in physiological characteristics of elderly people have a significant impact on pharmacotherapy plans and interactions e.g. the increased volume of distribution of lipophilic medicines as a result of an increase in adipose tissue e.g. diazepam (4). Consequently, if these changes are not put in consideration may lead to inappropriate prescribing.

The physiological changes and the high number of chronic diseases and morbidities that occur in elderly people may lead to some problems that are generally known as geriatric syndromes. Geriatric Syndromes is the collective name for a range of multifactorial health issues that involves the interaction between identifiable situation-specific stressors and underlying age-related risk factors, resulting in damage across multiple organ systems (5,6). The most common geriatric syndromes are delirium, falls, frailty, pressure ulcers, dizziness, syncope, functional decline and urinary incontinence (7).

Medicines can significantly improve a range of health outcomes, yet it can also cause considerable harm and other unexpected effects such as adverse drug reactions (ADR) and drug-drug interactions (DDI) especially in elderly people (8). Polypharmacy (commonly defined as the use of five or more regular medications) is also considered an important issue that are more seen in old ages due to the physiological changes and the high number of chronic diseases and morbidities (9). The prevalence of polypharmacy increases with age and has been estimated to occur in 20–40% of people at the age of 65 years (10,11). Polypharmacy is a complex problem that can often lead to non-adherence, ADRs, DDIs, and

increased emergency room visits, hospitalizations, and nursing home admissions (12). Polypharmacy has been also proven to be one of the risk factors of some geriatric syndromes as cognitive Impairments, delirium, falls and urinary incontinence (13).

Although a lot of drugs are consumed by elderly people, some are more consumed than others. A study revealed that the most common drug classes prescribed in a 1-year period for ambulatory Medicare patients were cardiovascular agents, antibiotics, diuretics, analgesics, antihyperlipidemics, and gastrointestinal agents (14). The most common nonprescription medications consumed by older adults were analgesics (aspirin, acetaminophen, and ibuprofen), cough and cold medications (diphenhydramine and pseudoephedrine), vitamins and minerals (multivitamins, vitamins E and C, calcium), and herbal products (ginseng, *Ginkgo biloba* extract) (15). Many of these drugs most commonly prescribed in older people have anticholinergic (16) and sedative effects (17,18), in addition inappropriate use of these medications is associated with ADRs (19).

Anticholinergic and sedative medications overuse has been associated with physical and cognitive limitations (20). The muscarinic receptor blocking action of anticholinergics may cause dry mouth, constipation, blurred vision, increased heart rate, and confusion (21). The ADRs of these drugs can be a reason for many of the geriatric syndromes to take place, which affects the quality of life of elderly people. For example, the use of drugs with central nervous system depressant effects as sedatives is associated with an estimated 50% increased risk of falling in older people (22,23). Benzodiazepine use has been associated with lower functional status decline in physical performance (24) and lower memory test scores (25). On the other hand, further evidence propose that physicians may be less aware that some medications that are not prescribed for their anticholinergic properties in older adults may have peripheral or central anticholinergic effects (6,27). This can be understood within the fact that more than 600 drugs have been shown to have some degree of anticholinergic activity (27).

Prescribing for older people requires careful assessment of the benefits and risks of all of the patient's medications (28). Medication management for older adults is fast becoming a challenge for health care professionals, and establishing the balance between the

benefits and risks of medication use is often difficult (29). Besides, Evidence to guide prescribing is limited by the exclusion of older adults with multiple medical conditions from participation in many of the controlled clinical trials (30). Thus, determination of potentially inappropriate medication use in older people is guided mainly by expert consensus statements such as the updated Beers criteria (31). Since a lot of studies have linked polypharmacy, anticholinergic and sedative drugs to wide range of ADRs in older adults, the need for evidence based risk assessment tools has been risen. One of these tools that has been developed in the past few years was the Drug Burden Index (DBI).

The DBI is an evidence based pharmacological risk assessment tool that measures a patient's total exposure to medications with anticholinergic and sedative properties (30). A higher DBI is associated independently with hospitalization, frailty, falls and impairments in function necessary for independent living in older adults (32). One of the most important features that categorize the DBI than other anticholinergic and sedative assessment tools, is that it includes the daily drug dose in the assessment (30).

The DBI has been tested in many countries in the world as Australia, Canada, USA, UK and Finland (29). However, it has not been thoroughly investigated in Turkey. Performing such a study and an investigation in Turkey will be important to determine if there is misuse of anticholinergic and sedative drugs in older patients in Turkey and determine the factors and reasons that may be behind this misuse. Moreover, there may be clinical recommendations that can be given to the health care professionals in Turkey according to the result of this research. Additionally, this data can be used for further researching and investigation about the use of drugs that have anticholinergic and sedative drugs in older people in Turkey especially in researches related to Alzheimer disease and other geriatric problems and syndromes.

The aim of this thesis is to determine the value of the DBI, the demographic and clinical factors that affect the DBI and evaluate the health care practitioners practice according to the DBI in older adults in Turkey by using the data of 520 prescriptions belongs to 40 years old and over patients that was randomly collected from 11 pharmacies from different regions of Turkey.

2. PHARMACOTHERAPY PROBLEMS IN AGING PEOPLE

According to the world report on ageing and health released by the WHO in 2015, ageing is the complex changes that are, at a biological level, associated with gradual accumulation of a wide variety of molecular and cellular damage, while over time, this damage leads to a gradual decrease in physiological reserves, an increased risk of many diseases, and a general decline in the capacity of the individual. Ultimately, it will result in death. Consequently, these problems associated with ageing needs to be well identified and solutions have to be made for these problems in order to increase the capacity and the functioning of elderly population especially with the increase of their percentage in nowadays societies and their predicted increase in tomorrow's societies as well.

2.1. Age-Associated Physiological and Pharmacological Changes

Pharmacotherapy of the elderly is very complex due to age-related physiologic changes, multiple comorbidities, multiple medications (prescription, over-the counter, and herbal), and multiple providers (prescribers and pharmacies). Age-related physiologic changes and disease-related changes in organ function affect drug handling (pharmacokinetics) and response (pharmacodynamics) (12).

Time modifies many biologic processes. Aging is characterized by progressive and broadly predictable changes that are associated with increased susceptibility to many diseases. Aging is not a homogenous process. Rather, organs in the same person age at different rates influenced by multiple factors, including genetic make-up, lifestyle choices, and environmental exposures (33). A Danish twin study found that genetics accounted for about 25 percent of the variation in longevity among twins, and environmental factors accounted for about 50 percent (34). However, with greater longevity (to age 90 or 100), genetic influences became more important.

2.1.1. Age-Associated Physiologic Changes

2.1.1.1. Physiological Rhythms

The organization of rhythmic physiologic processes is altered by aging. Age impacts the circadian pattern of body temperature, plasma cortisol, and sleep and can cause desynchronization or "internal phase drift." Phase advances can lead to the occurrence of some rhythmic functions (e.g. the 24-hour body temperature trough and sleep onset) one to two hours earlier in older adults (33). The pulsatile secretion of gonadotropins, growth hormone, thyrotropin, melatonin, and adrenocorticotropic hormone (ACTH) are attenuated with age (35). One source of this dysfunction appears to be neuronal loss in the suprachiasmatic nucleus in the hypothalamus (36). In addition, age may delay the ability to reset physiologic rhythms to a new photoperiod.

2.1.1.2. Loss of Complexity

Loss of complexity, a concept derived from the field of nonlinear dynamics, may be a general principle of all aging systems (37). This loss of complexity may result in decreased heart-rate variability, blood-pressure variability, electroencephalographic frequencies, response to auditory frequencies, and response to stress. Age-related loss of complexity may not be immutable, however; as an example, senior athletes show greater heart rate variability than sedentary age-matched controls (38).

2.1.1.3. Homeostenosis

Homeostenosis refers to the concept that, from maturity to senescence, diminishing physiologic reserves are available to meet challenges to homeostasis. This concept was first recognized by Walter Cannon in the 1940s (39). Homeostenosis leads to the increased

vulnerability to disease that occurs with aging. The endpoint of this process is frailty, where even the smallest challenge overwhelms the available reserves and results in disaster. The "precipice" may be variably defined: death, cardiac arrest, hospital admission, or onset of a symptom such as confusion or incontinence. Aging itself brings the individual closer to the precipice by the loss of physiologic reserves. With aging, the area in which the older person can bring themselves back to homeostasis by invoking their reserves narrows or becomes stenotic (33).

Maintaining homeostasis is a dynamic, active process. Frailty is the state when physiologic reserves are maximally invoked just to maintain homeostasis and any challenge will cross some threshold. Increased severity of illness and frailty have independent effects on patient outcomes (40). This increased vulnerability is in part because the older person is continually expending reserves to compensate for primary age changes, as well as other processes that are absent or trivial in the younger individual (33).

2.1.1.4. Major Physiological Changes in Organs and Systems During Aging

Table 2.1. Major organs and systems changes during aging (41)

Endocrine system	➢ Impaired glucose tolerance (fasting glucose increased 1 mg/dl/decade; postprandial increased 10 mg/dl/decade) ➢ Increased serum insulin and increased HgbA1C nocturnal growth hormone peaks lost, decreased Insulin-Like Growth Factor 1 ➢ Marked decrease in dehydroepiandrosterone (DHEA) ➢ Decreased free and bioavailable testosterone ➢ Decreased Triiodothyronine (T3) ➢ Increased parathyroid hormone (PTH) ➢ Decreased production of vitamin D by skin ➢ Ovarian failure, decreased ovarian hormones ➢ Increased serum homocysteine levels
Cardiovascular	➢ Unchanged resting heart rate (HR), decreased maximum HR ➢ Impaired left ventricular filling ➢ Marked dropout of pacemaker cells in sinoatrial node ➢ Increased contribution of atrial systole to ventricular filling

	➢ Left atrial hypertrophy ➢ Prolonged contraction and relaxation of left ventricle ➢ Decreased inotropic, chronotropic, lusitropic response to beta-adrenergic stimulation ➢ Decreased maximum cardiac output ➢ Decreased hypertrophy in response to volume or pressure overload ➢ Increased serum atrial natriuretic peptide (ANP) ➢ Large arteries increase in wall thickness, lumen, and length, become less distensible, and compliance decreases ➢ Subendothelial layer thickened with connective tissue ➢ Irregularities in size and shape of endothelial cells ➢ Fragmentation of elastin in media of arterial wall ➢ Peripheral vascular resistance increases
Blood pressure	➢ Increased systolic blood pressure (BP), unchanged diastolic BP ➢ Beta-adrenergic-mediated vasodilatation decreased ➢ Alpha-adrenergic-mediated vasoconstriction unchanged ➢ Brain autoregulation of perfusion impaired
Pulmonary	➢ Decreased FEV1 and FVC ➢ Increased residual volume ➢ Cough less effective ➢ Ciliary action less effective ➢ Ventilation–perfusion mismatching causes PaO_2 to decrease with age: 100 - (0.32*age) ➢ Trachea and central airways increase in diameter ➢ Enlarged alveolar ducts due to lost elastic lung parenchyma structural support result in decreased surface area ➢ Decreased lung mass ➢ Expansion of thorax ➢ Maximum inspiratory and expiratory pressures decrease ➢ Decreased respiratory muscle strength ➢ Chest wall stiffens ➢ Diffusion of carbon monoxide (CO) decreased ➢ Decreased ventilatory response to hypercapnia
Hematologic	➢ Bone marrow reserves decreased in response to high demand ➢ Attenuated reticulocytosis to erythropoeitin administration
Renal	➢ Decreased creatinine clearance and GFR 10 ml/decade

	➢ Decrease of 25% in renal mass, mostly from cortex with a relative increased perfusion of juxtamedullary nephrons ➢ Decreased sodium excretion and conservation ➢ Decreased potassium excretion and conservation ➢ Decreased concentrating and diluting capacity ➢ Impaired secretion of acid load ➢ Decreased serum renin and aldosterone ➢ Accentuated ADH release in response to dehydration ➢ Decreased nitric oxide production ➢ Increased dependence of renal prostaglandins to maintain perfusion ➢ Decreased vitamin D activation
Genitourinary	➢ Prolonged refractory period for erections for men ➢ Reduced intensity of orgasm for men and women ➢ Incomplete bladder emptying and increased postvoid residuals ➢ Decreased prostatic secretions in urine ➢ Decreased concentrations of antiadherence factor Tamm–Horsfall protein
Temperature	➢ Impaired shivering
Regulation	➢ Decreased cutaneous vasoconstriction and vasodilation ➢ Decreased sweat production ➢ Increased core temperature to start sweating
Muscle	➢ Marked decrease in muscle mass (sarcopenia) due to loss of muscle fibers ➢ Aging effects smallest in diaphragm (role of activity), more in legs than arms ➢ Decreased myosin heavy chain synthesis ➢ Small if any decrease in specific force ➢ Decreased innervation, increased number of myofibrils per motor unit ➢ Infiltration of fat into muscle bundles ➢ Increased fatigability ➢ Decrease in basal metabolic rate (decrease 4%/decade after age 50) parallels loss of muscle
Bone	➢ Slower healing of fractures ➢ Decreasing bone mass in men and women, both trabecular and cortical bone ➢ Decreased osteoclast bone formation

Joints	➢ Disordered cartilage matrix ➢ Modified proteoglycans and glycosaminoglycans
Peripheral nervous system	➢ Loss of spinal motor neurons ➢ Decreased vibratory sensation, especially in feet ➢ Decreased thermal sensitivity (warm–cool) ➢ Decreased sensory nerve action potential amplitude ➢ Decreased size of large myelinated fibers ➢ Increased heterogeneity of axon myelin sheaths
Central nervous system	➢ Small decrease in brain mass ➢ Decreased brain blood flow and impaired autoregulation of perfusion ➢ Nonrandom loss of neurons to modest extents ➢ Proliferation of astrocytes ➢ Decreased density of dendritic connections ➢ Increased numbers of scattered neurofibrillary tangles ➢ Increased numbers of scattered senile plaques ➢ Decreased myelin and total brain lipid ➢ Altered neurotransmitters, including dopamine and serotonin ➢ Increased monoamine oxidase activity ➢ Decrease in hippocampal glucocorticoid receptors ➢ Decline in fluid intelligence ➢ Slowed central processing and reaction time
Gastrointestinal (GI)	➢ Decreased liver size and blood flow ➢ Impaired clearance by liver of drugs that require extensive phase I metabolism ➢ Reduced inducibility of liver mixed-function oxidase enzymes ➢ Mild decrease in bilirubin ➢ Hepatocytes accumulate secondary lysosomes, residual bodies, and lipofuscin ➢ Mild decrease in stomach acid production, probably due to nonautoimmune loss of parietal cells ➢ Impaired response to gastric mucosal injury ➢ Decreased pancreatic mass and enzymatic reserves ➢ Decrease in effective colonic contractions ➢ Decreased calcium absorption ➢ Decrease in gut-associated lymphoid tissue
Vision	➢ Impaired dark adaptation

	➢ Yellowing of lens ➢ Inability to focus on near items (presbyopia) ➢ Minimal decrease in static acuity, profound decrease in dynamic acuity (moving target) ➢ Decreased contrast sensitivity ➢ Decreased lacrimation
Smell	➢ Detection decreased by 50%
Thirst	➢ Decreased thirst drive ➢ Impaired control of thirst by endorphins
Balance	➢ Increased threshold vestibular responses ➢ Reduced number of organ of Corti hair cells
Audition	➢ Bilateral loss of high-frequency tones ➢ Central processing deficit ➢ Difficulty discriminating source of sound ➢ Impaired discrimination of target from noise
Adipose	➢ Increased aromatase activity ➢ Increased tendency to lipolysis
Immune system	➢ Decreased cell-mediated immunity ➢ Lower affinity antibody production ➢ Increased autoantibodies ➢ Facilitated production of anti-idiotype antibodies ➢ Increased occurrence of MGUS (monoclonal gammopathy of unknown significance) ➢ More nonresponders to vaccines ➢ Decreased delayed-type hypersensitivity ➢ Impaired macrophage function (Interferon-gamma, TGF-beta, TNF, IL-6, IL-1 release increased with age) ➢ Decreased cell proliferative response to mitogens ➢ Atrophy of thymus and loss of thymic hormones ➢ Accumulation of memory T cells (CD-45+) ➢ Increased circulating IL-6 ➢ Decreased IL-2 release and IL-2 responsiveness ➢ Decreased production of B cells by bone marrow

2.1.2. Age-Associated Pharmacological Changes

2.1.2.1. Pharmacokinetic Changes

Pharmacokinetics describes the process of drug handling by the tissue, organ, or body (12). The 4 components of pharmacokinetics are absorption, distribution, metabolism, and excretion (42). These processes depend on the individual taking the medication and the properties of the medication itself. Every drug has a specific pharmacokinetic profile based on specific parameters such as age, sex, weight, body mass index, hepatic function, and renal function (4). These processes can change with age but also can vary greatly between individuals (43).

2.1.2.1.1 Absorption

Absorption, a passive process that takes place mostly in the small intestine, shows the least change with aging (12). The absorptive process includes appropriate absorptive surface, gastric pH, gastrointestinal (GI) blood flow, and GI motility (43). The aging process can reduce GI motility and GI blood flow. Gastric acid secretion is reduced in older adults and this can result in an elevation in gastric pH. Increased gastric pH and reduced gastric blood flow may cause reduced drug absorption, whereas reduced GI motility may result in more of the drug(s) being absorbed (4). Most medications undergo passive diffusion in the gastrointestinal tract and experience a delay in absorption but no overall change in the extent of absorption (44).

2.1.2.1.2. Distribution

Drug distribution refers to where the drug goes after it enters the bloodstream. For drugs that are administered orally, the distribution phase begins after absorption and first-pass metabolism (12). As the body ages, changes in body mass composition are usually seen. A 25% to 30% increase in the percentage of body fat is coupled with a decrease of 25% to 30% of muscle mass (44,45). Besides, a decrease in total body water and often somewhat decrease in serum albumin can be also seen in elders (43). These changes can affect the distribution of some drugs in various ways depending on the properties of the drug.

Hydrophilic drugs (e.g. digoxin, ethanol, and theophylline) have a lower volume of distribution, and lower doses will result in higher body concentration in older people. Therefore if the distribution volume of a drug is reduced in an elderly patient, then the loading dose that is necessary to achieve a desired concentration is reduced (4,12). On the opposite side, drugs that distribute in fats (lipophilic drugs) will have higher volume of distribution (e.g. Diazepam) and the half-life of these drugs may be increased (4,43). Drugs that bind to serum proteins can also be affected in older adults. Serum albumin levels may be decreased significantly in older adults with malnutrition or chronic diseases, resulting in an increase in the "free" active drug concentration to unacceptable levels despite "normal" total serum concentration (12,42). Decreased serum albumin concentration leads to increased free drug concentration of drugs that are highly protein-bound (e.g. phenytoin, valproic acid, warfarin, salicylates). In such circumstances, it is preferable, when possible, to measure free drug concentration, as total drug concentration can be misleading (12,46,47).

2.1.2.1.3. Metabolism

The liver is the primary organ responsible for drug metabolism. Ageing is associated with a reduction in liver mass and blood flow, so that the liver mass in a patient of advanced age can be 20% to 40% smaller and is accompanied by a 35% decrease in hepatic blood flow

(44,48). Consequently, decreased clearance of drugs metabolized by the liver through the phase I pathway of reactions, i.e. oxidation or reduction reactions by the enzymes of the cytochrome P450 (CYP450) system influencing first-pass metabolism and bioavailability (12). Therefore, the absorption and the bioavailability of drugs that undergo first-pass metabolism also may be increased in older people such as lipophilic Beta-adrenergic blockers (e.g. propranolol and labetalol) (4,48,49). However, prodrugs and drugs that need to be activated in the liver as for several ACE inhibitors (e.g. enalapril and perindopril) their first-pass activation might be slowed or reduced with advancing age (48,50,51). However, no significant changes with aging have been shown in the type II reactions that include conjugation and acetylation (52).

A large percentage of drug metabolism occurs through the CYP enzymes, a multigene family with >100 isoforms (12,52). The CYP groups of enzymes are predominant in the liver yet exists also in the brain, kidney and intestine (43). Drug interactions and their clinical consequences involving the CYP system are common and generally result from either enzyme induction or inhibition by a variety of drugs, food, chemicals, or toxins. That's why whenever prescribing a new drug for an elderly patient, health practitioners always have to check and see whether the drug inhibits or induces the CYP enzymes (12).

2.1.2.1.4. Excretion

Excretion or Elimination refers to the drug's final route of exit from the body which primary involves elimination by the kidney. Renal function may decrease with age to the extent of 50% by age of 85 compared to younger patients (43). The reduction in blood flow to the kidneys, the decrease in kidney mass, and the reduction in the size and number of functioning nephrons collectively results in decline in the glomerular filtration rate (GFR) and the tubular function (4,12). Reduction in renal function in elderly subjects, affects the clearance of many renally excreted drugs (e.g. digoxin, lithium, water-soluble antibiotics, allopurinol) and the active metabolites of other medications (e.g. morphine, meperidine, procainamide) and cause the prolongation of the half-life of these drugs (12).

Although blood urea nitrogen (BUN) and serum creatinine levels may be useful markers of renal function, it must be remembered that each might not be an accurate predictor of renal function in older adults. For example, the BUN reflects the concentration of urea in the blood. However, the origin of much of this urea is ingested protein, so that a malnourished older patient may not consume enough nitrogen to produce an appropriate rise in BUN, even in the case of renal impairment. Similarly, serum creatinine might be decreased in elder people due to the decrease in their muscle mass (43,53). That's why there are several formulas that have been developed and assessed for estimating patients' renal function such as the Cockcroft-Gault formula and the modification of diet in renal disease (MDRD) formula and these are more recommended to be used to estimate renal function in older adults (4,48).

2.1.2.2. Pharmacodynamic Changes

Pharmacodynamics describes how drugs exert their effect at the site of action and the time course and intensity of pharmacological effect (12). Pharmacodynamics is determined not only by the concentration of the drug at the receptor, but also by drug-receptor interactions (variation in receptor number, receptor affinity, second messenger response, and cellular response), variations in physiological or homeostatic mechanisms, and changes in functional reserves (12,54). Many drugs can have exaggerated or paradoxical effects in older adults (43). The aging process may induce more or less sensitivity to particular medications (increase sensitivity is greater response at a given concentration of drug at the organ site) (4,43). This is especially important for drugs that affect the cardiovascular and/or central nervous systems. Older adults are more sensitive to medications that depress the central nervous system e.g. benzodiazepines that may lead to delirium, confusion and agitation as side effects (43,55). Increased sensitivity to medications can also lead to hemorrhage with anticoagulants especially when combined with acetylsalicylic acid (43).

Although the end result is usually an increased sensitivity to the effects of a particular drug, a decrease in responsiveness to drugs also occurs. The responsiveness of cardiac β1-adrenergic receptors is weakened in elderly patients. Whether β1- adrenergic receptors

decrease in number with aging remains controversial. However, there are consistent data demonstrating weakened intracellular signaling after binding of catecholamines to β1-adrenergic receptors. In general, elderly patients have a decreased response to β1-adrenergic agonists such as isoproterenol and an increased response to β1-adrenergic blockers such as metoprolol (44,56,57).

Pharmacodynamics alterations in elderly individuals increase the complexity of proper dosing, and carefully monitoring the clinical response to medications becomes intensively important.

2.2. Geriatric Syndromes and Common Disorders in Elderly

Geriatricians have used the term ‘‘geriatric syndrome’’ widely to highlight the unique features of common health conditions in older people. A geriatric syndrome is a multifactorial clinical condition that involves the interaction between identifiable situation-specific stressors and underlying age-related risk factors, resulting in damage across multiple organ systems and do not fit into discrete disease categories (6,7,58). Geriatric syndromes have a negative effect on the elders' quality of life as they progress which may lead to significant disability, and are part of the "cascade to dependency" that can often result in institutionalization (6,59). Geriatric syndromes includes conditions such as delirium, falls, cognitive impairment, incontinence, and frailty. These geriatric syndromes may be induced by polypharmacy and some drugs specifically.

2.2.1. Delirium

Delirium is a common problem that affects older hospitalized patients, resulting in significant morbidity and mortality and affect the quality of life of older persons. Delirium is defined as an acute disorder in attention and cognition that develops over a short period of

time (60). It is often the sign of a serious underlying medical condition, especially in frail older persons with underlying dementia (61). Delirium affects as much as 50% of elderly people (i.e. those aged 65 years or older) in hospital, affecting more than 2.6 million older adults each year in the United States (62). Despite its high prevalence, it often remains unrecognized, with a recent study estimating the rate of undetected delirium to be as high as 60% (60,63).

Three forms of delirium have been recognized: the hyperactive, hyperalert form; the hypoactive, hypoalert, lethargic form; and the mixed form which combines elements of both. The hypoactive form is more common in older hospitalized patients and is associated with a poorer prognosis, yet it is often unrecognized. On the other hand, the hyperactive, agitated, combative and hallucinating delirious patient is rarely missed (61,64).

Although a single factor can lead to delirium, usually delirium is multifactorial in elderly people. Development of delirium is dependent on the interaction between vulnerable older patients with several predisposing factors and exposure to noxious insults or precipitating factors (61,62). The leading risk factors consistently identified in both medical and non-cardiac surgery populations are dementia or cognitive impairment, functional impairment, vision impairment, history of alcohol abuse, and advanced age (>70 years) (60). Precipitating factors vary across populations. In medical patients, polypharmacy, use of psychoactive drugs, and physical restraints were the leading factors, conferring as much as a four-and-a-half-times increased risk (62). It is estimated that medications alone may account for 12%–39% of all cases of delirium (13). Studies show that the most common drugs associated with delirium are sedative hypnotics (benzodiazepines), analgesics (narcotics), and medications with an anticholinergic effect. Other medications in toxic doses can also cause delirium too (64).

Delirium is a clinical diagnosis that is mainly based on establishing a patient's baseline cognitive functioning and monitoring the clinical changes occurring in it. The chief medical historical features of delirium are acute onset and fluctuating course, in which symptoms tend to come and go or increase and decrease in severity over a 24 hour period of symptoms including inattention, impaired consciousness, and disturbance of cognition (e.g.

disorientation, memory impairment, language changes), disturbance in sleep–wake cycle, perceptual disturbances (hallucinations or illusions), delusions, psychomotor disturbance (hypoactivity or hyperactivity), inappropriate behavior, and emotional lability (61,62).

Preventing delirium before it develops is the most effective strategy against complications associated with delirium. Drug adjustments (reduce or remove psychoactive drugs e.g. anticholinergics, sedatives or hypnotics and substitute less toxic alternatives), address acute medical issues (treating problems identified in examination e.g. infection and metabolic disorders, maintain hydration and nutrition and treating hypoxia), reorientation strategies (encourage family involvement and address sensory impairment e.g. provide eyeglasses and hearing aids), maintaining safe mobility and normalize sleep–wake cycle (60).

2.2.2. Cognitive Impairment and Dementia

Delirium and dementia are among the most common causes of cognitive impairment and they are often either unrecognized or mistaken for each other. Dementia is an insidious neurodegenerative condition that is characterized by chronic and progressive cognitive decline from a previous level of performance in one or more cognitive domains that interferes with independence in everyday activities. Many signs and symptoms can be used to distinguish delirium from dementia, however most substantially is the onset of clinical signs and symptoms; the onset of delirium is typically abrupt, over hours to days, whereas the onset of dementia is insidious and progressive, over months to years. (65)

The prevalence of dementia approximately doubles every 5 years after the age of 60 (66). It was estimated that in 2010 worldwide 35.6 million people lived with dementia, with numbers expected to almost double every 20 years, to reach 65.7 million in 2030 and 115.4 million in 2050 (67). Alzheimer's disease causes approximately 60–70 % of dementia cases while vascular dementia and Lewy body dementia are the other more common forms, as well as, a significant percentage of patients have combined diseases (66).

Cognitive function in the elderly ranges from cognitive changes seen in normal aging to mild cognitive impairment (MCI) to dementia (66). Compared with younger adults, older adults perform more slowly on timed tasks and have slower reaction times. Dementia is typically diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning. Mild cognitive impairment (MCI) is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities. Dementia, requires substantial impairment to be present in one or (usually) more cognitive domains that must be sufficient to interfere with independence in everyday life activities, while in MCI modest impairment in one or more cognitive domains and the individual is still independent in everyday activities, yet with greater effort (68).

There are a lot of risk factors that are associated with an increased incidence rate of dementia, higher odds of developing dementia, or earlier onset of the disease. Increasing age, female gender, lower educational levels are among the demographic risk factors (68). Family history and genetic factors as APOE*4 allele is associated with dementia caused by Alzheimer disease, Parkinson's disease, dementia with Lewy bodies (DLB),vascular dementia, and frontotemporal dementia in men (68-70). Cardiovascular disease is recognized as a risk factor for vascular dementia as well as for degenerative dementias, particularly Alzheimer disease. Heart disease has been associated with both dementia of the Alzheimer's type, and vascular dementia. Risk factors in midlife, including hypertension, high cholesterol, high body mass index, and diabetes mellitus are associated with increased risk of dementia in late life, showing the importance of risk exposures decades earlier (71-73). Some drug classes also can exacerbate dementia as for benzodiazepines, anticonvulsants and anticholinergic drugs such as tricyclic antidepressants (13). Other risk factors also includes depression, head trauma and injuries, smoking and excessive alcohol intake (66,68).

The diagnosis of cognitive impairment depends mainly on the patient history. Patient history should be obtained both from the patient and from a family member, caregiver, or other reliable informant. The changes in cognitive functioning as manifested in everyday activities should be focused on. At early stages, deficits are frequently noted in managing finances and medications, problem solving, multitasking, and dealing with new situations (68). According to the DSM-5, the functional limitations linked to impairment in different

cognitive domains are limitations in complex attention (normal tasks take longer, easily distracted and difficulty holding information in mind), executive functioning (difficulty with planning, organizing, multitasking, following directions and keeping up with shifting conversations), learning and memory (difficulty recalling recent events, repeating self, misplacing objects and increasing reliance on lists, reminders), language (word-finding difficulty, use of general phrases or wrong words and grammatical errors), perceptual-motor/ visuospatial function (getting lost in familiar places and difficulty using familiar tools and appliances) and social cognition (disinhibition or apathy, loss of empathy, inappropriate behavior and loss of judgment) (74).

Prevention of dementia should be aimed at preventing and treating its modifiable risk factors (66). At this time, no disease-modifying therapies are available for any of the neurodegenerative diseases. However, symptomatic and supportive treatments are usually of value (68). Symptomatic treatment contains cholinesterase inhibitors which increase cholinergic transmission at the synaptic cleft, potentially benefiting patients with cholinergic deficits as in Alzheimer disease. Three such drugs are currently available in the United States: donepezil, rivastigmine, and galantamine. They have comparable efficacy and provide modest improvements in cognitive function and everyday activities and behavior in Alzheimer disease (68,75). Rivastigmine is also approved for dementia in Parkinson's disease (76). NMDA Receptor Antagonist as, memantine, is approved for the treatment of moderate to severe dementia caused by Alzheimer disease. It is thought to be neuroprotective against excitotoxicity in the cortex and hippocampus (68,77).

2.2.3. Falls and Mobility Disorders

A fall is considered to have occurred when a person comes to rest accidentally on the ground or lower level. Falls are one of the most common geriatric syndromes threatening the independence of older persons. Between 30% and 40% of community-dwelling adults older than 65 years fall each year, and the rates are higher for nursing home residents (78). Falls are an important cause of morbidity and mortality and the leading cause of fatal and nonfatal

injuries among older adults. In 2014, an estimated of 29.0 million falls and 7.0 million fall injuries took place in the United States (79). Injury severity varies but 2.8 million were treated in emergency departments for fall-related injuries, approximately 800,000 of these individuals were hospitalized and nearly 27,000 older adults died because of falls during that same period (79).

Risk factors of falling in older adults includes advanced age, female gender, past history of falls, recent hospitalization, arthritis, gait problems, foot disorders, inability to get out of a chair, balance problems, pain, sarcopenia, frailty, cognitive impairment, stroke, Parkinson disease, decreased sensation, environmental hazards, hypotension and visual impairment (78,80). The use of multiple medications (four or more), and specific classes of medications, can lead to gait and balance disorders and increased rate of falls. Generally central nervous system affecting drugs especially opioids, benzodiazepines, diuretics, vasodilators, tricyclic antidepressants, skeletal muscle relaxants, β-blockers, antihistamine medications, and sleep aids, need to be used with caution in elderly individuals because of the effects that these could have altering the reaction time, memory, balance, and brain perfusion of the elderly people. Antiplatelet agents and anticoagulants, commonly used in the elderly because of cardiovascular comorbidities, add another risk for fall complications and more catastrophic injuries.(81)

Due to the multiple possible factors and contributors to falls a multifaceted approach to prevention is essential (80). Modification of home environment (lower bedrails, floor mats, nonslip tiles in the shower, and removal of unnecessary barriers), Management and treatment of cardiovascular abnormalities as postural hypotension, heart rate and rhythm abnormalities, exercise program of muscle strengthening and balance retraining, medication reconciliation (the process of reviewing all the medications that a patient is taking prescribed by any and all providers) and medication burden reduction especially tapering and discontinuation of psychotropic medications can reduce risk of falling (78,80,81).

2.2.4. Urinary Incontinence

Urinary Incontinence (UI) is defined as involuntary urination, or enuresis or complaint of involuntary leakage of urine (82). It is a very common and distressing problem amongst elderly population, which may have a deep impact on their quality of life. In the EPIC study, the prevalence of incontinence increased in men from 2.4% in those under 39 years old to 10.4% in those over 60, while in women increased from 7.3% to 19.3% for the same age groups, respectively (83). It is twice as common in women as in men and affects at least 1 in 3 older women (82). In the United States, It is estimated that the total cost of UI care, including evaluation, treatment, and use of absorbent products among community-dwelling individuals, was approximately $14 billion in the year 2000 (84).

UI can be divided broadly into 2 categories: acute or reversible UI and chronic UI. Potential causes of acute UI include infection, atrophic vaginitis, delirium, psychological disorder, reduced mobility, excess urine output, stool impaction, and medications (6). Several disorders can result in chronic urinary incontinence, but the majority is accounted for by stress UI (involuntary loss of urine on effort or physical exertion, or on sneezing/coughing) and urgency incontinence (involuntary loss of urine associated with urgency). A combination of the two is referred to as mixed UI. A closely related problem is that of overactive bladder (OAB), which is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency UI, in the absence of urinary tract infection or other obvious pathology. Other, less common but no less important, entities are nocturia (frequent nocturnal micturition), nocturnal enuresis (adult bedwetting) and ‘functional’ incontinence (incontinence caused by either physical or cognitive impairment, with no identifiable lower urinary tract disorder), all being associated with a considerable patient burden. (85)

Medications play a big role in the occurrence of the UI in older people. The use of multiple medications can exacerbate the problem. A study found that approximately 60% of patients with urinary incontinence were on at least four medications (86). There is also evidence that diuretics, prostaglandin inhibitors, alpha-adrenoceptor blockers, selective serotonin reuptake inhibitors, cholinesterase inhibitors and systemic hormone replacement

therapy drugs can predispose an older person to incontinence (85). Besides, the list of medications that theoretically can worsen incontinence is longer.

Most of older adults prefer to start with non-pharmacological therapies before considering medications or surgery to manage and treat their UI symptoms. For many older adults, multiple small improvements in various parameters associated with UI and bladder function may lead to significant subjective improvement in symptoms (84). Dietary modification and weight loss is very important to help improvement in UI. Patients with UI should restrict or eliminate the use of foods or beverages that have irritant effect on the bladder mucosa as caffeine, alcohols and acidic foods and beverages (e.g. citrus fruits and juices). Patients should be encouraged to drink adequate volumes of fluid to prevent dehydration and thus, concentration of the urine which in turn can lead to increased mucosal irritation, with urinary urgency and dysuria. Clinical trials have demonstrated that weight loss may be helpful to reduce stress incontinence symptoms in women who are moderately or severely obese (87). Other preventive interventions include timed voiding and bladder retraining techniques, pelvic floor muscle exercises, pessaries and absorbent products (84).

Medications have been used to treat various forms of UI, although most prescription medication is now used for urge incontinence and not stress UI (84). The antimuscarinic medications are commonly prescribed to treat urge UI by blocking cholinergic receptors in the bladder, which leads to a decrease in bladder contractility. Older medications such as oxybutynin are nonselective and tend to be associated with a higher rate of adverse events as dry mouth, constipation, dry eyes, blurry vision and central nervous system effects that may worsen confusion in older adults, particularly those with a history of mild cognitive impairment or dementia. Some of the newer agents are theoretically more uroselective and preferentially bind to the muscarinic receptors in the bladder. These may be associated with lower rates of adverse effects but are generally more expensive because of the lack of generic non-branded formulations (84). More recently, the B3-adrenoceptor agonist mirabegron has been licensed in the UK for treatment of over active bladder, early analysis of results in community-dwelling older people suggests benefit with acceptable safety (85). Lower urinary tract symptoms in older men, unless there is a complete absence of voiding

symptoms, should initially be treated with an alpha-adrenoceptor antagonist, for example tamsulosin (85).

2.3. Geriatric Therapeutics Problems

2.3.1 Polypharmacy

The definitions for polypharmacy are numerous, and the criteria vary from study to study. According to literature, polypharmacy is usually defined in two ways: by a simple count of medications, or by the administration of more medications than are clinically indicated (3). Although the use of multiple medications is widely referred to as polypharmacy, no consensus exists on what number should define the term. In the literature, polypharmacy has been arbitrarily defined as taking at least two to nine medications concurrently (13). However, the term is generally used when a non-hospitalized individual is taking five or more medications (88). Excessive polypharmacy or Hyper-polypharmacy is another type of polypharmacy that is defined by medication count that are generally the uses of 10 or more medications (13). Alternately, polypharmacy has also been defined as taking at least one medication that is not clinically indicated (89). This indication-based definition is argued to be more practical and appropriate because it is independent of the multiple medications necessary to treat the multiple comorbidities elderly patients are likely to have. This definition necessitates a medication review and takes medication appropriateness into account. Those that lack an indication or effectiveness or are determined to be a therapeutic duplication are considered as polypharmacy or unnecessary medications.

The incidence of polypharmacy varies greatly in the literature because of the differing definitions and study sample sizes, ranging from 5% to 78% in patient populations (90). The incidence of polypharmacy is probably greater than reported in these studies as only few of the studies included nonprescription medication use when assessing polypharmacy. Polypharmacy is more common in women, and its prevalence increases with advancing age as older adults often have a number of comorbidities requiring pharmacologic intervention,

making medication management a complicated but essential part of caring for the elderly (13,88). A recent analysis of trends in prescription drug use in the United States found that 39% of older adults used five or more prescribed medications (91). In another survey of prescription and nonprescription medication use in ambulatory adults in the United States too, found that 57% of women aged 65 years or older took at least five medications, and 12% took at least 10 medications (92). A recent study here in Turkey for a group of elder patients who attended a polyclinic visit concluded that the mean number of drugs per patient was 5.50, Polypharmacy (≥5 drugs) was in 62.3% of the participants and Hyper-polypharmacy (≥10 drugs) was present in 9.7% of the participants. In total, 19.2% drugs were on the list of the European Union Potentially Inappropriate Medications, and 65% patients were using at least one potentially inappropriate medication (93).

An elevated number of prescription medications and a higher load of diseases have also increased the unnecessary consumption of medication that are not indicated for the patient's clinical state and whose pharmaceutical combinations represent potential dangers for increased direct drug costs, patients are at higher risk for adverse drug reactions, drug interactions, non-adherence, diminished functional status, various geriatric syndromes, the risk of iatrogenic effects, hospitalizations and even death (13,94).

2.3.2. Adverse Drug Reactions

The World Health Organization defines an adverse drug reaction as any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and drug abuse (95). Adverse drug reactions (ADRs) risk increases with age-related changes in pharmacokinetics and pharmacodynamics, increasing burden of comorbidity, polypharmacy, inappropriate prescribing and suboptimal monitoring of drugs (96). The prevalence of adverse drug reactions (ADRs) increases with age, with twice as many patients aged 65 years and older being hospitalized because of ADR-related problems than their younger counterparts (97). There has been much debate on whether advancing age by itself is a cause of increased risk of ADRs or merely a marker for comorbidity, altered

pharmacokinetics, and polypharmacy. Some studies have concluded that patient-specific physiological and functional characteristics are probably more important than any chronological measure in predicting both adverse and beneficial outcomes associated with specific drug therapies, while other studies around the world have clearly shown that the risks of ADRs (including interactions) is related to the number of medicines taken and sometimes due to inappropriate use of medicines (98).

ADRs can be mainly classified into two types: type A or B (99). Type A refers to ADRs that are associated with the pharmacological action of a drug and are dose related, common and predictable (e.g. digoxin toxicity, serotonin syndrome with selective serotonin receptor inhibitors, or anti-cholinergic effects of tricyclic antidepressants). However they are potentially avoidable in nature Majority of ADRs (80%) causing admission or occurring in hospital setting are type A reactions (98). In contrast, type B ADRs are unrelated to the pharmacological action of a drug. They are often immunologically mediated, relatively uncommon, typically non-dose related, unpredictable or idiosyncratic and more serious in nature than type A reactions (e.g. penicillin hypersensitivity). Other ADR types in addition to the two main types are C, D, E and F (100). Type C ADRs are associated with long-term therapy and are related to cumulative dose (e.g. hypothalamic pituitary-adrenal axis suppression). While type D ADRs occur sometime after the use of a drug chronically and are usually dose related and uncommon (e.g. tardive dyskinesia after use of antipsychotics), type E ADRs occur soon after withdrawal of the drug (e.g. myocardial ischemia after a ß-blocker withdrawal), although they are also uncommon. In contrast, type F ADRs are often caused by a drug-drug interaction, are dose related, common and often cause failure of therapy. (101)

Since ADRs are a major cause of morbidity and mortality, it is important to demonstrate a causal relationship between the drug and the adverse drug reaction in order to decide if an adverse clinical event is an ADR or due to deterioration in the patient's disease state (102). Several standardized methods of assessing ADRs causality exist, yet neither any of them is universally accepted or used in everyday clinical practice, nor any of them is specifically validated for use in older patients with multiple comorbidities and multiple medications (96). The most widely used and generally accepted causality assessment scales in clinical practice are the probability scales developed by the World Health Organization

Collaborating Centre for International Drug Monitoring - Uppsala Monitoring Centre (WHO-UMC) and the Naranjo ADR Probability Scale (103,104). According to the WHO-UMC criteria the causality of ADRs is classified into Certain, Probable, Possible, Unlikely, Conditional-unclassified and Unassessable-unclassifiable. On the other hand, The Hallas criteria categorize ADR avoidability into four groups: definitely avoidable, possibly avoidable, unavoidable and unclassifiable (105). Where ADRs that are definitely or possibly avoidable are usually those in which organ dysfunction, homeostatic dysregulation, age-related changes in pharmacokinetics and pharmacodynamics and known drug–drug interactions predictably and adversely influence drug handling and response (96).

Advancing age can contribute to a significant increase in sensitivity to particular drugs and a corresponding increase in the incidence of ADRs (102). Older patients demonstrate an exaggerated response to central nervous system-active drugs (e.g. benzodiazepines, anesthetics, opioids) and a decreased response to some cardiovascular agents (e.g. beta-adrenergic agents) (54). Also, the most important pharmacokinetic changes in older people include decrease in the excretory capacity of the kidney, as well as, decline in the rate of hepatic drug metabolism, consequently, medications with a narrow therapeutic index and prolonged half-life cause the most trouble for the elderly patients (43). The most frequent ADRs causing hospital admission in older patients are typically gastrointestinal disorders, cardiovascular and metabolic/endocrine complications (102). The lists of medicines most likely to be used in the elderly include antibiotics, anticoagulants, digoxin, diuretics, hypoglycemic agents, antineoplastic agents and non-steroidal anti-inflammatory drugs (NSAIDs) and these are responsible for 60% of ADRs leading to hospital admission and 70% of ADRs occurring in hospital (98).

It is often difficult to predict the occurrence of ADRs in older patients for several reasons. The presentation of an ADR is often atypical and nonspecific in nature, which can be misinterpreted as a new medical problem or a complication relating to a preexisting diagnosis. This may lead to the addition of another drug to treat the symptoms (a phenomenon known as “prescribing cascade”), which will again increase polypharmacy and therefore the risk of drug–drug interactions and another ADRs (102).

2.3.3. Inappropriate Prescribing and Potentially Inappropriate Medications

Inappropriate prescribing is the use of medications that introduce a significant risk of an adverse drug event when there exists evidence for an equally or more effective but lower-risk alternative therapy for treating the same medical condition (106). Inappropriate prescribing also includes overuse of drugs at higher frequencies or longer durations, underuse of drugs that are medically indicated based on guidelines, and use of multiple medications with drug-drug interactions (12). Inappropriate prescribing has been identified in 12–40% of nursing home residents (107) and 14–23% of community-dwelling older people (108). Besides, inappropriate prescribing was associated with ADRs as some evidences showing that 50% of ADRs in older adults are due to inappropriate prescribing (109).

On the other hand, Potentially inappropriate medications are medications or medication classes that pose more risk than benefit and should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available (110). In a study of nursing home residents in North America, 40% of participants were prescribed at least one inappropriate medication (111). Furthermore, in a study conducted on older adults visitors to a polyclinic in Turkey, in total of the drugs used by participants 317 (19.2%) drugs were listed as potentially inappropriate medications, and 65% of patients took a minimum of one potentially inappropriate medications (93). Exposure to potentially inappropriate medications was associated with a significant increase in unplanned hospitalizations (112) and an increase in inpatient visits in older patients (113). Potentially inappropriate medications was also linked to increased risk of ADRs in elderly. Potentially inappropriate medications are significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalization when adjusted for age, sex, burden of comorbidity, dementia, baseline functional status and number of medications (114). Economically, in a study of the 2000/2001 Medical Expenditure Panel Survey in the United States, the total estimated healthcare expenditures related to the use of potentially inappropriate medications was $7.2 billion (115).

The two most cited principal validated explicit screening tools in the literature are the American based Beers Criteria and the Irish based STOPP/START criteria (Screening Tool of Older Persons Prescriptions/ Screening Tool to Alert doctors to the Right Treatment), where both of them have been developed by consensus expert opinion based on reviews of primary research evidence (96,110). These criteria contains lists of potentially inappropriate medications that should be avoided or used with caution in older adults, either independent of clinical condition, considering clinical condition or considering co-prescribed medications.

Beers Criteria was first published by Dr. Mark Beers in 1991 and endorsed by the American Geriatrics Society, the Beers Criteria identifies possible harmful effects of certain commonly prescribed medications to help guide and modify pharmacologic treatments, particularly in adults older than 65 (88,116). The Beers Criteria classifies medications into three categories; potentially inappropriate medications that should be avoided or dose adjusted in elderly, drugs that are potentially inappropriate in patients with certain conditions or syndromes and drugs that should be prescribed with caution in older adults (117). The most recent update of Beers criteria was in 2015 (31). In that update the American Geriatrics Society 2015 Beers Criteria Update Expert Panel added possible adverse effects of medications based on a patient's hepatic or renal function, the effectiveness of the medication, and possible drug interactions. The latest update also takes into account recently published evidence of increased adverse drug events resulting from drugs such as antipsychotics and proton pump inhibitors (118).

Less widely used is the STOPP/START Criteria, an evidence-based set of guidelines consisting of 65 STOPP (Screening Tool of Older Person's potentially inappropriate Prescriptions) and 22 START (Screening Tool to Alert doctors to the Right Treatment) criteria (88,119). Although they may be used individually, STOPP and START are best used together to determine the most appropriate medications for an elderly patient. The STOPP guidelines help determine when the risks of a medication may outweigh the benefits in a given patient. STOPP includes recommendations for the appropriate length of time to use a medication; for example, PPIs should not be used for more than eight weeks and benzodiazepines for more than four weeks. START helps clinicians recognize potential

prescribing omissions and to identify when a medication regimen should be implemented based on a patient's history. Examples of START criteria include suggestions of when to initiate calcium and vitamin D supplementation for prevention of osteoporosis and when to begin statins in patients with diabetes and cardiovascular diseases. STOPP/START is organized by physiologic system, which allows for greater usability, and it addresses medications by class rather than specific medications. (The Beers Criteria was criticized for these reasons, as well as its limited transferability outside the United States.) When assessed in systematic reviews, the STOPP/START criteria were found to be fundamentally more sensitive than the Beers Criteria. Overall, it was concluded that the use of the STOPP/START criteria resulted in an absolute risk reduction of 21.2% to 35.7% and greatly improved the appropriateness of prescribing medication to the elderly. Its use also resulted in fewer follow-up appointments with primary care physician. (88,119)

2.3.3.1. Drugs with Anticholinergic and Sedative Adverse Reactions

Anticholinergic drugs and sedative drugs are among the medications most commonly prescribed to elderly patients and among the most likely to contribute to ADRs, some of which may cause physical and cognitive function impairment (88). The drugs with anticholinergic effects tends to non-selectively and competitively inhibit the binding of acetylcholine to muscarinic acetylcholine receptors, consequently, the adverse effects may be widespread. Approximately 100 active ingredients are reported to cause clinically relevant anticholinergic adverse drug reactions, including peripheral effects, such as dryness of the mouth, urinary disorders, and constipation as well as central nervous system effects, such as falls, confusion, and cognitive and mental impairment, which result in fractures, hospitalization, and institutionalization. (120). Medicines specifically prescribed for their anticholinergic properties (e.g. oxybutynin, and benztropine) are well recognized by clinicians. However, clinicians may be less aware that some medicines prescribed for other purposes also have anticholinergic properties (26). Medicines with sedative properties include benzodiazepines and other hypnotics, antipsychotics, anticonvulsants,

antidepressants, opioid analgesics and tramadol, and histamine H1 receptor antagonists commonly used for allergic conditions. Many anticholinergic medicines also have sedative properties. Medicines with sedative properties have been linked to depressive symptoms, worsening cognition, respiratory depression, impaired muscle strength, falls and fractures (26).

Anticholinergic drugs are commonly prescribed to elderly patients for cardiovascular (include β-blockers, calcium channel blockers, diuretics, and ACE inhibitors) and neurologic disorders (include amitriptyline, quetiapine, nortriptyline, prochlorperazine, haloperidol, and paroxetine) (88). Besides, anticholinergic and sedative medications are prescribed in older adults to treat medical conditions that usually occur later in life, such as urinary incontinence, sleep and pain disorders, Parkinson disease, chronic obstructive pulmonary disease, and mental illness. However, evidence suggests that often the benefits do not justify the risks for some medications in older adults, for example chronic sedative medication use for insomnia (29). In many cases, patients are prescribed anticholinergic or sedative medications to control symptoms of a disease, not to cure it, which means patients may be taking these medications for years. This cumulative exposure is called the anticholinergic burden/sedative burden (88).

2.3.3.2. Anticholinergic and Sedative Adverse Reactions Screening Methods

2.3.3.2.1. 4 Grades Anticholinergic Burden Scales

The cumulative effect of taking multiple medicines with anticholinergic properties termed as anticholinergic burden can adversely impact cognition, physical function and increase the risk of mortality. Expert opinion derived risk scales are routinely used in research and clinical practice to quantify anticholinergic burden (121). These scales rank the anticholinergic activity of medicines into four categories, ranging from no anticholinergic activity (= 0) to definite/high anticholinergic activity (= 3). Examples of these scales include Anticholinergic Drug Scale (ADS), Anticholinergic Burden Classification (ABC), Clinician-rated Anticholinergic Score (CrAS), Anticholinergic Risk Scale (ARS), Anticholinergic

Activity Scale (AAS), Anticholinergic Loading Scale (ACL), and the Anticholinergic Cognitive Burden (ACB) scale which is the most frequently validated expert based anticholinergic scale for adverse outcomes (121). The ACB score assigns a value between 0 and 3 for a given medication. A medication is assigned a 0 if there is no anticholinergic activity, and a 1 if there is possible anticholinergic activity suggested by serum anticholinergic activity or in vitro affinity to muscarinic receptors. For medications with known clinically relevant anticholinergic effects, a 2 or 3 is given, based on the drug's ability to cross the blood– brain barrier and its association with delirium (20).

2.3.3.2.2. Drug Burden Index

The Drug Burden Index (DBI) was developed and published in 2007 and measures the effect of cumulative exposure to both anticholinergic and sedative medications on physical and cognitive function in older adults (30). The DBI was intended to be an evidence-based risk assessment tool to guide appropriate medication use, linking clinically relevant data such as functional measures to medication exposure, which would be consistent with current practices in clinical decision making to guide prescribing in older people. Furthermore, The DBI is one of the few cumulative medication exposure measures that considers the dose (29).

Medication exposure according to the DBI was quantified using data which was derived from cross-sectional data collected in year 1 in the Health ABC population in Australia (28,29,30). A pharmacological equation was postulated by maintaining a classical dose–response relationship, in which the researchers hypothesized that the cumulative effect of anticholinergic and sedative medications would be linear, and a simple additive model was used to establish the total anticholinergic and sedative burden. The dose of each anticholinergic and sedative medication was used to determine a score from 0 to 1 for each drug in these classes. The relationship between an individual's DBI and their physical and cognitive performance was then evaluated in a cohort of community-dwelling older adults.

It was shown that each additional unit of DBI had a negative effect on physical function similar to that of three additional physical morbidities.

Mathematically, the drug burden is calculated for every patient according to the formula Total Drug Burden = B_{AC} + B_S, where B indicates burden, AC indicates anticholinergic, and S indicates sedative. Assuming that the anticholinergic and sedative effects of different drugs are additive in a linear fashion. It was postulated that B_{AC} and B_S may be proportional to a linear additive model of pharmacological effect (E). This led to the formation of the equation,

$$\frac{E}{\alpha} = \sum \frac{D}{D + DR_{50}}$$

Where α is a proportionality constant, D is the daily dose, and DR50 is the daily dose required to achieve 50% of maximal contributory effect at steady state. Furthermore, as the general DR50 of anticholinergic and sedative effect is not identifiable and doses need to be normalized, the DR50 was estimated as the minimum recommended daily dose (δ) as listed by the medication product information approved by the US Food and Drug Administration.

$$DBI = \sum \frac{D}{\delta + D}$$

Where D represents the total daily dose of any sedative or anticholinergic medication, and δ is the minimum recommended daily dose. Besides, medications that are reported to be both sedative and anticholinergic are considered as anticholinergic to prevent double entries, and therefore a separate anticholinergic DBI can be calculated from the DBI. As there are some differences between countries in the δ of medications, subsequent studies using the

DBI have used the minimum recommended daily dose in the study population setting (29). This flexibility allows the tool to be suited for specific countries.

Increasing DBI exposure has been associated with poorer physical function (122,123), frailty (124) and falls (125,126). Concerning hospitalization, a higher DBI has also been associated with increased hospital days (127,128), increased hospitalization for delirium (9), and readmission to hospital (127). There have been mixed reports on the association of DBI with mortality and cognition (29). One study conducted in people living in residential care facilities in Australia reported a non-significant association between high DBI and mortality (129). A population-based study of older people in New Zealand found that DBI exposure increased the risk of mortality (125) and a study in Finland found an association of high DBI exposure with mortality in people with and without Alzheimer's disease (130). Regarding cognition, the original validation study found that increasing DBI was associated with impaired cognition in community-dwelling older people when measured using the digit symbol substitution test (30). However, no associations were observed between DBI and cognition in a cohort of community-dwelling older men in Australia (131). In a cross-sectional analyses of individuals recruited from residential aged care facilities in Australia, Multi-level linear models showed there was a significant association between a higher Drug Burden Index and lower quality of life according to the EuroQol Five Dimensions Questionnaire (132).

3. PATIENTS AND METHODS

3.1 Study Population and Data Collection

Prescriptions of male and female patients 40 years old or more was randomly collected from 11 pharmacies from six different cities in Turkey, distributed as follows; 6 in Istanbul (n = 228) and 1 in each of Kocaeli (n = 46), Balıkesir (n = 39), Erzincan (n = 75), İzmir (n = 94) and Tekirdağ (n = 38). The prescriptions were collected in the period between 01/07/2016 and 31/08/2016. A total of 551 prescription were collected. Afterwards, the collected prescriptions were revised according to the following Inclusion/Exclusion criteria;

Inclusion Criteria:

(1) Patients $\geq$ 40 years old from both genders
(2) The Medications were dispensed via a prescription
(3) The prescription was issued by an institution
(4) The patient's diagnosis was already identified
(5) The prescription was dispensed in the same day
(6) The absence of any emergency disease

Exclusion Criteria:

(1) Patients < 40 years old from both genders
(2) The medications were dispensed without a prescription
(3) The prescription was not issued by an institution
(4) The patient's diagnosis was not identified yet
(5) The prescription was not dispensed in the same day
(6) The presence of any emergency disease
(7) The prescription was unable to be read
(8) The drug has been taken by an old prescription (Repeated prescription)

After the prescriptions were adjusted according to the previous Inclusion/Exclusion criteria, 6 was under 40 years old, 5 was unreadable, 20 was repeated by old prescriptions and 520

prescription were included in this study. The pharmacies from where the data was collected was generally community pharmacies (10 pharmacies) except one was a Hospital pharmacy. Consequently, the data can be considered to be of community dwelling elder people.

Data from the prescriptions was extracted and classified according to patient's age, gender, diagnosis, number of morbidities, physician's specialty, total number of drugs and total price of prescription. The Drug Burden Index was then calculated for each prescription and a retrospective analysis was performed according to the previous covariates, in order to indicate the medication burden done by drugs with anticholinergic and sedative effects and evaluate health care practitioners and other factors that affect this drug burden in Turkey.

3.2 Drug Burden Index (DBI)

Medication exposure was quantified using the DBI. Briefly, medications were characterized with respect to risk into 2 groups: drugs with anticholinergic effects and drugs with sedative effects. Medications with both anticholinergic and sedative effects were classified as anticholinergic to prevent duplication. The following factors were used in the equation for total drug burden (TDB): $TDB=B_{AC}+B_S$, where B_{AC} and B_S each represent the linear additive sum of $D/(\delta + D)$ for every anticholinergic (AC) or sedative (S) drug to which the subject is exposed, D is the daily dose taken by the subject, and δ is the minimum efficacious daily dose. Both prescription and over-the-counter drugs were included in the analysis. However, topical preparations without significant systemic effects and PRN (used when needed) drugs were excluded.

3.3 Medication Inventory

Medications with anticholinergic or sedative effects that the study population was exposed to were adopted from the DBI included drugs appendix published by Hilmer et al 2009 (28) and the drugs included in the Anticholinergic Cognitive Burden (ACB) scale - the 2012 update (133). These drugs are shown in Table 3.1 and Table 3.2.

Table 3.1- Medications with anticholinergic effects included in the study.

Alimemazine	Clidinium	Fluoxetine	Morphine	Ranitidine
Alprazolam	Clomipramine	Fluphenazine	Nefazodone	Risperidone
Alverine	Clonazepam	Fluvoxamine	Nefopam	Scopolamine
Amantadine	Clorazepate	Furosemide	Nifedipine	Selegiline
Amitriptyline	Clozapine	Guanethidine	Nortriptyline	Sertraline
Amoxapine	Codeine	Guanfacine	Nortryptyline	Solifenacin
Aripiprazole	Colchicine	Haloperidol	Olanzapine	Tamsulosin
Asenapine	Cyclobenzaprine	Hydralazine	Opipramol	Temazepam
Astemizole	Cyproheptadine	Hydrocodone	Orphenadrine	Terazosin
Atenolol	Darifenacin	Hydrocortisone	Oxazepam	Theophylline
Atropine	Desipramine	Hydroxyzine	Oxcarbazepine	Thioridazine
Azatadine	Dexbrompheniramine	Hyoscyamine	Oxybutynin	Tizanidine
Belladonna	Dexchlorpheniramine	Iloperidone	Oxycodone	Tolterodine
Benztropine	Dextromethorphan	Imipramine	Paliperidone	Tramadol
Brompheniramine	Diazepam	Isosorbide	Paroxetine	Trazodone
Bupropion	Dicyclomine	Lamotrigine	Perphenazine	Triamterene
Buspirone	Digoxin	Levocetirizine	Pheniramine	Triazolam
Captopril	Dimenhydrinate	Loperamide	Phenyltoloxamine	Trifluoperazine
Carbamazepine	Diphenhydramine	Loratadine	Phenytoin	Triflupromazine
Carbinoxamine	Diphenoxylate	Loxapine	Pimozide	Trihexyphenidyl
Carisoprodol	Dipyridamole	Meclizine	Pramipexole	Trimethobenzamide
Cetirizine	Disopyramide	Meperidine	Prazosin	Trimipramine
Chlordiazepoxide	Doxazosin	Metaxalone	Prednisone	Triprolidine
Chlorpheniramine	Doxepin	Methadone	Prochlorperazine	Trospium
Chlorpromazine	Doxylamine	Methocarbamol	Promethazine	Valproic acid
Chlorprothixene	Escitalopram	Methotrimeprazine	Propantheline	Venlafaxine
Chlorthalidone	Estazolam	Metoclopramide	Propiverine	Warfarin
Cimetidine	Fentanyl	Metoprolol	Propoxyphene	Ziprasidone
Citalopram	Fesoterodine	Mirtazepine	Quetiapine	
Clemastine	Flavoxate	Molindone	Quinidine	

Table 3.2- Medications with sedative effects included in the study.

Benzonatate	Opium
Butalbital	Papaverine
Chlorzoxazone	Pentazocine
Clonidine	Phenelzine
Dichloralphenazone	Phenobarbital
Flurazepam	Primidone
Gabapentin	Reserpine
Guanabenz	Ropinerole
Hexobarbital	Tiagabine
Levetiracetam	Tranylcypromine
Lorazepam	Tripelennamine
Meprobamate	Zaleplon
Methyldopa	Zolpidem

The minimum recommended daily dose was calculated mostly according to the medication product information approved by the US Food and Drug Administration (FDA). Yet, some drugs in the Turkish market are not approved or has been withdrawn from the US market by the FDA. In this case, the minimum recommended daily dose was determined according to the medication product information approved by the Turkish authorities. Example of the minimum recommended daily doses of some drugs with anticholinergic and sedative effects are shown in the table 3.3.

Table 3.3- Example of minimum recommended daily dose (MRDD) of some drugs with anticholinergic and sedative effects.

Name of drug	MEDD	Name of Drug	MEDD
Alimemazine	5 mg	Atenolol	50 mg
Alprazolam	0.75 mg	Atropine	0.05 mg
Alverine	60 mg	Azatadine	1 mg
Amantadine	100 mg	Belladonna	16.2 mg
Amitriptyline	25 mg	Benzonatate	100 mg

3.4 Covariates

Patients were divided according to age into 4 groups (40-50, 51-60, 61-70 & older than 70) and according to number of diseases diagnosed (comorbidities) into 3 groups (1 disease, 2 diseases & 3 or more diseases). In addition, physicians were divided according to their specialties into 14 groups as follows;

1 General Practitioner , Family Doctor
2 Internal Medicine; Infectious Diseases, Emergency Doctor, Endocrinological Disorders
3 Gynecology and Obstetrics
4 Dermatology
5 Physical Medicine and Rehabilitation
6 Eye Diseases
7 Cardiology
8 Respiratory Diseases
9 Orthopedics and Traumatology
10 Urology
11 Ear, Nose and Throat diseases
12 Neurology
13 Psychiatry
14 Surgery, Anesthesiology and Radiology

Similarly, Diagnosis of the patients were divided into 15 group according to the nature of disease and the affected organ as follows;

1 CVS Disorders
2 Respiratory Disorders
3 GIT Disorders
4 Urinary and Genital System Disorders
5 CNS and Neurological Disorders
6 Psychiatric Disorders
7 Endocrinological Disorders
8 Hematological and Immunologic disorders
9 Orthopedic Disorders (Bone, Joint & Muscles)
10 Oncologic disorders
11 Infectious Diseases
12 Dental Problems and Surgical Operations
13 Dermatologic Disorders
14 Nutrition and Metabolic Disorders
15 Eye Disorders

3.5 Statistical Analysis

Relationship between Drug Burden Index and other variables tested were evaluated by Pearson correlation analysis. All results are expressed as Mean ± SEM. The statistical significance of results was determined by using Student T-test, one-way analysis of variance (ANOVA) followed by Tukey Post Hoc tests for multiple comparisons of group means. All data were analyzed using IBM SPSS statistics 20 software, (IBM Corporation 2011).

4. RESULTS

4.1 Demographics and Characteristic Patients' Information

In this thesis, 520 prescriptions of patient's ≥ 40 years old were reviewed. Out of the 520 prescriptions, 272 belongs to female patients (52.3%) while 248 were males (47.7%). The mean age for all patients was 62.43 ± 0.57 years with range 40-96 years. The mean age for female patients was 61.00 ± 0.78 (range; 40-96) while for male patients the mean age was 64.00 ± 0.83 (range; 40-91). The patients were divided into 4 age groups as follows; 117 of the patients (22,5%) were 40-50 age, 111 of the patients (21,3%) were 51-60 age, 138 of the patients (26,6%) were 61-70 age and 154 of the patient were over the age of 70 (29.6%).

Table 4.1 - Demographics and Age characteristics of patients

AGE	N	Mean	Minimum	Maximum	Std. Error of Mean	% of Total Sum
MALE	248	64.00	40	91	.830	48.9%
FEMALE	272	61.00	40	96	.775	51.1%
TOTAL	520	62.43	40	96	.570	100.0%

Age Categories				
	Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
40-50 Age	117	22,5	22,5	22,5
50-60 Age	111	21,3	21,3	43,8
60-70 Age	138	26,6	26,6	70,4
70-100 Age	154	29,6	29,6	100,0
Total	520	100,0	100,0	

4.2 The Relationship between Number of Prescribed Drugs and Patients' Gender and Age Group

In all of the prescriptions reviewed, 1412 drug was prescribed with a total mean of 2.72 ± 0.065 drug per prescription. For each gender separately, males had a mean of 2.67 ± 0.085 (range; 1-7) and females a mean of 2.77 ± 0.099 drug (range; 1-8) drug per prescription. According to age groups, in the 40-50 years old group the mean number of drugs consumed was 2.3 ± 0.119 while in the 51-60, 61-70 and 70-100 the mean was found to be 2.83 ± 0142, 2.86 ± 0.132 and 2.82 ± 0.119 respectively. The increase in number of drug consumption between age groups was found to be statistically significant (F (3,516) = 4.081, p = 0.007) in one way ANOVA analysis and then separately in Tukey Post Hoc test as in Figure 4.1.

Table 4.2 - The relationship between the number of prescribed drugs and patients' gender.

Number of Drugs	N	Mean	Minimum	Maximum	Std. Error of Mean	% of Total Sum
MALE	248	2.67	1	7	0.085	51.30%
FEMALE	272	2.77	1	8	0.099	48.70%
TOTAL	520	2.72	1	8	0.065	100.00%

Table 4.3 - The relationship between the number of prescribed drugs and age groups

Age Groups	**n**	**Mean**	**Std. Error**
40-50	117	2.3	0.119
51-60	111	2.83	0.142
61-70	138	2.86	0.132
70-100	154	2.82	0.119
Total	520	2.72	0.065

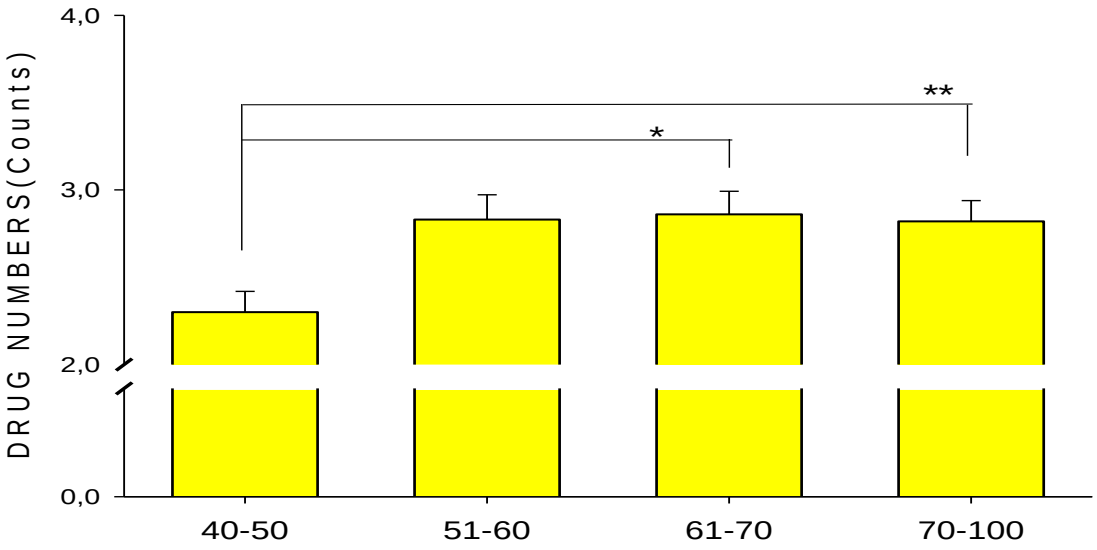

Figure 4.1 – The effect of age groups on number of prescribed drugs.

The number of drug increased significantly by age. (*) Represent significant difference (P = 0.014) by Tukey post hoc test. (**) Represent significant difference (P = 0. 019) by Tukey post hoc test. Each data point represents Mean ± SEM.

4.3 Distribution of Patient's Prescriptions according to Physicians' Specialties.

Among the 520 prescription included in this study, 221 (42.5%) were written by general practitioners and family doctors, while 299 (57.5%) were written by specialist physicians. Table 4.3 include the number and percentage of prescription written by different physicians' specialties.

Table 4.4 - The number and percentage of prescription written by different physicians' specialties

	DEPARTMENTS	**Frequency**	**Percent (%)**
1	General Practitioner, Family Doctor	221	42.5
2	Internal Medicine, Infectious Diseases, Emergency Doctor, Endocrinological Disorders	75	14.5
3	Gynecology and Obstetrics	11	2.1
4	Dermatology	19	3.7
5	Physical Medicine and Rehabilitation	20	3.8
6	Eye Diseases	30	5.8
7	Cardiology	46	8.8
8	Respiratory Diseases	8	1.5
9	Orthopedics and Traumatology	15	2.9
10	Urology	10	1.9
11	Ear, Nose and Throat diseases	16	3.1
12	Neurology	13	2.5
13	Psychiatry	7	1.3
14	Surgery, Anesthesiology and Radiology	29	5.6
	Total	**520**	**100**

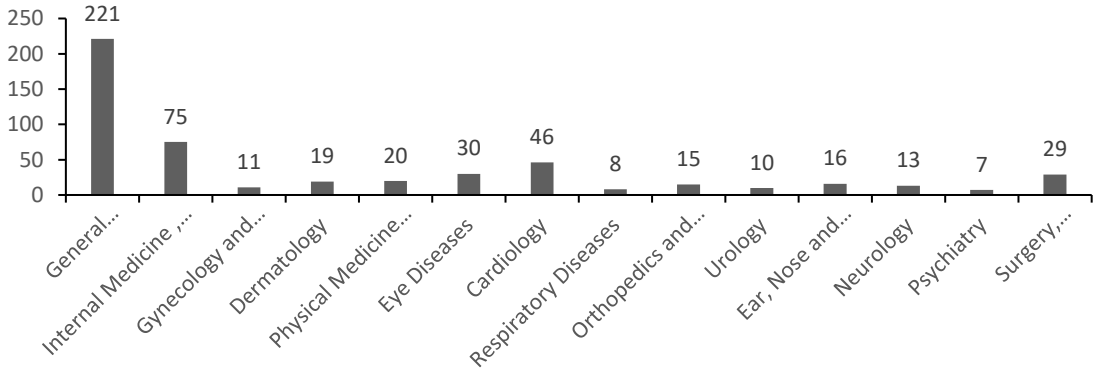

Figure 4.2- Histogram of the number of prescription written by different physicians' specialties.

4.4 Distribution of Diseases (Morbidities) Diagnosed in the Patient's Prescriptions

A total of 914 disease or morbidity was diagnosed in all of the prescriptions. Cardiovascular, Gastrointestinal, Orthopedic and Infectious diseases were found to be the most diagnosed disorders. The detailed data are shown in Table 4.4 and Figure 4.3.

Table 4.5 – The number and percentage of diseases (morbidities) diagnosed in the patient's prescriptions

Symbol Number	Diagnosis Category	Frequency	Percent %
1	CVS Disorders	190	20.8
2	Respiratory Disorders	61	6.7
3	GIT Disorders	118	12.9
4	Urinary and Genital System Disorders	41	4.5
5	CNS and Neurological Disorders	29	3.2
6	Psychiatric Disorders	44	4.8
7	Endocrinological Disorders	70	7.6
8	Hematological and Immunologic disorders	18	2
9	Orthopedic Disorders (Bone, Joint & Muscles)	111	12.1
10	Oncologic disorders	6	0.7
11	Infectious Diseases	102	11.2
12	Dental Problems and Surgical Operations	17	1.8
13	Dermatologic Disorders	45	4.9
14	Nutrition and Metabolic Disorders	21	2.3
15	Eye Disorders	41	4.5
	Total	**914**	**100**

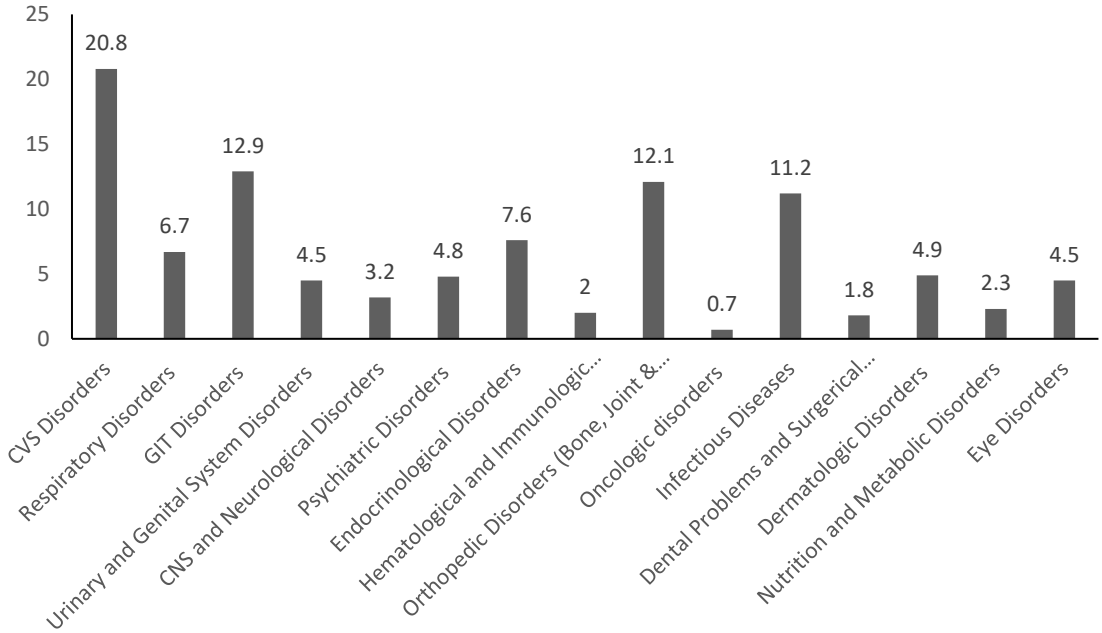

Figure 4.3- Histogram of the percentage of diseases (morbidities) diagnosed in the patient's prescriptions.

4.5 The Relationship between Drug Costs and Age Groups

After the data from the prescriptions was extracted, statistical analysis between the drug costs and age groups of the patients was conducted in order to determine if their relationship between the price of drugs per prescriptions and the age of the patient. The total mean cost for all prescriptions was found to be 67.71 ± 7.05 TL. The detailed data for the mean costs of the patient's different age groups is shown on Table 4.5. There was increase in the cost of drugs consumption between 40-50 age group and the three other older age groups spotted, yet, it was found to be statistically insignificant ($F(3,516) = 2.352$, $p = 0.071$) in one way ANOVA analysis as shown in Figure 4.4.

Table 4.6 – The mean of drug costs (TL) per prescription for every age group

Age Group	n	Mean	Std. Error
40-50	117	41.394	7.052
51-60	111	74.268	12.567
61-70	138	72.689	7.569
70-100	154	78.513	13.276
Total	520	67.71	5.426

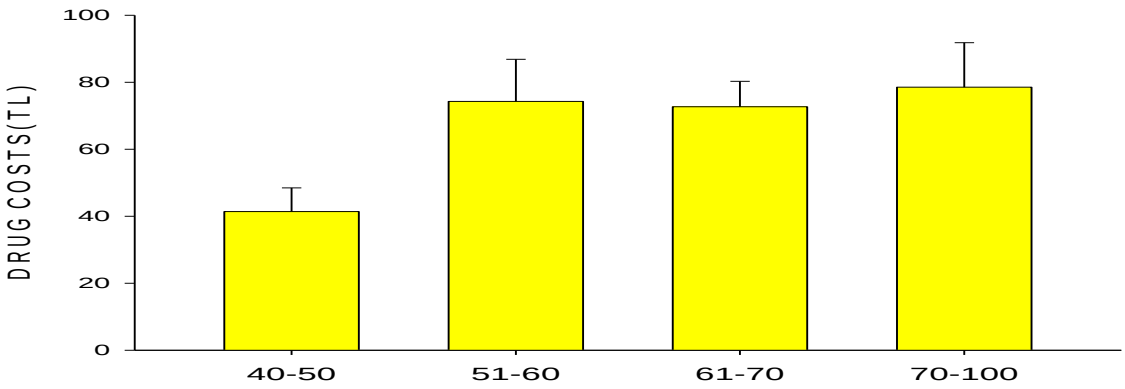

Figure 4.4 – The change of drug costs according to patients' age groups.

Each data point represents Mean ± SEM. The difference was found to be insignificant by one-way ANOVA test.

4.6 The Change in Drug Burden Index According To Other Covariates

In this thesis, the Drug Burden Index (including its Anticholinergic and Sedative parts separately) was tested for relation between each of the following factors; gender of the patient, age groups, number of drugs taken, count of diseases diagnosed, nature of disease and physicians' specialties. Generally, the mean DBI of all patients was found to be 0.206 ± 0.017, the Anticholinergic Drug Burden Index (Ach-DBI) was found to be 0.196 ± .016 and Sedative Drug Burden Index (Sed-DBI) was found to be 0.01 ± 0.004. Besides, in the 520 prescriptions reviewed in this study, 156 prescription included at least one drug with anticholinergic or sedative effect, with prevalence percentage of DBI > 0 of 30% and prevalence percentage of DBI ≥ 1 of 5.8% of total prescriptions.

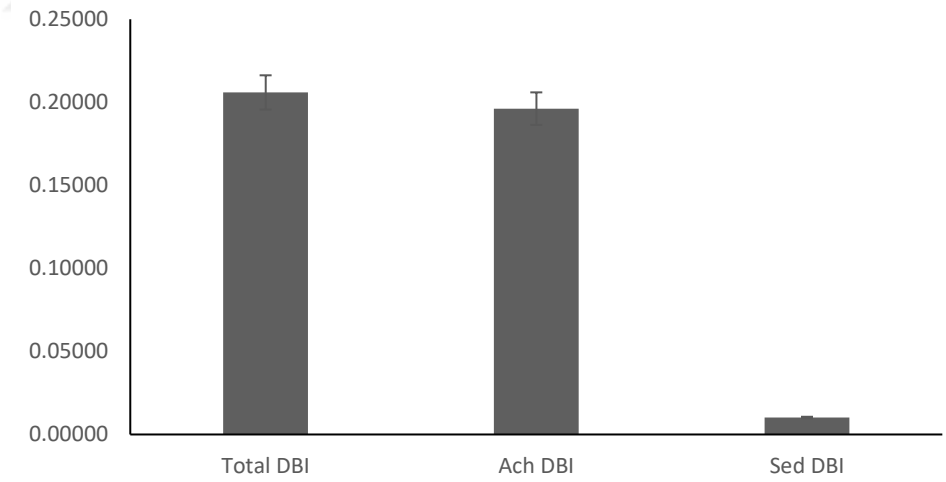

Figure 4.5 – The mean of DBI and its contents of all patients included in the study.

Each data point represents Mean ± SEM.

4.6.1 The Change in Drug Burden Index According To Gender

Across patients of the two genders the DBI was calculated and the difference between the two means was statistically analyzed for significance by T - test. The mean DBI for male patients was higher than that of the female patients (0.228 ± 0.027 and 0.186 ± 0.02 respectively), however, the difference was found to be statistically insignificant (t (1) = 1.565, p = 0.211) by the T - test. Similarly, the Ach-DBI of male patients was higher than the female Ach-DBI (0.215 ± 0.025 and 0.179 ± 0.02 respectively). However, the Sed-DBI of female patients was higher than that of male patients (0.012 ± 0.006 and 0.008 ± 0.005 respectively). Yet, the difference in Ach-DBI and Sed-DBI between female and male patients was found to be statistically insignificant by T - test by (t (1) = 1.281, p = 0.258) and (t (1) = 0.427, p = 0.514) respectively.

Table 4.7 – The change in drug burden index according to gender

Descriptive	N	Mean of DBI	Std. Error	Minimum	Maximum
Female	272	0.186	0.020	0.000	1.550
Male	248	0.228	0.028	0.000	3.148
Total	520	0.206	0.017	0.000	3.148

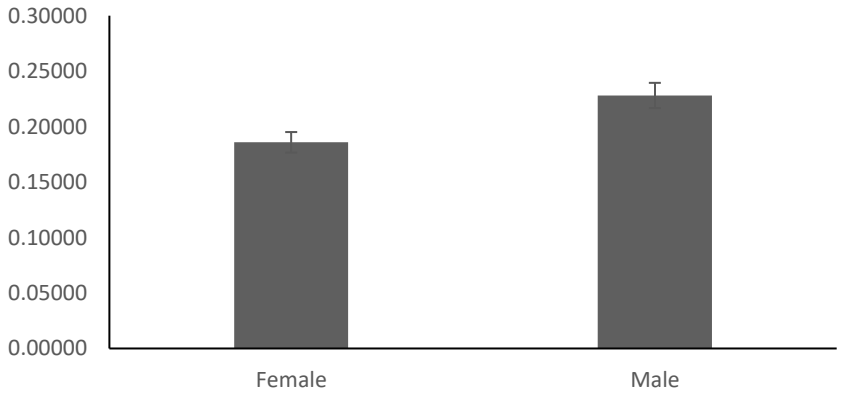

Figure 4.6 – The mean DBI of male and female patients.

The difference was found to be insignificant by T- test.

4.6.2 The Change in Drug Burden Index According To Patient's Age groups

In this part of the study the DBI was assessed according to the age of the patients to determine if their relationship between the DBI with its two components the anticholinergic and the sedative. Despite there was a slight increase in the DBI with aging, this increase was not found statistically significant by one-way ANOVA test ($F(3,516) = 0.949$, $p = 0.417$) and Tukey Post Hoc test. All data and results are summarized and presented below.

Table 4.8 - The change in drug burden index according to patients' age groups.

Descriptive	N	Mean	Std. Error	Minimum	Maximum
40-50	117	0.175	0.035	0.000	2.038
51-60	111	0.195	0.035	0.000	1.500
61-70	138	0.194	0.028	0.000	1.571
70-100	154	0.248	0.036	0.000	3.148
Total	520	0.206	0.017	0.000	3.148

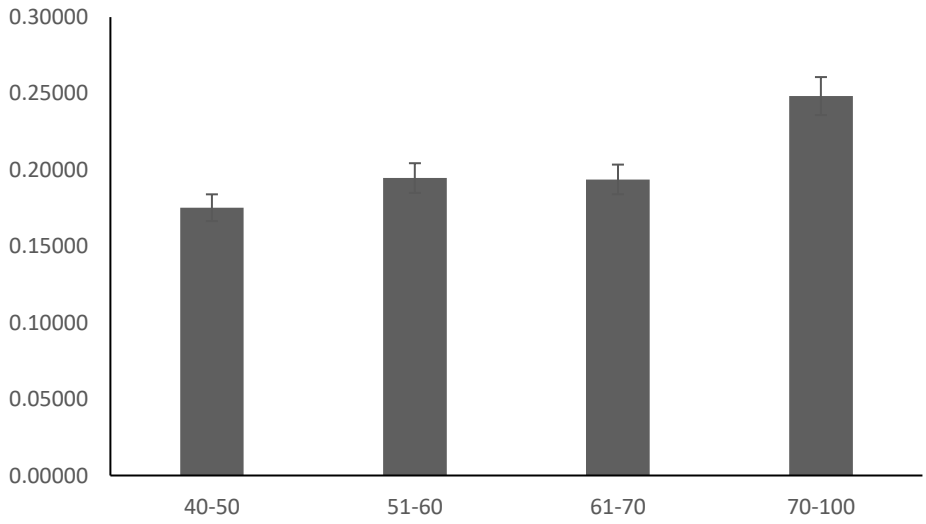

Figure 4.7 – The mean DBI of patients' age groups.

The difference was found to be insignificant by one-way ANOVA test.

Table 4.9 – The changes in Ach-DBI according to patients' age groups.

Descriptive	N	Mean	Std. Error	Minimum	Maximum
40-50	99	0.199	0.040	0.000	2.038
51-60	95	0.222	0.040	0.000	1.500
61-70	125	0.207	0.029	0.000	1.571
70-100	143	0.247	0.034	0.000	2.290
Total	462	0.220	0.018	0.000	2.290

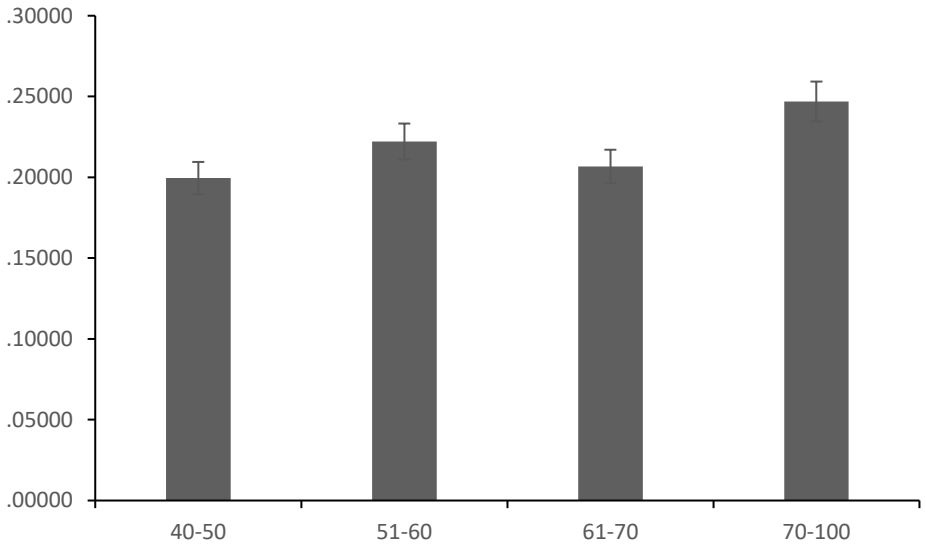

Figure 4.8 – Mean of the Ach-DBI in patients' age group.

The difference was found to be insignificant by one-way ANOVA test ($F(3,458) = 0.383$, $p = 0.765$).

Table 4.10 - The changes in Sed-DBI according to patients' age groups.

Descriptive	N	Mean	Std. Error	Minimum	Maximum
40-50	116	0.000	0.000	0.000	0.000
51-60	109	0.010	0.008	0.000	0.750
61-70	137	0.007	0.005	0.000	0.500
70-100	152	0.020	0.010	0.000	0.889
Total	514	0.010	0.004	0.000	0.889

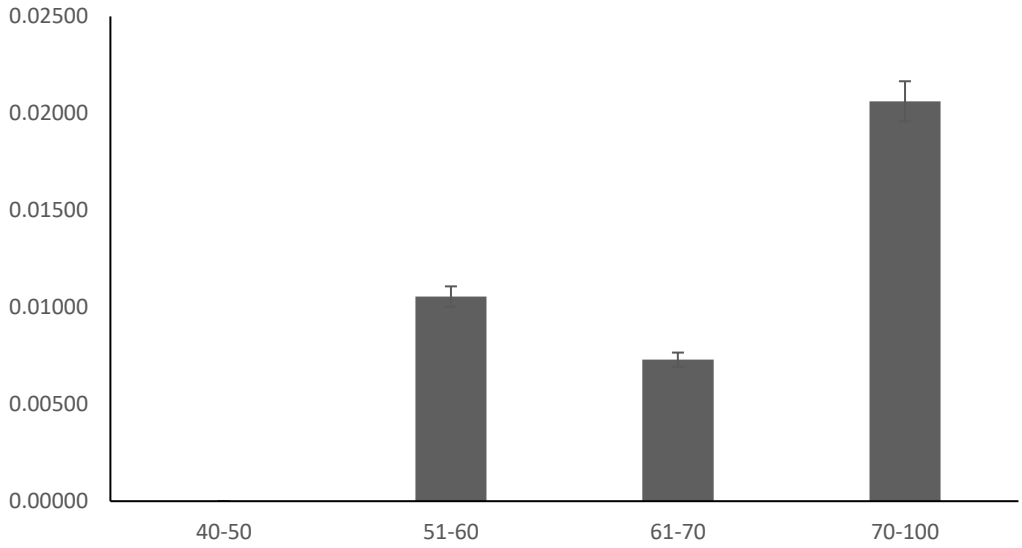

Figure 4.9 - Mean of the Sed-DBI in patients' age group.

The difference was found to be insignificant by one-way ANOVA test ($F(3,510) = 1.366$, $p = 0.252$).

Total Exposure percentage of sedative drugs = 1.5% (n=8).

4.6.3 The Change in Drug Burden Index According To Number of drugs

The drug burden index was also compared to number of drugs used by patients. The patients were divided according to number of drugs into patients using 1,2,3,4 and 5 or more drugs. The DBI were then compared to the five groups. The mean DBI of those taking 1 drug was 0.074 ± 0.0178, those taking 2 drugs was 0.1076 ± 0.0204, those taking 3 drugs was 0.274 ± 0.043, those taking 4 drugs was 0.281 ± 0.039 and those taking 5 or more drugs was 0.493 ± 0.125. The difference between means was found statistically significant with one-way ANOVA test ($F(7,512) = 11.197$, $p < 0.0001$) showing increase in the DBI with the increase in number of drug consumed.

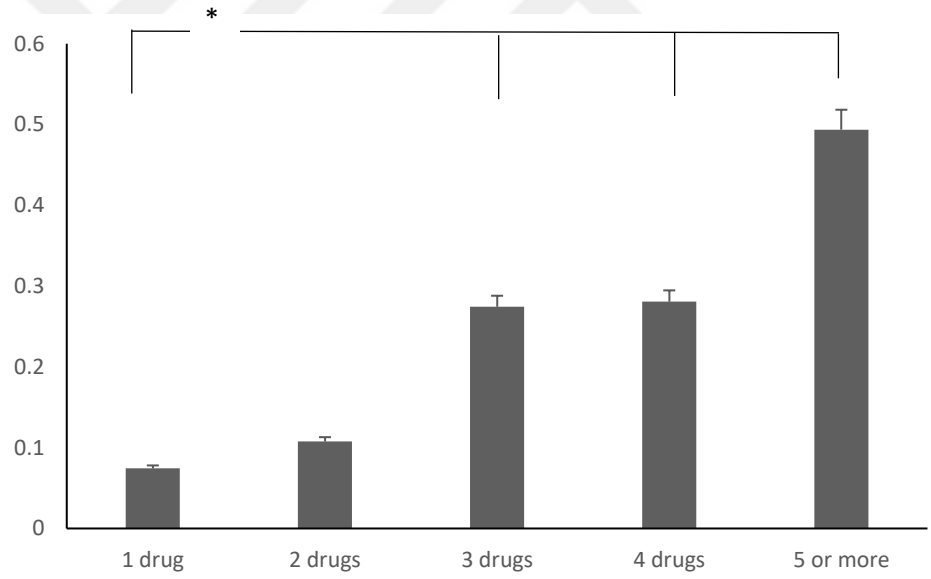

Figure 4.10 - The change in drug burden index according to number of drugs.

The difference between means was found statistically significant with one-way ANOVA test ($F(7,512) = 11.197$, $p < 0.0001$). (*) the difference between means was found statistically significant ($p < 0.05$) in Tukey Post Hoc test.

4.6.4 The Changes in Drug Burden Index According To Number of Diseases

In this section of the thesis, patients were divided into three groups according to the number of disease diagnosed into three groups; patients with one disease diagnosed, patients with two diseases diagnosed and patients with three or more diseases diagnosed. Afterwards, the three groups were compared statistically to the DBI. There was statistically significant difference in the one-way ANOVA test ($F(2,517) = 13.177$, $p < 0.0001$) between the three groups showing the increase in the DBI with the increase in the number of disease diagnosed. Tukey Post Hoc test was then applied for comparison between groups. The results and data are shown in the tables and figures below.

Table 4.11 – The change in DBI according to number of disease diagnosed.

	N	Mean	Std. Error	Minimum	Maximum
1 Disease	268	0.139	0.021	0.000	3.148
2 Diseases	156	0.219	0.029	0.000	1.867
3 Diseases	96	0.368	0.046	0.000	1.571
Total	520	0.206	0.017	0.000	3.148

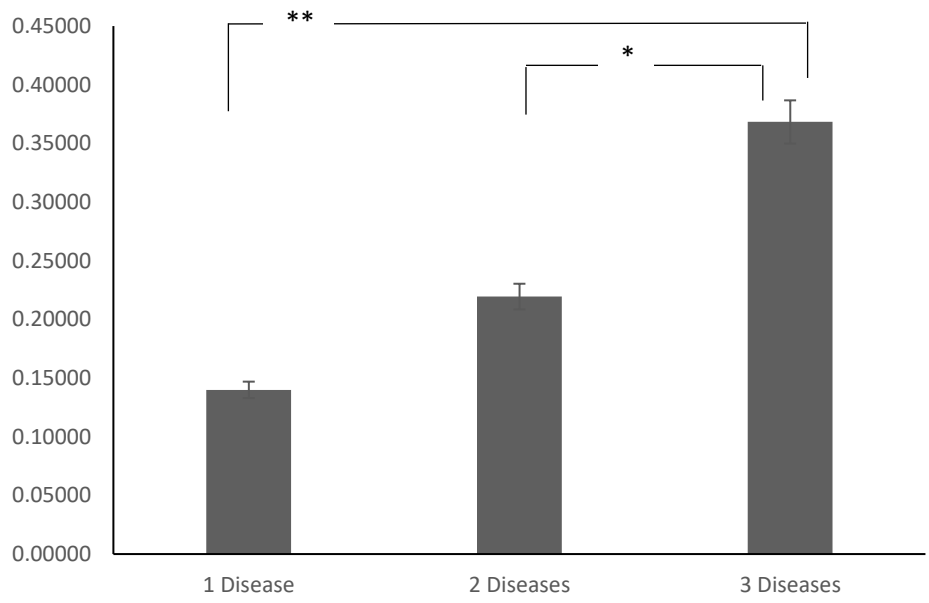

Figure 4.11 - The change in drug burden index according to number of diseases.

(*) The difference between means was found statistically significant by P = 0.007 in Tukey Post Hoc test.

(**) The difference between means was found statistically significant by P < 0.0001 in Tukey Post Hoc test.

4.6.5 The Changes in Drug Burden Index According To Type of Disease Diagnosed

As mentioned before, patient's diagnosis were divided into 15 groups according to the type or the nature of the disease. In here we compared the DBI according to each of the diagnosis group. Patients' with psychiatric (0.507 ± 0.154), cardiovascular (0.309 ± 0.033), central and peripheral nervous system (0.261 ± 0.077) and respiratory disorders (0.245 ± 0.057) had the highest DBI scores. All of the data are summarized in the chart below.

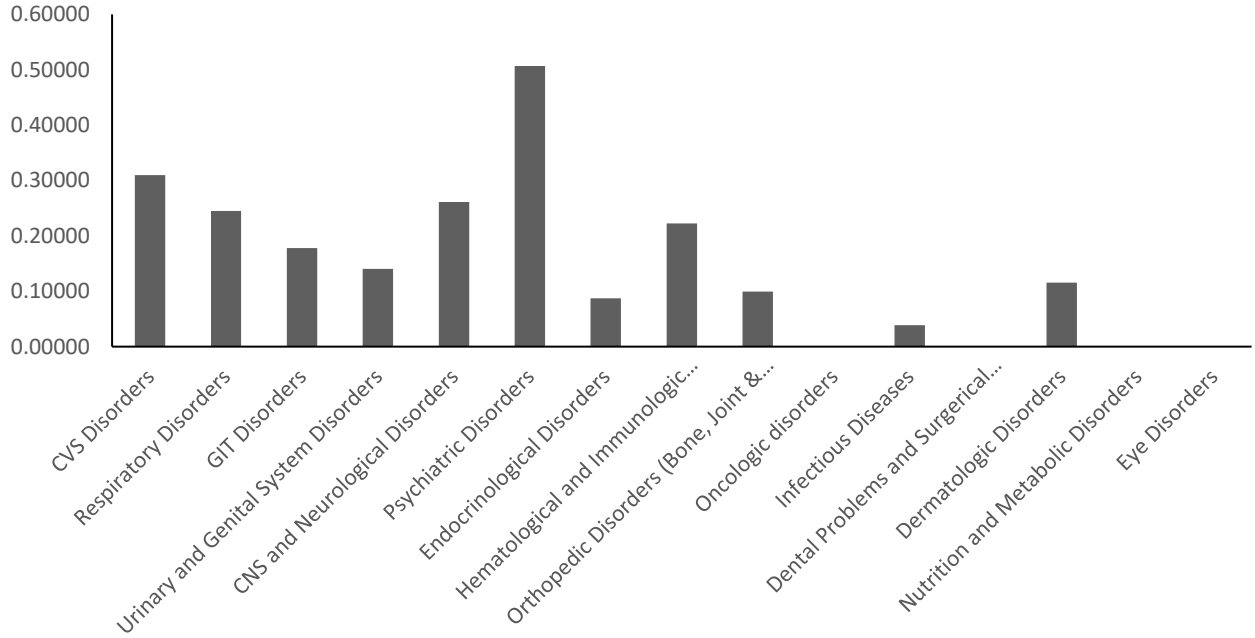

Figure 4.12 - The change in drug burden index according to patient's type of disease diagnosed.

4.6.6 The Changes in Drug Burden Index According To Physicians' Specialties

As mentioned earlier, the prescriptions were divided according to the specialty of the physicians who prescribed them into 14 groups. The DBI was then compared to each of these group. Prescriptions written by psychiatrists (0.624 ± 0.258), Neurologists (0.328 ± 0.123), Cardiologists (0.286 ± 0.087), General practitioners (0.265 ± 0.026) and chest disease specialists (0.256 ± 0.109) had the highest DBI scores. All of the data are summarized in the chart below.

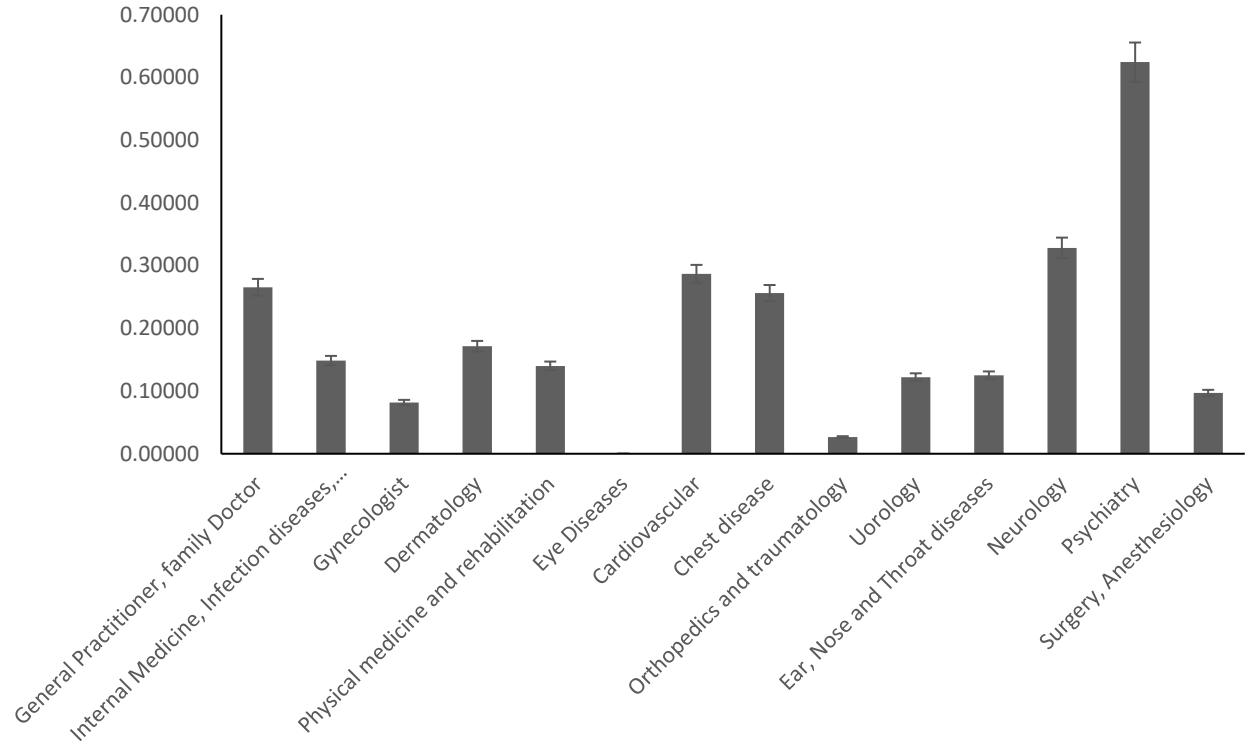

Figure 4.13 - The change in drug burden index according to physicians' specialties.

4.7 The Most Prescribed Drugs with Anticholinergic and Sedative Effects

Drugs with anticholinergic and sedative effects were prescribed exact 200 times in all of the prescriptions. Among these drugs, the most prescribed pharmacological groups was antihypertensive drugs (26.5%), antihistaminic drugs (17.5%), antidepressants (17%), opioid drugs (5%), anticoagulants (4.5%), Anticonvulsants (3.5%) and antipsychotics (3%). The most prescribed drugs within those with anticholinergic or sedative effect was the beta blocker Metoprolol (15%), the antidepressant Escitalopram (7%), the diuretic Furosemide (5.5%) and the anticholinergic Scopolamine (5%).

5. DISCUSSION AND CONCLUSION

5.1 Demographics and Characteristic Patients' Information

In this study, 520 prescriptions were obtained from community pharmacies, which means that the population included in this study are community dwelling elder people. In the studies used to determine the Drug Burden Index before, the sample size varied a lot where some were higher than the sample size used in this study while others were lower (29). According to that, the sample size used in this study may be satisfactory yet it could have been better if we had the ability to extract more data and expand the sample size of our study both quantitatively and geographically. The prescriptions of female patients was 52.3% and the prescriptions of male patients was 47.7%. Therefore, female to male ratio between patients was 1.1 to 1, which is normal and homogenous. Although patients with 40 years old or more were accepted in this study, 56.2% of the patients were above 60 years old, with the mean age for all patients was 62.43 ± 0.57 years. Among the prescriptions included in this study, the highest number of prescriptions were written by general practitioners (42.5%), internal medicine specialists (14.5%) and cardiologists (8.8%), while the most diagnosed types of disease were cardiovascular diseases (20.8%), gastrointestinal disorders (12.9%), orthopedic diseases (12.1%) and infectious diseases (11.2%). These results are similar to that in a previous research done in Turkey as well, cardiovascular diseases were the chronic diseases with the highest prevalence followed by orthopedic and endocrinal diseases respectively (134). The absence of gastrointestinal diseases among the highest results in that research is most probably due to the inclusion of only chronic diseases in the count.

5.2 Number of Drugs Consumed and Its Relation with Patients' Gender and Age

In all of the 520 prescriptions reviewed, 1412 drug was prescribed with a total mean of 2.72 ± 0.065 drug per prescription. In this study, 23.3% of the prescriptions included one drug, 28.7% two drugs, 20.2% three drugs, 16.5% four drugs and 11.3% were using five and more drugs. This result are supported by many consonant data from the literature (3,10,90).

In a previous study on elderly individuals (aged >65 years) who visited a family medicine polyclinic in Istanbul – Turkey, The mean number of drugs per patient was 5.50 ± 2.84 (93). In another research performed to identify the quantity of drug utilization in a sample of nursing home residents over 60 years old in 23 cities in Turkey, 28.2% of the participants were using one drug, 24.3% two drugs, 18.5% three drugs, 11.7% four drugs and 17.3% were using five and more drugs (134). The difference in results between these studies and our study is most probably relative to the difference in the age and the type of the sample of population included in each study. For example, in the study conducted in the family medicine polyclinic in Istanbul the age of the participants was 65 years or more and the population were polyclinic outpatients while in ours 40 years or over community dwelling elder people's prescriptions were included.

On the other side, the number of drugs consumed was found to be increasing significantly with the increase in the age of the patients ($p = 0.007$). This result is supported by many consonant data from the literature. In a study performed in Denmark, the prevalence of polypharmacy increased with age, and from the age of 70 years, two thirds of all drug users were polypharmacy users (10). Another study performed in Brazil on community dwelling population over than 60 years old, the prevalence of concomitant use of five or more medications was associated with increasing age (94).

5.3 The Relationship between Drug Costs and Age Groups

The total mean cost for all prescriptions was found to be 67.71 ± 7.05 TL. There was increase in the cost of drugs consumed between 40-50 age group and the three other older age groups spotted, yet, it was found to be statistically insignificant ($p = 0.071$). Although it was not significant the p value was very low and possibly if the population was larger it would have been statistically significant result. This is also more logic since the relation between the consumed drug number and increase in age was statistically significant. Besides, there are other researches from the literature that supports this result. In a retrospective study conducted in the USA on community dwelling older persons, the drug costs were found to increase within age groups (135).

5.4 The Change in Drug Burden Index According To Other Covariates

One of the aims of this study was to calculate the DBI in the Turkish outpatient elderly population and compare it with other results from around the world. According to the findings of this study the average DBI was found to be 0.206 ± 0.017 and the prevalence percentage of DBI greater than zero (DBI > 0) was 30%. In USA and Australia, a similar Cross-sectional study conducted on community-dwelling older adults 70 years or older had a mean DBI of 0.18 ± 0.35 (30,136). In Finland, two Cross-sectional study conducted on community-dwelling older adults 75 years or older had the prevalence percentage of DBI greater than zero (DBI > 0) of 36.7% and 37.5% (122,137). In a previous study conducted in a community pharmacy in Çanakkale, Turkey in 2012, from 100 participating patients 75% had DBI greater than zero (DBI > 0) and 9% had DBI score of one or more (DBI ≥ 1) (138).

Apparently, there is not a big difference found between the values of the DBI calculated here in Turkey and the values obtained from DBI researches performed in other countries on similar patient population. However, there is some factors that should be kept in mind when assessing the results of this study. In our study, only drugs written in the prescriptions were included, yet there may be other OTC drugs or drugs that the patients take by themselves (not included in the prescriptions) which cannot be known for certain unless direct contact with the patient is conducted. Besides, the geographical areas from where the data analyzed in our study were extracted are mostly big cities from the western part of Turkey, which is known for being economically better and the medical services is more developed than the rural and eastern part of Turkey. Moreover, about half of the prescriptions (42.5%) were written by general practitioners and family doctors, while prescriptions written by other important physician specialties as psychiatrists were only 1.3% of the total prescriptions. Consequently further researches may be needed to determine whether these factors may have influence on the result of the DBI scores obtained from this study or not.

The increase in number of drugs consumed by the patients and the number of diseases diagnosed per patient was found to be significant factors that increase the DBI value ($p < 0.0001$). This means that the increase in the number of diseases diagnosed was followed by

increase in the number of drugs prescribed without paying attention to the anticholinergic or sedative side effects of the drugs prescribed leading to the increase in the drug burden and the risk of poor physical and cognitive performance associated with it (29).

Psychiatric (0.507 ± 0.154) and neurological diseases (0.261 ± 0.077) were among the diagnosis related with the highest DBI score. Besides, the prescriptions written by psychiatrists (0.624 ± 0.258) and neurologists (0.328 ± 0.123) were the prescriptions accompanied by the highest DBI score too. This can be understood within the fact that a lot of the drugs used to treat these diseases work centrally in the nervous system and often has either anticholinergic or sedative side effects. Cardiovascular diseases (0.309 ± 0.033), respiratory disorders (0.245 ± 0.057) and gastrointestinal disorders (0.178 ± 0.046) came as the next highest DBI scores. This is also reasonable as the cholinergic (parasympathetic) system play an important role in the functioning of the cardiovascular, respiratory and the gastrointestinal system. For example, anticholinergic drugs as scopolamine are used to prevent nausea and vomiting and antihistaminic drugs found in a lot of the combinations used for upper respiratory disorders.

In this study, the most prescribed pharmacological groups with anticholinergic and sedative effects were antihypertensive drugs (26.5%), antihistaminic drugs (17.5%) and antidepressants (17%). Furthermore, the most prescribed drugs within those with anticholinergic or sedative effect were the beta blocker Metoprolol (15%), the antidepressant Escitalopram (7%), the diuretic Furosemide (5.5%) and the anticholinergic Scopolamine (5%). In the cross-sectional study conducted on community-dwelling older adults in Australia, with respect to drug burden exposure, the most frequently used drugs were antidepressants (7.8%), sympathomimetics (5.3%), parasympathomimetics (5%) and anxiolytics (4.5%) (136). According to another cross-sectional study conducted in residential aged care facilities in Australia, the most prevalent medication classes contributing to the DBI were antidepressants (mirtazapine, sertraline, escitalopram, and citalopram) and opioid analgesics (buprenorphine, fentanyl and oxycodone) (132). According to these data, the antihypertensive drugs was more than quarter of total of the drugs with anticholinergic and sedative effects investigated in this study. There is a lot of alternatives for antihypertensive drugs with no anticholinergic and sedative effects that can replace the drugs used in these prescriptions, for example, Metoprolol was the drug with anticholinergic effect with the

highest incidence, yet there is other antihypertensive drugs with no anticholinergic effects that can be used instead.

The role of pharmacists in medication review in elderly people is very important. In a retrospective study conducted in Australia, the median DBI scores were reduced after medication review by pharmacists from 0.50 to 0.33 in aged care facilities residents and from 0.50 to 0.22 in community-dwelling individuals (139). However, it is important first to educate pharmacists and increase their knowledge about DBI calculation and the risks of high anticholinergic and sedative burdens on elderly people. In a research conducted in Australia, after Continuing Professional Development (CPD) educational article surrounding the DBI and its application in practice, 81.8% of 2522 pharmacists participated were able to calculate the DBI score correctly for a given patient data (32). Therefore, more investigation are needed to identify the ways to make use of the DBI as a pharmacologic assessment tool to assess patients' anticholinergic and sedative burden in the clinical regular procedures, methods to educate health care practitioners about it and the ways to manage medication therapy in order to reduce the drug burden on older people in Turkey (e.g. drug reconciliation and deprescribing) (140).

CONCLUSION

In this thesis the number of prescribed drugs has increased with the increase in patients' age. The Anticholinergic component of the Drug Burden Index was much higher than the sedative component. The DBI score increased slightly with the increase in patients' age, however, this increase was not statistically significant. Besides, there was no significant difference between the DBI scores in male and female patients. The DBI score increased significantly with the increase in the number of drugs consumed by patients and the number of diseases diagnosed per patient. Psychiatric disorders and department were related to higher DBI score.

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7. APPENDICES

7.1. Ethical Approval

Ethical approval of the study was accepted by; Yeditepe University Clinical Researches Ethical committee (Report date: 06 January 2017, Number: 684).

8. CURRICULUM VITAE

Personal Information

Name	Abdelrahman	**Surname**	Salhin Abdelbary
Place of Birth	Cairo	**Date of Birth**	26/09/1991
Nationality	Egypt	**ID No.**	
E-mail	abdo1991@gmail.com	**Phone No.**	

Education

Degree	**Domain**	**Graduated From**	**Graduation Year**
Master Degree	Clinical Pharmacy	Yeditepe University	2018
license	Pharmacy	Misr International University	2013
High school	Sciences	Nobel Language School	2008

Foreign Languages

Languages	**Grade**
Arabic	Mother language
English	IELTS 7.5
Turkish	C1

Work Experience

Position	**Institution**	**Period**
Pharmacist	EL-Refaiy Pharmacy	2013
Pharmacist	Ras Gharib Military Hospital	2014-2015

Computer Skills

Program	**Level**
Microsoft Office (Word,Excel,Powerpoint)	Good