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YEDİTEPE UNIVERSITY INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF CLINICAL PHARMACY

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MASTER THESIS

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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.

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Emine YÖNEL

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LIST OF SYMBOLS AND ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADE	Adverse Drug Events
ALT	Alanine Aminotransferase
ARF	Acute Renal Failure
AST	Aspartate Aminotransferase
BD	Bipolar Disorder
BUN	Blood Urea Nitrogen
BZD	Benzodiazepine
CEDIA	Cloned Enzyme Donor Immunoassay
CNS	Central Nervous System
DSM	The Diagnostic and Statistical Manual of Mental Disorders
DDI	Drug Drug Interactions
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra Acetic Acid
EHRs	Electronic Hospital Records
EIA	Enzyme Immunoassay
EIR	Electronic Inpatient Record
FBG	Fasting Blood Glucose
FDA	Food And Drug Administration
FPIA	Fluorescence Polarization Immunoassay
GC-MSMS	Gas Chromatography- Mass Spectrometry/Mass Spectrometry
GFR	Glomerular Filtration Rate
ICD	International Classification of Diseases
LAAM	Levo-Alpha-Acetylmethadol
LC	Liquid Chromatography
LC-MSMS	Liquid Chromatography- Mass Spectrometry/Mass Spectrometry
MDMA	3,4-Metilenedioksi-N-Metilamfetamin
NICE	National Institute For Health And Care Excellence
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PGB	Pregabaline
RIA	Radioimmunoassay
SGOT	Serum Glutamic Oxaloacetic Transaminase

SGPT	Serum Glutamic Pyruvic Transaminase
TCA	Tricyclic Antidepressant
TDM	Therapeutic Drug Monitoring
THC	Tetrahydrocannabinol
UHPLC-MS/MS	Ultra-High Performance Liquid Chromatography- Mass Spectrometry / Mass Spectrometry

ABSTRACT

Yönel, E. (2016). The Effects of Polypharmacy on Plasma Concentrations of Therapeutic Drug Monitoring in Patients with Dependence and Bipolar Disease: A Retrospective Study for Turkish Population. Yeditepe University, Institute of Health Science, Department of Clinical Pharmacy, MSc thesis, İstanbul.

The aim of the study is to examine the prevalence of polypharmacy and its effects on the changes of therapeutic drug levels and also to examine patient and practice characteristics associated with polypharmacy. Data for all 12.734 registrations pertaining to 1.530 inpatients were from NP Hospitals. Aim of the study is to analyze the changes related to the number of drugs and to detect the risk of potentially serious therapeutic drug levels and biochemical parameters over time. As part of clinical routine; serum levels of antidepressants, antipsychotics, fasting blood sugar, AST, ALT, creatinine, urea were recorded from patients' charts of in-patient and evaluated retrospectively. The mean age for all patients was 35.23 ± 0.12 (Mean ± SEM) years. The average of total prescribed drugs for these hospitalized patients is 6.51 ± 0.26 (range, 1-23) drugs. For male, it is 6.69 ± 0.03 (range, 1-21) and for female it is 6.14 ± 0.04 (range, 1-23) drugs. Firstly, the probable effects of polypharmacy on diagnostic types, age and blood chemistry values were examined. Significant increases were observed about the number of drugs in patients with alcohol dependence (7.86±0.08), substance dependence (6.51±0.03); and also number of drugs were highest in their late years. Greater than 70 years old it was (9.3±0.15) and in 20-29 age group it was (5.97 ± 0.03). The number of drugs did not change the levels of fasting blood glucose. The levels of fasting blood glucose (FBG) were increased significantly in diagnosis of substance dependence groups compared to other diagnosis groups. The effects of number of drugs, age, diagnosis and gender on ALT levels were also analyzed but not observed significant effects on ALT. AST levels were not changed by the number of drugs and age, but the gender and diagnosis of the patients significantly changed AST levels. Creatinine levels were not changed by the number of drugs, but the gender, age and diagnosis changed the levels of creatinine. Pearson correlation coefficients between the number of drugs and creatinine levels were r =-0.27, r =-0.209 of male and female, respectively. The number of drugs, gender, age, and diagnosis indicated significant changes on the levels of urea. In male patients group and patients with bipolar disorder, the number of drugs increased the levels of urea. In female patients group, 13 and upper amount of drugs increased the levels of urea more than the other number of drug groups. Secondly, the effects of number of drug on plasma concentrations of drug were analyzed. The number of drug significantly; increased the plasma concentrations of Aripiprazole in 4-6 and 7-9 drug used groups; decreased the plasma concentrations of Bupropion in 7-9 and 13 and upper amount of drugs used groups; decreased the plasma concentrations of Clomipramine in 4-6, 7-9, 10-12 and 13 and upper amount of drug

used groups; increased the plasma concentrations of pregabaline in 7-9, 10-12 and 13 and upper amount of drugs used groups; increased sulpiride plasma concentrations in all drug groups; decreased the plasma concentrations of valproic acid in 7-9 and 10-12 drugs group, except 13 and upper drugs group ; increased the plasma concentrations of Zuclopenthixol in 4-6, 7-9, 10-12 and 13 and upper amount of drugs groups. When examined the plasma concentrations of drug abuse, the number of drugs significantly; increased the plasma concentrations of benzodiazepine in 7-9, 10-12 and 13 and upper amount of drugs used groups; not changed the plasma concentrations of phencyclidine; increased plasma concentrations of ecstasy in all drug groups, except 1-3 drugs used group; not changed the plasma concentrations of opioids in all drug groups.

As a conclusion, the study showed that there were significant correlations between the number of drugs and alcohol dependence, and also between the number of drugs and age. The number of drugs did not change FBG and ALT and AST levels, but increased creatinine levels in female patients, and urea levels in both male and females. The number of drugs significantly increased the plasma levels of aripiprazole, bupropion, pregabaline, sulpiride, zuclopenthixol, benzodiazepine, ecstasy and opiate but, decreased clomipramine, valproic acid.

Key words: Polypharmacy, Aripiprazole, Bupropion, Pregabaline, Sulpiride, Zuclopenthixol, Benzodiazepine, Ecstasy, Opiate, Clomipramine, Valproic Acid, Fasting Blood Sugar, Ast, Alt, Creatinine, Urea, Bipolar Disorder, Dependence, Electronic Health Records.

ÖZET

Yönel, E. (2016). Depresyonlu ve Bağımlı Hastalarda Polifarmasinin İlaç İzlem Plazma Konsantrasyonuna Etkisi: Türk Toplumuna Yönelik Retrospektif Bir Çalışma. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Klinik Eczacılık AD, Master tezi, İstanbul.

Bu çalışmanın amacı polifarmasinin yaygınlığını ve terapötik ilaç düzeylerine olan etkisini ve aynı zamanda hastaların bireysel ve klinik uygulama özelliklerinin polifarmasi ile ilişkilerini araştırmaktır. Veriler, NP hastanelerinde bulunmuş olan 1.530 hastanın 12.734 kayıdına aittir. İlaç sayısından kaynaklanan değişiklikler, zaman içerisinde terapötik ilaç düzeyine ciddi risk oluşabilmesi ve biyokimyasal parametreler incelenmiştir. Rutin klinik uygulamanın bir parçası olan; antidepresan ve antipsikotik ilaçların kan ilaç düzeyleri ile birlikte, açlık kan şekeri, AST, ALT, kreatinin ve üre değerleri yatan hastaların dosyasından kaydedildi ve retrospektif olarak değerlendirildi. Hastaların yaş ortalaması 35.23 ± 0.12'dir. Tüm hastaların reçetelerindeki toplam ilaç sayısı ortalama 6.51 ± 0.26'dır. Erkek hastalarda toplam ilaç sayısı ortalama 6.69 ± 0.03, ve kadın hastalar için 6.14 ± 0.04'dir.

İlk olarak; ilaç sayısının tanı, yaş ve kan kimyasalları üzerine olası etkileri incelendi. İlaç sayısındaki anlamlı deşiklikler şu şekildeydi; Alkol bağımlılığı olan hastalarda ortalama ilaç sayısı arttı (7.86±0.08), madde bağımlılığı olan hastalarda daha az arttı (6.51±0.03); 20-29 yaş grubunda daha az arttı (5.97 ± 0.03); 70 yaş üstü hasta grubunda daha çok arttı (9.3±0.15). İlaç sayısı açlık kan şekeri düzeyini hiç bir grupta değiştirmedi. Açlık kan şekeri düzeyi, diğer tanı gruplarıyla karşılaştırıldığında, madde bağımlılığı grubunda anlamlı bir artış gösterdi. İlaç sayısı, yaş, tanı ve cinsiyetin ALT düzeyleri üzerine de etkileri incelendi, fakat anlamalı bir etki gözlenmedi. AST düzeyleri ilaç sayısı ve yaşla değişmedi fakat cinsiyet ve tanılar AST düzeylerini anlamlı olarak değiştirdi. Kreatinin düzeyleri ilaç sayısı ile değişmedi, fakat cinsiyet, yaş ve tanı kreatinin düzeylerini değiştirdi. İlaç sayısı ve kreatininin düzeyleri arasındaki korelasyonun katsayısı erkeklerde r =0.27 ve kadınlarda r =-0.209 dir. İlaç sayısı, cinsiyet, yaş ve tanı, üre düzeyleri üzerinde anlamlı değişiklikler gösterdi. Erkek hastalarda ve bipolar bozukluğu olan hastalarda ilaç sayısı, üre düzeyini arttırdı. Kadın hastalarda, 13 ve daha fazla ilaç kullanımı üre düzeyini diğer ilaç gruplarından daha fazla yükseltti.

İkinci olarak; ilaç sayısının ilaçların serum konsantrasyon düzeylerine etkileri incelendi. İlaç sayısı anlamlı olarak; 4-6 ve 7-9 ilaç kullanan hasta gruplarında aripiprazol konsantrasyonunu arttırdı; 7-9 ve 13 ve daha fazla ilaç kullanan gruplarda bupropion konsantrasyonlarını azalttı; 4-6, 7-9, 10-12 ve 13 ve daha fazla ilaç kullanan gruplarda plazma klomipramin konsantrasyonlarını azalttı; 7-9, 10-12 ve 13 ve daha fazla ilaç kullanan gruplarda plazma pregabalin konsantrasyonlarını arttırdı; plazma sulpirid konsantrasyonunu tüm ilaç gruplarında arttırdı; 7-9 ve 10-12 ilaç kullanan gruplarda

plazma valproik asit konsantrasyonunu azalttı; 4-6, 7-9, 10-12 ve 13 ve daha fazla ilaç kullanan gruplarda plazma zuklopentiksol konsantrasyonunu arttırdı. Suistimal edilen ilaçların konsantrasyonları incelendiğinde, ilaç sayısı anlamlı olarak; 7-9, 10-12 ve 13 ve daha fazla ilaç kullanan gruplarda plazma benzodiazepine konsantrasyonunu arttırdı; plazma fensiklidin konsantrasyonunu değiştirmedi; plazma ekstazi konsantrasyonunu 1-3 ilaç kullanan grup hariç tüm ilaç gruplarında arttırdı; tüm gruplarda opioid konsantrasyon düzeyini değiştirmedi.

Sonuç olarak; bu çalışma ilaç sayısı ve alkol bağımlılığı yanında ilaç sayısı ve yaş arasında da anlamlı bir korelasyon bulunduğunu gösterdi. İlaç sayısı açlık kan şekerini, ALT ve AST düzeylerini değiştirmedi fakat kadınlarda kreatinin düzeylerini, hem erkeklerde ve hem de kadınlarda üre düzeylerini arttırdı. İlaç sayısı; aripiprazol, bupropiyon, pregabalin, sülpirid, zuklopentiksol, benzodiazepine ve ekstazi plazma düzeylerini analamlı olarak arttırdı fakat klomipramin ve valproik asit plazma düzeylerini azalttı.

Anahtar Kelimeler: Polifarmasi, Aripiprazol, Bupropiyon, Pregabalin, Sülpirid, Zuklopentiksol, Benzodiazepin, Ekstazi, Opioid, Klomipramin, Valproik Asit, Açlık Kan Şekeri, Ast, Alt, Kreatinin, Üre, Bipolar Bozukluk, Bağımlılık, Elektronik Hastane Kayıtları.

1. INTRODUCTION

Drugs prescribed by physicians significantly improve a range of health outcomes, but also cause considerable harm and other unexpected effects such as adverse drug events (ADE), drug-drug interactions (DDI) and polypharmacy. The practice of polypharmacy is a huge concern for drug-drug interactions. Drug therapy becomes more complex with polypharmacy. It leads to increase morbidity, mortality and increases healthcare expenses(1). Pharmacists are greatly positioned in the healthcare system, which gives them the opportunity to suggest pharmacotherapy which is not only effective but also safe. Monitoring DDIs is not only required for drugs which are relatively contradicted, but also equally important for combinations which are considered beneficial in certain conditions. Several studies have been conducted to assess the frequency of DDIs worldwide (2,3).

Drugs can do serious harms at all ages, although they are commoner in older people, who are more vulnerable to drug toxicity because of polypharmacy, multimorbidity, and age-related changes in pharmacokinetics and pharmacodynamics. So, polypharmacy can be defined as prescribing in the way that leads to clinical outcomes of polypharmacy or prescribing which does not align with rational use of medicines principles (4,5). And also, polypharmacy has been associated with risk of adverse events (6), high cost (7), syndromes (3) and reduced adherence to medications by patients (8). Therefore, many treatment guidelines emphasize monotherapy as a first principle (9). However, polypharmacy is very common in real clinical practice and previous studies have found a broad range of polypharmacy rates (30 %) (10,11).For this reason, a number of indicators have been proposed to quantify high risk prescribing in patients, but only polypharmacy or multiple medication usage is an avoidable and preventable clinical event and it can be measured using different risk assessment tools (12,13). Polypharmacy is not only considered as high risk prescribing in older adults (14,15), but also associated with increased risk of harm in mental health care (16,17). Particularly, patients with bipolar disorder and patients with alcohol-and other dependencies have been unluckily expected to take many drugs for long periods during diagnose and treatment process.

In the observational analysis of the pharmacotherapy of 2231 psychiatric inpatients with a current episode of bipolar depression, it has been reported that overall

81.3% of patients received antidepressants (AD), 7.8% monotherapy, 57.9% antipsychotics (AP), 50.1% anticonvulsants (AC), 47.5% tranquilizers, and 34.6% lithium (Li) (18).

The rate of polypharmacy has been changed with wide intercountry variations and results were likely to be influenced by the features of clinics as well as cultural and personal practice factors. The high rate of polypharmacy indicated that, available pharmacological treatments and treatment guidelines are still far from meeting all the needs in the management of diseases.

Anticonvulsant, antidepressant, and antipsychotic drugs can be associated with significant liver injury or liver failure, but this is relatively rare compared to other non-psychotropic drug classes. Prevalently, mild asymptomatic elevations in liver function tests are seen and these are not predictive signs of progression to severe liver injuries. Atypical antipsychotic drugs commonly cause asymptomatic increase in the liver enzymes levels (19). 0.5%-3% of patients treated with antidepressants may develop asymptomatic mild elevation of serum aminotransferase levels (20). Clinical monitoring for signs and symptoms suggesting hepatotoxicity or hypersensitivity reactions that affect the liver is more important. Therefore, the biomarkers of liver and renal functions, such as fasting blood glucose (FBG)(mg/dL), alanine amino transferase(ALT) (IU/L)- aspartate amino transferase (AST) (IU/L) levels, creatinine (µmol/L) and urea (mg/dL) levels have potential to be utilized as bridging markers to monitor acute drug-induced liver and renal injury in patients with bipolar disorder and dependence.

Recently, the surveillance and/or investigation of clinical outcomes and prescription patterns were quantified by electronic health records (EHRs) or electronic databases which are related with patients in hospitals (21). Researches investigating prescription databases (22,23) have been successful in deriving medication data for large populations and over long periods of time by generally extracting data from electronical fields (23). However, these researches have been restricted by the limited nature of the recorded information (22). Data on drug prescription, as well as related recorded information, is usually embedded in free-text fields in mental health care. In this area, EHRs contain large volumes of detailed information in free-text and structured fields, provide an important resource for conducting analyses by using large samples and investigate a multitude of patient characteristics and outcomes simultaneously.

Generally, extracting free-text information has necessitated manual coding. Researcher reads free-text and codes it by hand according to a defined set of coding rules, but this is time and labour intensive and therefore, not always feasible on a large scale. This can result in investigating a smaller than ideal sample. Although this has involved the identification of drugs, there have been no attempts to develop and validate techniques for characterizing meta-data such as polypharmacy (25).

A thorough investigation of prescription patterns for the treatment of bipolar disorder, dependence and alcohol dependence in Turkey will have particular significance in several ways. The information obtained will assist psychiatrists to make sound clinical judgements regarding the appropriate psychotropic medications for an individual. Furthermore, clinical evidence concerning Turkish psychiatric patients with specific clinical circumstances and cultural customs will aid in the development of proper therapeutic strategies for this particular population. A study of this nature will also gather data about prescription patterns across the decades and establish a basis for future research investigating bipolar disorder and dependence treatments in Turkey. Conducting a local study in this way is necessary because the findings of similar studies conducted in other countries may not necessarily be generalized to the Turkish population due to the varied availability of specific drugs and preferred treatment modalities in Turkey. We know also the fact that unique health care system in Turkey may restrict certain prescriptions.

In this study, we have used electronic databases related with bipolar disorder and dependent patients, to examine changes in polypharmacy and the risk of potentially serious therapeutic drug levels over time. The aim of this study is to examine the prevalence of polypharmacy and its effects on the changes of therapeutic drug levels and also to determine patient and practice characteristics associated with polypharmacy and the presence of a potentially serious liver and renal function alterations by using data for all 12734 prescriptions pertaining to 1530 adults with bipolar disorder and dependence cases.

2. POLYPHARMACY AND COMORBID DISEASES

2.1. Polypharmacy

The concurrent use of multiple medications in a single patient is refered "Polypharmacy". However, the use of the term polypharmacy in the published literature is somewhat uncertain and has different meanings with regard to different authors. Mostly, the definition of polypharmacy is made according to the specific number of medications prescribed.

Polypharmacy is alternatively described as the use of two or more psychiatric medications in the same patient (26), or as the use of two or more medications to treat the same condition, use of two or more drugs of the same chemical class, or use of two or more drugs with the same or similar pharmacologic actions (27), or as prescribing of three or more medications for the same indication, or prescribing of two or more medications with the same or similar mechanisms of action(s) used for the same indication(26).

However, using an accurate numeric threshold to define polypharmacy is naturally inexact, because the number of medications considered optimal does vary for different psychiatric conditions.

2.1.1. Polypharmacy and age

Polypharmacy means using multiple drugs simultaneously. It is a common problem for both clinicians and patients, mostly seen among elderly due to comorbid diseases causing undesireable drug interactions.

As mentioned, there is no certain numerical value of polypharmacy but it can be identified by using more than 4-5 drugs at the same time (28). However this definition is practically limited in clinics in which the patients' usage of more than 4-5 drugs can be essential, yet it is still an independent risk factor of side effects (29,30).

In short, prescribing more drugs from clinical indication or at least one unnecessary drug is polypharmacy (31).

There are some differences betwen countries when it comes to frequency of polypharmacy. In United States, some researches have shown that women above 65

years and between 75-85 ranges use more than 5 drugs. The ratio is 23%, 35-40% respectively. (32,33) In England 36% of individuals above 75 uses more than 4 drugs.

Despite the fact that there is no comprehensive study in our country; acccording to a recent research, individuals above 65 years of age who use more than 5 drugs are given fairly high percentages in both women (63,2%) and in men (55.3%). The reason for this high rate probably results from the fact that the research mentioned studied individuals who applied to polyclinics, as opposed to random sample from the Street (28).

Emerging medical technologies and treatments prolonged human lifespan. However, age-related chronic diseases and disability have also increased. According to a survey conducted by the ministry of health in our country; among the elderly population above 65 years, 90% has one, 35% has two, 23% has three and 14% has simultaneously at least four chronic diseases (28).

A geriatric research in our country also reported 2.8, the average number of chronic diseases for female patients over 65 years. 61.1% of the participants had at least three chronic diseases. And the most common three diseases were hypertension 75.3%, depression (45.5%), dementia (39.4%) (34).

The reason of polypharmacy in elderly is multiple comorbidities. Increased number of diseases bring increased numbers of drug with them.

Another important factor is that, individuals with multiple diseases often consult different specialists which means that they write drug prescriptions unaware of eachother (35,36). Correlate with all these, falls are also common in patients using multiple medications.However, there was found a distinct positive association between diuretics, quinine and derivates, and psychotropic drugs (especially anxiolitics and hypnotics) with falling (37,38,39). Consequently, contribution of identifiable risky drugs (mentioned above) to polypharmacy is associated with an increased fall risk, rather than polypharmacy itself (39).

Seemingly, the main reason of polypharmacy is that clinical guidelines for chronic diseases are not often modified for the elderly and patients with multiple comorbidities (28).

2.1.1.1. Polypharmacy and prescribing cascade

Prescribing cascade, an iatrogenic error, is defined when a physician misinterprets an adverse drug reaction as a new disease and initiates an inappropriate drug to treat the symptoms that was caused by the other drug. (40)Unfortunately, prescribing a new drug to compensate for the unforeseen effect of the current medication is common in geriatric cases (41). The resultant morbidity and mortality and its related cost is an enormous burden for society via medical assistance programs that provides hospital expense and medical expense (40).

Older people consume wide range of medications and the increasing number of medications is associated with increased risk for adverse drug effects and possibly ends up with hospitalization. Besides, prolonged hospital stay is associated with other serious complications(40).

Prescribing antiparkinson drugs for the extrapyramidal symptoms relating to the usage of neuroleptics, administration of another (anticholinergic) drug for the urinary incontinence which was caused by the cholinesterase inhibitors used in the treatment of dementia are some examples of polypharmacy in elderly (28).

It has been shown that patients who received antipsychotic treatment over the past 90 days were prescribed anti-Parkinson's medication more than 5.4 times compared to those without in a case-control study among 3512 patients (42).

Primarily used drugs should be controlled and revised in the course of evaluating new symptoms that occur in these conditions.

There is an important published case report about using irrational drug combinations which can be defined as prescribing cascade (40).A 80-year-old Japanese female patient who was unnecessarily prescribed guaifenesin and levofloxacin for the symptom of a persistant cough due to physician's inability to diagnose enalapril as the cause of the cough, leading to opioid-related changed mental status and pseudomembranous colitis.

The patient had a dry cough from enalapril but the physician misinterpreted as of pneumonia and treated with antibiotics. The antibiotics bring with pseudomembranous colitis. The opioid-based syrup and dehydration from colitis contributed to patient's acute delirium as well.

As it is seen, the patient is at risk of developing additional adverse effects related to non-essential treatment (40).

The best prevention of a prescribing cascade is obtaining an accurate list of current medication list, re-evaluating the necessity for starting any new drug, and thus avoiding polypharmacy (43).

2.1.2. Polypharmacy and drug interactions

Several types of drug interactions exist: These are drug-drug, drug-disease, drug-food, drug-alcohol, drug-herbal products, and drug-nutritional status.

Some software programs can help clinicians to detect drug interactions, but many of them have not been updated with the evolving knowledge of these interactions (44).

Most undesirable drug events occur in older adults, a fact that is attributable to their greater use of drugs, increased vulnerability due to underlying medical conditions, and age-related physiologic changes (45).

'The effect that one drug has on another' is the definition of drug-drug interaction. Drug-drug interactions can be pharmacokinetic or pharmacodynamic in nature, and they are not restricted to older adults.

Pharmacokinetics (what the body does the drug) include the effects of one drug on the absorption, distribution, metabolism, or excretion of another drug. These interactions can result in changes in blood drug concentrations and they might change the clinical response (44). The most prevalent pharmacokinetic drug-drug interactions involve multiple hepatic cytochrome P450 isoenzymes and drug transporters such as organic anion transporters and P-glycoprotein (46,47).

Pharmacodynamics (what the drug does the body) is associated with the pharmacological activity of interacting drugs (44) .

2.1.3. Types of polypharmacy

National Association of State Mental Health Programme Directors (NASMHPD) categorized polypharmacy due to its comlexity and increasing prevalence in psychiatry.

1. **Same-class polypharmacy:** Means the use of more than one medication from the same class (e.g. use of two selective serotonin reuptake inhibitors in a case of depression).
2. **Multi-Class Polypharmacy:** Refers to the use of full therapeutic doses of more than one medication from different classes for the same symptom cluster (e.g. use of valproate together with an atypical antipsychotic, such as olanzapine, for treatment of mania).
3. **Adjunctive Polypharmacy:** Refers to the use of one medication to treat the side effects of another medication from a different class. (such as, using trazodone for insomnia that caused by bupropion).
4. **Augmentation Polypharmacy:** Is the use of one medication at a lower than normal dose along with another medication from a different class in full therapeutic dose for the same symptom cluster (e.g. addition of low dose haloperidol in a patient responding partially to risperidone); or the addition of a medication that would not be used alone for the same symptom cluster. (augmentation of antidepressants with lithium or thyroid hormone).
5. **Total Polypharmacy:** The total count of medications that used in a patient, or total drug load of the patient (48).

2.1.4. Polypharmacy in psychiatry

There has been an increase in the use of polypharmacy in psychiatry possibly due to the newer drugs, greater availability of these new drugs, excessive confidence in clinical trial results, prescribing psychotropic medications by primary care providers widely, and pressure to augment with additional medications for unresolved side effects or for the greatest efficacy with in possibility, even the new generation of medications may not hold significant advantages over older ones. There may be additional safety risks due to carrying out polypharmacy widely.

On the other hand washout provides incomparable benefits to the physician. For example, it helps identify medication efficacy from their adverse effects, provides clarity regarding interpretation about diseases and potential reduction of drug treatments, drug interactions, and certainly the costs. It may also reduce adverse events.

If necessary, physicians may be able to choose the appropriate polypharmacy more effectively and safely, after washout process.

While the above passage focuses on the advantages of washout, tapering a patient off their existing medications is not recommended for everyone. Withdrawing from specific medications (e.g neuroleptics), as well as severity of illness, speed of withdrawal, and patient status (in patient versus outpatient), are all variables to be considered before the decision of washout (49).

The reasons of increased polypharmacy in psychiatry may be multifactorial, such as an increasing number of suitable medications targeting new and different symptoms and receptors, or even the enforcement on psychiatrists to focus on medication treatment (26).

Some recent resarches (as Insel's study 2009) raise doubts about the degree to which psychopharmacological treatment has kept pace with our advances in understanding the brain and psychiatric disorders. Insel observed that, second generation medications have consistently demonstrated no significant advantage compared with first-generation medications in multiple comparative effectiveness studies that funded by the National Institute of Mental Health (50).

According to frequency of polypharmacy study; at least three medications at hospital discharge for bipolar disorders or unipolar depression, polypharmacy increased from 3.3% of patients (1974–1979), to 9.3% (1980–1984), to 34% (1985–1989), and to 43.8% (1990–1995) (51). Correlatively, in another study conducted between 1996 and 2005, psychiatrists significantly increased their use of polypharmacy so that two or more prescribed psychotropic drugs increased from 42.6% in 1996 to 59.8% in 2005 and three or more drugs prescribed nearly doubled in outpatients. (16.9% to 33.2%) (52).

There are a lot of new psychiatric medications; fortunately, in recent years there is growing awareness that these new generation medications may not hold significant advantages over older medications despite their relatively higher costs (26).

Besides of the increased danger of adverse events and excess side effects, not to mention increased cost of care, the authors noted that psychiatrists often got stuck when trying to switch patients to another drug; you know, they became fearful of removing the current medication by erroneously thinking that even if it is clearly not working, it may be better than nothing at all, and adding another agent might help. This causes the

patient to be put on an additional medication instead of purely changing medications (52).

Adherence to medication regimen like that is a topic in itself. Several studies indicate that the number of medication and regimen complexity are key factors. This requires to limit both the number of medications prescribed and to simplify the regimen whenever possible (45).

For most psychiatric disorders, adherence to medication regimens is often problematic and it is a major cause of poor treatment outcomes. For example, non adherence with prescribed antipsychotics is associated with poor functional outcomes, such as higher risk of relapse, hospitalization and increased risk of suicide, in schizophrenia (53-55).

2.1.4.1. Polypharmacy and inreased usage of antidepressants and antipsychotics in different patient populations

An important recent study reported regarding usefulness of polypharmacy, funded by the National Institutes Of Health, testing whether starting several antidepressants (with synergistic pharmacological effects) at the same time would be associated with increased efficacy. Patients with major depressive disorder were randomized to a 12 week treatment with escitalopram plus placebo, escitalopram plus buproprion sustained-release, or venlafaxine extended-release plus mirtazapine. Participants who experienced substantial benefit in the acute phase were recorded in an additional 16 week continuation treatment. In either the acute phase or the continuation phase there was no significant difference observed between the response or remission rates.

But in the two polypharmacy arms side effect burden was significantly higher (56).

Addition of atypical antipsychotics (except approved indications) into the polypharmacy mix is another worrrying trend of modern psychopharmacology.

Furthermore, between 1997 and 2000, 30% of antipsychotics were prescribed by nonpsychiatric physicians (57). Recent trends eventually represent increased prescribing of atypical antipsychotics for treatment resistant depression and bipolar disorder which are indications approved by the FDA, but also for treating irritability in autism, which is not.

Moreover, a search of Clinical Trials.gov demonstared hundreds of additional trials underway for a wide variety of new atypical antipsychotic indications, including trials of quetiapine for irritable bowel syndrome, insomnia, fibromyalgia and benzodiazepine replacement, alongside agreat number of additional nonpsychotic psychiatric disorders (26).

2.1.4.2.Substance dependence and psychiatric comorbidite

There is a high percentage of psychiatric comorbidite among patients with cocaine addiction perhaps due to the absence of a generally effective medication.
The major comorbid disorders studied have been ADHD, schizophrenia and depression. (58) Some previous studies suggested that bupropion and desipramine reduced both depressive symptoms and cocaine use in cocaine-abusing, methadone maintained patients with comorbid depression but not in cocaine abusers without comorbid depression (59,60). In a randomized clinical trial with schizophrenic patients, desipramine was more likely than placebo to reduce cocaine use during active treatment and nearly two months following the discontiuation (58).
Also disulfiram decreased cocaine use in cocaine abusers with alcohol abuse or dependence and among methadone maintained cocaine abusers without dependence and abuse of alcohol (61-63).

By the way, behavioral interventions, particularly contingency management have been examined in drug dependent individuals. It has been seen that contingency management provides some efficacy in facilitating illicit drug abstinence in dually cocaine- and opioid-dependent individuals(64,65). Contingency management has also been shown to promote treatment retention in cocaine abusers (66).In the course of opioid maintenance treatment, dually cocaine- and opioid-dependent individuals with and without post-traumatic stress disorder (PTSD) have similar treatment outcomes in the presence of contingency management procedures. However, in the absence of contingency management, patients with PTSD may have worse treatment outcomes (67).

As you see, substance dependence is often associated with particularly poor mental health problems, poor treatment outcomes, inferior social and educational conditions, stigmatization, domestic violence and homelessness (68-70).In the US, a

comorbidity survey has shown that ‘One-half of people with a lifetime substance use disorder have at least one mental health problem lifetime.’ (71,72).Co-occuring mental health issues and substance use disorder influence eachother and (73) patients with mental disorders often increase their usage of illicit drugs (74).Meanwhile, males are more likely to have substance dependence with or wirhout co-occuring disorders. Conversely, females are more likely to have mental disorders only (75).

When it comes to co-occuring mental disorders in different genders; females are more likely to have anxiety and mood disorders whereas males are more likely to have antisocial disorders(76).

Furthermore, stigmatization is still an important barrier to all dependent patients’ rehabilitation. That’s why some studies suggest that stigmatization induces greater psychological pain than mental disorder or addiction itself (77).

2.1.4.3.Polypharmacy in schizophrenia

Antipsychotic drugs have been playing a momentous role in the treatment of schizophrenia for more than 50 years Antipsychotic treatment significantly improves acute symptoms and reduces the risk of relapse; however, this also causes unwanted adverse events, including, cognitive, metabolic, and cardiovascular side effects

Several treatment guidelines have been developed to achieve optimal psychopharmacological treatment for schizophrenia. Nonetheless, in reality, daily clinical practice has been reported to deviate from those guideliness.

Dosing antipsychotic drugs outside the recommended ranges and antipsychotic polypharmacy have been shown to be common in previous cross-sectional prescription surveys. In the US 53,661 prescription drug records of patients with schizophrenia showed antipsychotic dose was outside the range suggested by treatment guidelines for schizophrenia.Correlatively, another study suggested that 47% of patients diagnosed with schizophrenia were not dosed within the recommended rage. In clinical practice antipsychotic polypharmacy is also common despite limited empirical support.

In a longitudinal antipsychotic prescriptions in 300 patients with schizophrenia, a wide variety of combinations were found to be performed; the most frequent actual combination was risperidone plus chlorpromazine, followed by aripiprazole plus

quetiapine, risperidone plus quetiapine, risperidone plus olanzapine and risperidone plus aripiprazole. This study was conducted in 4 participating psychiatric clinics in Tokyo.

Researchers found that physicians sometimes judged antipsychotics as being 'ineffective' without sufficiently exploring the entire dose ranges. And interestingly, polypharmacy was employed in as short as 2 months and with as few as a single antipsychotic trial, suggesting that physicians may apply antipsychotic polypharmacy without trying an adequate number of drugs in the treatment of schizophrenia. And antipsychotics were switched to another, nearly half of the antipsychotic monotherapy episodes eventhough the maximum dose of the previous drug did not reach even the lower limit of the recommended dose range that mentioned in guidelines (78).

2.1.4.4.Polypharmacy in bipolar disorder

Despite a lack of emprical evidence for any combination of three or more medications, patients treated for bipolar disorder receive wide range of psychotropic medications concurrently.With a skillful management of a complex medication regimen, it can be helpful as well as problematic for patients with bipolar disorder.

Polypharmacy may be helpful in two circumstances. The first is when clinicians use combinations of treatments consistent evidence based guidelines. Secondly, it can be acceptable for bipolar patients with inadequate response to proven combinations but who apparently benefit from powerful complex care regimens.

Beyond these two groups, polypharmacy often leads to inadequate response to five or more psychotropic medications over six months. And this is a common problem for both the patients and their clinicians.

Recommendations from treatment guidelines arised from modest number of double blind clinical trials showing better efficacy for combinations of lithium or valproate with atypical agents. Additionally, the subjects recruited in these studies were often randomized from the patients who have not responded to monotherapy(79).

2.1.4.5.Antipsychotic polypharmacy in developmental disabilities

Antipsychotic medication rate in adults with developmental disabilities is accompanied by the mentioned trend above. Significant attention has been paid to the use of antipsychotic medications because of some recent research demonstrating their

inefficacy in treating aggression, one of the more common reasons they are prescribed in this population.

The main topic was that this vulnerable population would have high rates of antipsychotic use in addition to the use of their current medications.

Findings from several studies suggested these patients are at highest risk for being prescribed two antipsychotics at once. In 2012; a study is conducted about rates of antipsychotic use in adults with developmental disability who had experienced a psychiatric crisis showed that nearly half of their sample were prescribed antipsychotics. And polypharmacy was common with 22% of those prescribed antipsychotics taking two or more antipsychotics at once. According to the research predictors of multiple antipsychotic use included gender, residence, psychiatric diagnosis and previous hospitalizations. And implications of polypharmacy to this vulnerable population are discussed.

Researches in the US, UK and Australia have shown high rates of psychotropic medication in adults with DD living in the community with antipsychotics most commonly prescribed (80).

2.1.4.6.The reasons and evidence based clinical outcomes related to polypharmacy

In most cases the evidence does not support the use of antipsychotic polypharmacy; such as, one randomized, double blind, placebo-controlled trial failed to demonstrate any added efficacy of the addition of aripiprazole to risperidone or quetiapine.However, a possibility of effectiveness of treatment with combined antipsychotics cannot entirely be rejected in treatment resistant cases.

According to another prior report, quetiapine and clozapine were most often part of antipsychotic polypharmacy.Indeed quetiapine often seems to be combined at a lower dose for sleep induction, anxiety, and agitation due to not increasing extrapyramidal side effect burden. Combining clozapine with another antipsychotic agent is arguably most justified, as there are no other options for difficult-to-treat clozapine resistant patients and/or those intolerant of higher doses. Further, the best evidence involves clozapine combinations.

Antipsychotic polypharmacy has been studied mainly because of the lack of evidence for its effectiveness and safety.Previous surveys that participated physicians

who prescribed antipsychotic polypharmacy demonstrated that polypharmacy was used because of a failure of antipsychotic monotherapy and/or their disbelief in treatment guidelines.In another study clinicians were asked how much certain clinical scenarious justified antipsychotic polypharmacy. They mentioned the following scenarious justified antipsychotic polypharmacy most: cross-titration, failed clozapine trial, randomized controlled evidence, and clozapine intolerance.

Overall, there is an increasing concern that physicians may perform an antipsychotic switch without exploring the entire dose range and they resort to antipsychotic polypharmacy without trying an adequate number of antipsychotics. And prior co-treatment was reported being a strong predictor and relatively appropriate justification of future polypharmacy (78,81).

2.1.5. The probable effect of polypharmacy on blood chemistry values

2.1.5.1.Glucose

Glucose is a metabolic fuel for tissues. Dietary carbohydrate, gluconeogenesis and hepatic glycogenolysis are the sources of glucose. The principal storage form of glucose is glycogen. Glycogen is also exist in skeletal muscle but the glucose derived from there is not released into the circulation (82).

Glucose levels of 80-110 mg/dl named as normoglycemia in other words ‘tight glycemic control’ decreased morbidity and mortality of critically ill patients (83).

Commonly it is measured spectrophotometrically by using enzymatic methods.

As you know, causes of the high levels of blood glucose concentrations include; impaired glucose tolerance, impaired fasting glycemia and no wonder DM.

Probable causes of hypoglycaemia are; insulin or oral antidiabetic usage, tumours, alcohol and other drugs, chronic liver or kidney disease, sepsis, etc... (82).

According to a recent research in UK, the average prevelance of diabetes was 4 % with an alarming increase compared to data for previous years(84).Another previous study showsglucose variability and their association with intensive care and mortality state. Inspite of the heterogeneity of the studies, design, methodological and reporting limitations;glucose variability is referred as a significant clinical tool and found to be associated with mortality by increasing oxidative stress, neuronal damage, and coagulation activitity (82).

2.1.5.2.Aspartate aminotransferase(AST), alanine aminotransferase (ALT)

AST and ALT are called liver enzymes and related tests are called liver function tests although the enzymes are not specific to the liver. As follows, you see AST in muscle, heart, kidneys, red cells, brain, small bowel except existing in the liver. ALT is not widely spread but you also see it in the muscle and kidney (85).So far AST and ALT are called serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), respectively (86).

Normal serum concentrations are 0 to 35 U/L for AST and 7 to 56 U/L for ALT (87).

ALT is solely in cytoplasm, cytosol. But AST exists two different isoforms which are immunologically distinct, the mitochondrial and cytoplasmic form (85).

Primarily, measurements of the liver enzymes are crucial in the diagnosis and assessment of liver disease (86). Not specific for liver disease, it can be used in combination with other enzymes to monitor the course of multiple liver disorders as well. ALT released in the blood is catabolised in the liver with a resulting plasma half-life about 47 hours whereas the half life of AST is about 17 hours (86).

When body tissue or an organ such as liver or heart is diseased or damaged levels of these enzymes are rised in the bloodstream. The amount of AST and ALT is directly related to the extent of the tissue damage. After the occurance of severe damage, AST levels rise 10-20 times greater than normal value, whereas ALT can reach up to 50 times greater than normal. Moreover, the ratio of AST/ALT may help determine whether the liver or another organ has been damaged (88-90).

The administration of many medications has been associated with elevated levels of transaminases such as opiates, salicylates...And comparable increases of these enzymes are highly characteristic of acute viral, toxic or nonethanol drug induced hepatitis (91).

2.1.5.3.Urea

Urea is an organic compound and has a vital role in the metabolism of nitrogen-containing compounds.

During the process of protein catabolism, urea cycle enzymes convert amino acid nitrogen to urea in the liver. More than 90% of urea is excreted by the kidneys, with

losses through the gastrointestinal tract and skin which are responsible for most of the minor fraction. Eventually, kidney disease is associated with accumulation of urea in the blood and so measurement of blood and serum urea has been used for many years as an indicator of kidney function. Recently it is accepted that creatinine measurement provides better information on that however, serum and urinary urea still provide useful clinical information in particular cases. (92)

As you know, expressing results of an urea assay in units of urea nitrogen appears to be entrenched worldwide.

The reference interval for blood urea nitrogen is 6-20 mg/dl (2.1 to 7.1 mmol/L) in healthy adults, as to the adults older than 60 years of age, the reference interaval is 8 to 23 mg/dL (2.9 to 8.2 mmol/L). Serum concentrations slightly higher in males than females and tend to be slightly lower in childhood and pregnancy.

The measurement of urea is based on the hydrolysis of urea with urease. Then the generated ammonia is quantified by various spectrophotometric systems(92).

The probable causes associated with abnormal BUN results briefly stated below:

Highest values are seen in established renal failure, urinary tract obstruction, shock, dehydration, burns, congestive hearth failure, gastrointestinal bleeding, nephrotoxic drugs.

Low values are seen in low-protein and high carbonhydrate diets, hepatic failure, nephrotic syndrome (93).

2.1.5.4.Creatinine

Creatinine is produced from the breakdown of creatine and phosphocreatine. Creatine is synthesized in the liver, pancreas and kidneys from arginine, methionine and glycine amino acids by transamination reactions. Then creatine is converted to phosphocreatine in the skeletal muscle and brain following the circulation throughout the body.

The majority of the creatinine is produced in the muscle, so patient’s muscle mass influences plasma creatinine concentrations.

Compared to BUN, creatinine is less affected by diet and more available as an indicator of renal function.

The measurement of creatinine concentrations in plasma and urine samples demonstrates the filtration capacity of the glomerulus. (GFR)

Creatinine is an endogeneous product and freely filtered by the glomerulus. Therefore creatinine is a useful endogenous marker for creatinine clearance. If the GFR is decreased, as in renal disease, creatinine clearance via the renal system is compromised. Reduced GFR will end up with an increase in plasma creatinine concentration. The measurement of plasma alone should not be used to assess renal function. For each 50% reduction in GFR, serum creatinine nearly doubles.

Plasma creatinine levels may not be affected until significant renal damage has occured. Creatinine may be measured either chemically or enzymatically by using serum, plasma, or urine specimens. Multiple enzymatic methods utilizing creatiniase have been used to measure creatinine by spectrophotometric techniques.

The normal serum creatinine level is 0.6 to 1.2 mg/dL. In short, causes of the high values of plasma creatinine may be renal failure, urinary tract obstruction, hypothyroidsm and nephrotoxic drugs whereas the reasons of the low levels are cachexia, reduced muscle mass, and aging (94,95).

2.2. Substance Dependence

A pleasure system that is prabably responsible for drug reward and addiction is discovered in 1960; ever since, researchers examined the mechanisms by which drug abuse affect central nervous system and lead to addiction (95).

According to a previous study in 2002, all drugs of abuse direct or indirectly stimulate the dopaminergic neurons located in the ventral tegmental area and thereby increase the dopamine tone.

The brain rewad system consists of predominantly dopaminergic neurons whose cell bodies are located in the ventral tegmental area and whose projection targets are in forebrain structures such as prefrontal cortex, nucleus accumbens, hippocampus and amygdala (97).And the brain stress system which is in close functional relation with the reward system consists of the main parts of the limbic system, including the amygdala,hypothalamus, hippocampus, pituitary gland and the adrenal gland (98,99).Recent studies have shown that drug addiction prevention is associated with

avoiding from stress and stabilization of the brain stress system(96). Moreover, stress-relieving treatments can improve the stability of drug addiction treatments.

As you know, substance misuse disorder is still a major health challenge. The initial treatment goal is harm reduction by reducing illicit drug use. The ultimate harm reduction goal is abstinence. You know, a totally medication free life may represent the last stage of recovery.

Effective pharmacotherapies for opioid dependence and withdrawal contain methadone, LAAM, naltrexone, buprenorphine, and clonidine. And drugs for cocaine addiction include dopamine agonists or blocking agents, anti-craving agents, antidepressants, and treatment of co-morbid psychiatric disorders.And other developments include ultra-long-acting formulations some of which have already been produced or are in early clinical practice. Efficacy rates can vary widely because the addicted population is heterogeneous. The corollary is that there is no one best treatment for all dependent patients and these heterogeneity requires a variety of approaches.

Achieving sustained recovery is a common problem for patients with both heroin and cocaine dependence. Some addicts have another psychiatric problems as well as substance use disorder. Treating them will not cure the addiction but relapse is much more likely to occur if the concomitant psychiatric disorder is not diagnosed and treated (58,100).

The other reasons of continued use of illicit drugs during and after the treatment may be prior treatment for opiate addiction, no prior abstinence from opiates, high stress, unemployment/employment status and association with substance abuse friends (101).

Longer duration in treatment; having skilled, well compansated jobs instead of having extensive free time, an intact marriage and sure being voluntary are all associated with better outcomes (58).

2.2.1. Opioid dependence

Heroin use has risen since the mid-1980s, ascended by increased purity and decreased price. Roughly, one in every four individuals who tries heroin ends up meeting criteria for DSM-IV dependence.

There was a little doubt that it is wrong to treat addiction with ‘other drugs’ such thinking sets chemical dependence apart from other chronic diseases. O’Brien and McLellan has suggested several similarities between substance use disorder and other chronic disorders such as hypertension, asthma, diabetes, containing the rates of successful treatment outcomes. There is no one best reatment in any of the above chronic disorders. However, the right treatment for each patient includes a combination of physiologic and behavioral components. For example, in diabetes; some patients need oral hypoglycemics, some need insulin and some can alter eating habits. Insulin-dependent diabetic is not inspected as a lesser person. Likewise using medications to treat drug dependence does not mean that these patients are weaker or less moral. The same way, pharmacotherapy for addiction is not ‘curative’, with the exception of the drugs for withdrawal or overdose. Withdrawal from heroin use is easily ‘cured’ by medications like clonidine and its overdose is reversed by naloxone.

Perhaps some day mankind will learn how to reverse the brain changes relevant to addiction that prevent it from being cured in the way that infection is cured by antibiotics.For now opiate addiction pharmacotherapy includes agonists, partial agonists, antagonists, anti-withdrawal agents, and anti-craving agents (58).

2.2.1.1.Methadone

The two principal agonists used for opiate dependence are methadone and the long-acting form of methadone, L-alpha acetylmethadol (LAAM) (58).

Both the NICE guidelines and the Drug Misuse and Dependence UK guidelines, suggest the evidence base supporting opiate substitution treatment and both sets of guidelines refer the usual maintenance dose range for methadone as 60-120 mg per day. However, methadone has a high dependence potential, like other opiates, and sure risk of fatal overdose (100).

A recent research based on prescribed methadone or buprenorphine over a 16-year period (1990 to 2015) by using data from UK General Practice Research Database has shown that the overall risk of death during treatment was lower than the risk of death out of treatment (102). The initial 4 weeks of treatment associated with increased risk of overdose mortality (102-105) probably due to any use of other respiratory depressant drugs, too high initial dose of the maintenance agent (e.g. methadone) and

polysubstance misuse. Therefore, appropriate assessment and titration of doses are essential at treatment induction (106-108).

Patients who prescribed >100 mg of methadone per day with comorbidities such as heart or liver disease, electrolyte abnormalities and also patients who are on concomitant treatment with other medicines should be carefully monitored due to risk of QTc interval prolongation on ECG (100,109,110,111).

Methadone is an orally effective, 24-hour opioid with minimal psychoactive effects in the tolerant addict. On the contrary, heroin is relatively ineffective (when taken orally), short acting and so euphorigenic. If the methadone dose is high enough, it can block the effects of routine doses of heroin by cross-tolerence. When the methadone dose is <40mg per day, concomitant use of heroin is high; above 80 mg per day it is sharply lower. Patients often prefer lower dose of methadone for experiencing the euphoric effects of heroin.

Methadone can be a difficult drug in the course of tapering off the doses about 25-30 miligrams. Because the therapeutic effects may not last 24 hours and the patient go into withdrawal and unluckily they are exposed to undesirable adverse side effects.

2.2.1.2. Levo-alpha-acetyl-acetylmethadol

When it comes to LAAM, it appeared to be an easier drug from which to withdraw and its affect could last as long as three days so required fewer clinic visits. However LAAM poses risks in terms of fatal ventricular arrhythmia. For this reason FDA does not recommend LAAM as a firs-line therapy for the treatment of opiate addiction. Moreover LAAM is more expenive than methadone and necessitate periodic EKGs (58).

2.2.1.3.Buprenorphine

Buprenorphine is a synthetic partial opioid agonist (with a high affinity to μ receptors) and also a kappa antagonist. It is available as a single agent or in a branded combination with naloxone named ‘Suboxone’.

As a partial μ agonist, it has less respiratory depression thus decreases the likelihood of fatal overdose. The ceiling agonist effect is roughly at 32 mg of the sublingual tablet.

Compared to methadone or heroin, the withdrawal syndrome from buprenorphine is very mild. It can be used as a maintenance agent or a transition agent from agonist to antagonist (58). For transition to buprenorphine, patients receive no higher than 40 mg of methadone according to current protocols.

Buprenorphine should not be administered to the opioid dependent patient until that person is experiencing withdrawal because if it is given to somebody already dependent on opiates, withdrawal can be precipitated by its too high (antagonist effect) or too low (inadequate cross-tolerance) dose. So starting patients on this therapy is not a simple approach.

Combination of buprenorphine and naloxone are available in pharmacies intended for sublingual administration. Naloxone is added as an abuse frustrating agent, thus it is available outside of methadone clinics.

Naloxone is a short acting opioid antagonist. Sublingual formulation is designed because minimal naloxone absorbtion and bio-availability is targeted to avoid narcotic withdrawal symptoms.

Buprenorphine monotherapy is planned for use during pregnancy.

Being much safer in overdose, easier withdrawal, necessitate fewer clinic visits are all advantages of buprenorphine (58).

Its high affinity for the receptor prevents the euphoriant effects of opiates taken alongside of the prescribed medication.

The maintenance dose range of 12-24 mg per day is recommended for buprenorphine and newly prescribed drug is advised to be taken under supervision roughly the first three months due to the compliance concerns.

As you know, buprenorphine has a high affinity for μ-receptors and binds more tightly than heroin or methadone so it prevents the receptors from additional opioids during the treatment. Buprenorphine indirectly affects craving such that, at doses 16 mg or above, its blockade effect increases then the patient give up using non-prescribed opiates (100).

In some European countries another oral option is slow release oral morphine that is primarily used for the management of acute and chronic pain (112).

2.2.1.4. Injectable Opioids

A previous study evaluated the forms of opioid substitution for those individuals whose oral methadone was unsuccessful. In one arm of the study participants received injectible diamorphine under direct supervision; in the second arm they received injectable methadone under direct supervision; and those in the third arm received oral methadone. The injectable diamorphine arm included the option of oral methadone to provide stability overnight bccause of the shorter half life of diamorphine.

Consequently, it is found that at 6 months the proportions of participants achieving 50% or more negative samples for street heroin were highest in the injectable heroin group 66% followed by injectable methadone 30% oral methadone 19%. And also some other randomised trials have all reported that; injectable heroin should be provided with close monitoring for the chronic heroin addicts (113).

Supervised injectable opiate treatment is accepted as a second line treatment by English Department of Health for the people who have repeatedly failed to respond standart methadone treatment (100).

2.2.2. Naltrexone

Naltrexone blocks the ability of opiates to access the μ receptor by competitive antagonism and has approximately 140 times greater affinity than morphine for the μ receptor. It is orally effective and the effect lasts from 24 to 72 hours. If it is applied to somebody who currently is addicted to opiates, it precipitates severe withdrawal.

In 1984 it was approved by the FDA for the treatment of opioid addiction and alcoholism (58).

2.2.3. Detoxification

Detoxification can be the entrance into treatment but many addicts who enter detoxification do so only to lower their level of dependence for making their habit cheaper. NICE recommends both methadone and buprenorphine for use as detoxification agents but the most common method is methadone taper.

Another detoxification method necessitates the use of α-2 adrenergic agonists such as clonidine or lofexidine. They require no special license because they are not

opioid. They provide relief of some symptoms (such as tachycardia, sweting, rhinorrhoea and shivering.) However they are not effective as a sole agent in those with substantial opioid dependence (58,100,114). Their antihypertensive properties warrant blood pressure monitoring (58,100). Withdrawal symptoms not relieved by methadone or the α-2 adrenergic agonists are treated with agents such as NSAIDs or baclofen for muscle aches; various hypnotics, zolpidem, chloral hydrate, or trazadone for insomnia (58).

A third alternative for withdrawal method is the rapid detoxification. The goal is displacing opiates from the receptor sites and precipitating immediate withdrawal by using a narcotic antagonist. The techniques vary widely. For example the patient can be switched from heroin to buprenorphine for one day, then the clonidine/naltrexone procedure is initiated for tolerable withdrawal symtomps. The other form is ultra rapid detoxification which includes heavy sedation for 4-6 hours with midazolam or general anesthesia. Next withdrawal is initiated with an antagonist such as naltrexone or nalmefene. And multiple medications are administered to decrease withdrawal symptoms and so on. Unfortunately, the procedure has been associated with a number of deaths, particularly related to pulmonary edema (58).

2.2.4. Stimulant drugs addiction

Amphetamines and cocaine are stimulant drugs. They have high dependence potential and withdrawal syndromes such as agitation, significant distress and physical discomfort leading to admission to hospital.

Nearly one in five who tries cocaine ends up dependent. The proportion for alcohol is around 15%, and 9% of those who ever try marijuana meet criteria for DSM-IV dependence. As yet, there is no satisfactorily pharmacological treatment for amphetamine and cocaine abuse and dependence.

Withdrawal arising from cocaine, nicotine and marijuana is relatively mild. Unlike heroin addiction their withdrawal produce mainly psychological symtoms and minimal physical ones (58,100).

The main treatments of cocaine and amphetamine are still psychosocial interventions and contingency management. The use of dopamine agonists,

antidepressants or anticonvulsants is not recommended with the exception of those patients comorbid with cocaine dependence and depression (58,100).

Cannabis use is common, particularly among young people and regular use of cannabis associated with a number of health, emotional, social, and legal problems. Pregnant and mentally ill people especially at risk of related harms.

Treatment of cannabis dependence based on gradual reduction of intake with symptom control to help avoid relapse and self medication. And sure, co-morbid psychiatric diseases should be assessed and treated (100).

2.2.5. Dependence of prescribed medications and over the counter (OTC) drugs

Analgesics (Dihydrocodeine, tramadol), anxiolitics and hypnotics (benzodiazepines,zolpidem,zaleplon,zopiclone), stimulants used to treat ADHD (methylphenidate), anticonvulsants and mood stabilising drugs are the major groups of misused drugs (100).

Prescription opioid misuse has currently become a common problem in the US in 2007. The population with prescription opioid dependence are characterized by their experiences with pain or their histories of heroin use (115).

Dependence on prescribed opiates like codeine-based analgesics can be treated by opioid substitution with buprenorphine. And naltrexone may have an enormous potential role of the treatment of highly motivated opiate users such as medical staff (116).

No medications are recommended for treating benzodiazepine dependence. It is treated with gradual reduction or patients are switched to non-benzodiazepine anxiolitics or they are prescribed antidepressants or mood stabilisers where a diagnoses of depression has been made. Additional behavioral and psychosocial approaches improve the effectiveness of gradual dose reduction, especially in patients with panic disorder and insomnia (117).

2.3. Therapeutic Drug Monitoring

Clinicians were widely dependent on trial and error to determine the appropriate drug dosage for a particular patient previous to the advent of therapeutic drug monitoring (TDM).

Trial and error terapy unluckily placed both the patient and the physician at the mercy of an unknown factor that is the kinetics of the drug in a particular individual.

Owing to the usage of TDM, more accurate titration of dosage, adherenece monitoring and proper individualization of drug therapy can be made. TDM often allows patients to be maintained on monotheraphy and perevents them from the risk of adverse side effects, potentially toxic levels.

Clinical guidelines for antipsychotics and the treatment of schizophrenia recommend TDM for clozapine. Recently updated TDM-specific European guidelines 'strongly recommend' TDM for risperidone, amisulpride, and olanzapine. This recommendation is understandable in light of evidence from UK-based studies of clozapine, risperidone, amisulpride, and olanzapine that argued high degree of variance in drug concentration plasma levels. Only 29%-45% of samples were in the recommended range, many of them exceeded the limit. You know, clinical guidelines can give direction to prescribing decisions, but antipsychotic dose adjustment remains a complex process. So, exploring potential tools that could improve this clinical process deserves further researches.

Clinicians felt that TDM should be applied either establishing dose or as indicated in certain circumstances.

The truth is that; TDM allaows safer prescribing and might decrease unnecessary exposure to antipsychotics. It means TDM is a potentially useful tool for individualized treatment decisions. (118)

3. PATIENTS AND METHODS

The increased usability of electronic health/hospital record (EHR) systems have facilitated the use of routine healthcare data in observational retrospective studies. Pooling EHR data among data partners provided to afford statistical datasets for evaluating rare outcomes and so those of diverse populations has been recognized. Confidentiality issues remain serious obstacles when seeking to consolidate healthcare data from different data holders (119). EHR or Observational Health Data from Neurology and Psychiatry Hospital database included the demographic characteristics of patients, important clinical signs and symptoms and the laboratory test results. In thesis, the demographic characteristics of patients and laboratory test results are evaluated.

3.1. Patients

Male and female patients between 18–88age ranges with a diagnosis of depressive disorder and dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, were eligible for this study. Prescribed drugs for inpatient individuals at the Neuropsychiatry Hospitals of Üsküdar Universitywere determined in this study and patients were included if they visited and hospitalized at least once between January 1, 2012 and June 30, 2015.

NP Hospitals are connected with Üsküdar University. Uskudar University is the unique thematic university in Turkey. NP group contains; NP İstanbul Hospital, NP Etiler Polyclinic, NP Feneryolu Polyclinic and NP Altunizade Polyclinic.

We retrospectively reviewed the data mainly from NP İstanbul Hospital where the most antidepressant and antipsychotic medications prescribed.

Patients were diagnosed with bipolar disorder, dependence and alcohol dependenceaccording to the international classification of diseases (ICD) codes which are used byhealth professionals worldwide. Codes describe the features of a given mental disorder (according to DSM IV criteria) and indicate how the disorder can be distinguished from another (120).

The study was conducted in accordance to Declaration of Helsinki and was approved by the clinical researches ethical committee of Üsküdar University for the use

of all electronical data and exempted from the requirement for informed consent for the thesis. Because the study involved deidentified data acquired during routine care.

We reviewed the chart of every patient with bipolar disorder and dependence who had an electronic record related to prescribed drugs, routine chemical tests and periodic drug related laboratory results about drugs concentration. Data extracted from electronic medical records included subject's age, gender, prescribed drugs, drug dose (mg/day), diagnosis, current medications, and the results of routine laboratory testing (1) after to initiating therapy, (2) at the time clinical problem occurs and (3) at the time TDM was performed. Routine laboratory monitoring included a complete blood count with automated cell differential, liver and renal function profiles collected according to the discretion of the clinician.

Inclusion criteria

(1) Ability to read, understand, and provide written informed consent (done by hospital staff before hospitalization).

(2) Age ≥ 18

(3) Ability to meet therapy requirements (ie, able to take medications, or health security etc.)

(4) Meets DSM-IV criteria for current bipolar disorder, alcohol and other dependence,

(5) Have a current physical dependence and need for medical assistance for therapy.

(6) Have a good general health or, if requires ongoing medical treatment for other diseases.

(7) Willingness to provide general information for health records.

Exclusion criteria

(1) A medical condition that would make participation medically hazardous

(2) A known allergy or sensitivity to drug

(3) An acute severe psychiatric condition

(4) Dependence on sedative-hypnotics or stimulants,

(5) If female, participant is pregnant, lactating, or unwilling to follow study required measures for pregnancy prevention

(6) Liver function tests > 5 times the upper limit of normal

(7) Current participation in formal substance abuse treatment

3.2 Methods

I. BiochemistryLaboratory (Routine chemical tests)

Serum Fasting Blood Sugar, AST, ALT, creatinine, and UREA values were recorded from patients' charts as available. We assessed the clinical relevance of elevated AST or ALT levels by using liver failure criteria—two fold for acute liver failure, even so two fold for determining prognosis from chronic liver disease.

a) Liver Function Test Parameters Aspartate transaminase (AST), Alanine Aminotransferase (ALT)

Liver transaminases (AST or SGOT and ALT or SGPT) are useful biomarkers of liver injury in a patient with some degree of intact liver function. Although most liver diseases cause only mild symptoms, they must be detected early. Hepatic (liver) involvement in some diseases can have crucial importance. This testing is performed on a patient's blood sample. In clinical practice, some tests are associated with functionality (e.g., albumin), some with cellular integrity (e.g., transaminase). These two enzymes were formerly referred to as SGPT and SGOT, respectively. The serum ALT activity (hereafter termed ALT) has been regarded as a reliable and sensitive marker of liver disease. ALT may also be a good indicator of overall health, particularly in the context of obesity, the metabolic syndrome, and presence of cardiovascular disease. Many patients affected by these conditions also are at risk of having non-alcoholic fatty liver disease (124).

The elevation of AST/ALT is prior instead of ALP elevations, they favor liver cell necrosis as a mechanism over cholestasis. When AST and ALT are both over 1000 IU/L, causes of the differential can include acetaminophen toxicity, shock, or fulminant liver failure. When AST and ALT are greater than three times from normal degree but not greater than 1000 IU/L, the reason for this can be alcohol toxicity, drug-induced level, sepsis, Wilson's disease, post-transplant rejection of liver.

b) Renal Function Test Parameters, Creatinine, Urea

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy, so improves clinical outcome.

Recently, research and utilization of biomarkers has evolved substantially. National Institute of Health (NIH) 2001 defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathologic processes, or pharmacologic responses to a therapeutic intervention.

Markers of renal function are; creatinine, urea, uric acid and electrolytes for routine analysis but in thesis, we put emphasize on creatinine and urea.

Creatinine

Creatinine is a metabolite (breakdown product) of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body depending on muscle mass. Creatinine is a commonly used as the measure of kidney function.The normal creatinine clearence test value is 110-150ml/min in male and 100-130ml/min in female.Some of the Kidney Disease Education Programs recommend calculating glomerular filtration rate from serum creatinine concentration. The creatinine clearance test is used to monitor the progression of renal disease. The diagnosis of renal failure is usually suspected when serum creatinine is greater than the upper limit of the “normal” interval. In chronic renal failure and uremia, an eventual decrease occurs in the excretion of creatinine by both the glomeruli and the tubules. Creatinine production process and also its levels may be affected by some factors. It is not a simple product of muscle mass so influenced by muscle function, muscle composition, activity, diet and health status.

The increased tubular secretion of creatinine in some patients with kidney dysfunction could give false negative value.The increased levels are also seen in muscular dystrophy paralysis, anemia, leukemia and hyperthyroidism.

The decreased levels are associated with glomerulonephritis, congestive heart failure, acute tubular necrosis, shock, polycystic kidney disease, and dehydration (125).

Urea

Urea is major nitrogenous end product of protein or amino acid catabolism, produced by liver and distributed to the intracellular and extracellular fluid.Urea is filtered out of blood by glomeruli in renal systems and is partially being reabsorbed with water.In clinics, the most determined clinical indices for estimating renal function depends upon concentration of urea in the serum. It is useful in differential diagnosis of

acute renal failure and renal conditions where blood urea nitrogen–creatinine ratio is increased. Urea clearance is still a good indicator of glomerular filtration rate as its over production rate depends on several non renal factors, including diet and urea cycle enzymes. Increased blood urea nitrogen (BUN) is seen when there is a kidney disease or failure,blockage of the urinary tract by a kidney stone, congestive heart failure, dehydration, fever, shock and bleeding in the digestive tract. The high BUN levels can sometimes occur during late pregnancy or can result from eating large amounts of protein-rich foods.

Higher than 100 mg/dL BUN level points to severe kidney damage whereas decreased BUN is observed in fluid excess.Low levels are also seen in trauma, surgery, opioids, malnutrition, drug and anabolic steroid use (125).

c) Fasting Blood Sugar

The measurement of blood glucose is a well established procedure and routinely used for many clinical and research purposes. In epidemiological studies, blood glucose parameter is often measured as a risk factor, mediator or confounder. Blood glucose levels are influenced by external factors such as high calorific value intake that results in an increase of blood glucose or incremental metabolic demands like muscle activity results in a decline of blood glucose. One of the routinely requested basic condition for pre-analytical blood sampling is the fasting state in order to obtain unbiased blood glucose measurements. The fasting state is defined by several disciplines. Pre-analytical blood sampling schemes range from overnight fast, which means fasting duration between 8 h and 12 h, ≥12 h.

Glucose meters are widely used in hospitals, outpatient clinics, emergency rooms, ambulatory medical care (ambulances, helicopters, cruise ships), and home self-monitoring. Glucose meters provide fast analysis of blood glucose levels and allow management of both hypoglycemic and hyperglycemic disorders with the goal of adjusting glucose to a near-normal range, depending on the patient group.

The enzyme portion of the glucose meter is generally packaged in a dehydrated state in a disposable strip or reaction cuvette. Glucose in the patient’s blood sample rehydrates and reacts with the enzymes to produce a product that can be detected. Some meters generate hydrogen peroxide or an inter-mediary product that can react with a dye. By

this way, the reaction ends up with a color change proportional to the concentration of glucose in the sample solution. Other meters incorporate the enzymes into a biosensor that generates an electron that is detected by the meter.

There are three principle enzymatic reactions utilized by current glucose meters: glucose oxidase, glucose dehydrogenase, and hexokinase. Each enzyme has characteristic advantages and limitations.

II.Toxicology laboratory

Blood samples for TDM have to be accompanied by laboratory order form carrying detailed information about the current medications of patients. Serum levels of drugs or drugs of abuse were determined in the TDM laboratory of Neuropsychiatry Hospital by using spectrophotometric immunoassay (Cannabinoids (THC), opiates, phencyclidine, amphetamines, benzodiazepines, MDMA (Ecstasy), barbiturates, alcohol (ethanol) in urine, benzoylecgonine, Lithium, Quetiapine, Olanzapine, Zuclopenthixol, Lamotrigine, valproic acid).

III. Therapeutic drug monitoring Laboratory

TDMof antipsychotics and antidepressants is a valuable tool for patients in medical treatment for a psychiatric disorder. The indications for using TDM are numerous; including treatment start-up, changes in dose, occurrence of unwanted side effects, lacking therapeutic effect, control for compliance, and pharmacokinetic interactions (122).

This large number of indications combined with the marketing of new drugs so all these are increased the focus on drug use in psychiatry and caused to augment the use of TDM naturally (126).

Serum samples were taken just prior to the morning dose of the medications (trough concentration). After routine analysis, the remainder of the serum samples was sent to the Toxicological Centre where samples were analyzed by a fully validated UHPLC–MS/MS method for quantification of antipsychotics, antidepressants, antiepileptics and metabolites in serum as described in literature (123).Briefly, sample preparation involved liquid–liquid extraction with methyl tert-butylether at pH 9.5 by using 200 μL of patient serum. After transfer and evaporation of the upper organic

layer, the extract was reconstituted in acetonitrile, and injected into the UHPLC–MS/MS system, which was operated in dynamic multiple reaction monitoring mode.

In thesis, there are the quantification of mirtazapine, O-desmethylvenlafaxine, quetiapine,venlafaxine, and ziprasidone (group1), and amitriptyline, citalopram, clomipramine, clozapine, desmethylclomipramine, desipramine, imipramine, and nortriptyline (group2) and zuclopenthixol, carbamazepine, quetiapine, Risperidone, 9-OH Risperidone, biperiden, Clomipramine, oxcarbazepine, sulpiride, lorazepam, Clonazepam, Valproic Acid (VPA total), aripiprazole, paroxetine, sertraline, flupentixol, Fluoxetine, venlafaxine, haloperidol, clozapine, escitalopram, lamotrigine, Duloxetine HCL, amisulpride, fluvoxamine, gabapentin, Alprazolam, donepezil, (group3) in human serum for therapeutic drug monitoring.The method was developed to replace old techniques which applied solid phase extraction and ultra-violet detection.

The old methods had reached their limit of capacity regarding the number of samples and co-medicated drugs (were) interfering with the detection. Serum samples were precipitated with zinc sulphate and methanol containing a stable isotope labelled analog for each analyte.

Immunoassays

Immunoassays are a type of drug screening that returns either a yes or no outcome. The results are highly sensitive and specific. Three types of immunoassays mentioned above are common in clinical practice. 1) enzyme immunoassay (EIA), 2) fluorescence polarization immunoassay (FPIA) and 3) radioimmunoassay (RIA). These three tests are all based on the same general principle. Binding antibodies are used to detect specific drugs or groups of drugs.

Enzyme Immunoassay (EIA)

With EIA testing, any drugs that are found in the sample are labeled by using an enzyme. The enzyme attaches itself to the antibody and in this state it is inactive. If there are drugs in the sample, then the enzyme becomes displaced from the antibody and is activated. The extent of this reaction will depend on the quantity of the present drug in the sample

Cloned Enzyme Donor Immunoassay (CEDIA)

Cloned enzyme donor immunoassay (CEDIA) method is a novel approach which uses the new DNA technology to produce enzyme immunoassays for drugs. The principle of this method is illustrated in Figure 3.1. Enzyme donor units combine with enzyme acceptor units to form a complete and active tetrameric enzyme molecule, which reacts with a colourless substrate to produce coloured product. An enzyme donor-drug conjugate is prepared by linking the drug molecule to the enzyme donor fragment. Competitive binding reaction results in the formation of active enzyme and consequently coloured product, which is directly proportional to the concentration of the drug present. This assay is rapid and has high throughput. Successful cloned enzyme donor immunoassay methods were developed for analysis of amphetamine, ethamphetamine, barbiturates, opiates, phencycline, phenytoin, and benzodiazepines,. The CEDIA methods were validated, in terms of the sensitivity and precision, in reference to gas chromatography- mass spectrometry, and their validity was proved for application in routine drug screening (121).

CEDIA has proven to be the consummate screening immunoassay for drugs-of-abuse screening, therapeutic drug monitoring, immunosuppressant drug monitoring and toxicology testing. CEDIA® assays are simple to perform, delivering rapid, reliable and inexpensive results and are easily automated for large-volume testing requirements.

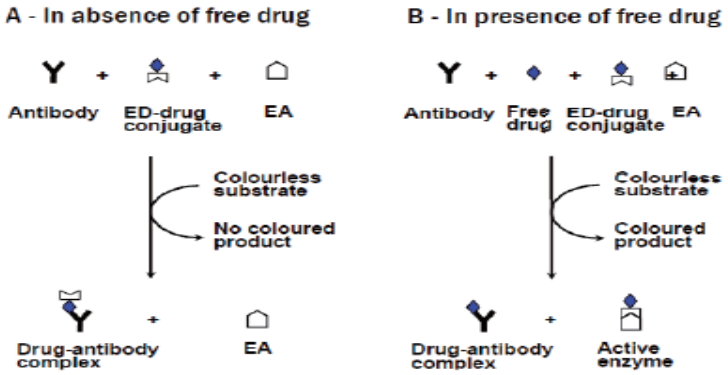

Figure 3.1 The principle of Cloned Enzyme Donor Immunoassay

(From Darwish IA 2006 Int J Biomed Sci. 2(3): 217-35)

Serum Samples

As part of clinical routine, serum levels are also determined in case of antidepressants and antipsychotics usage both at the beginning and before the end of in-patient treatment. Blood was collected from patients who had been treated with antidepressant or antipsychotics for at least 24 hours. Blood samples were collected in EDTA tubes for routine complete blood counts. The samples were taken in the morning (trough levels) before ingestion of the first dose of the day. And they were sent to biochemistry and toxicology or pharmacogenetic laboratories of Neuropsychiatry Hospitals for routine TDM and biochemistry analysis.

Instrumentation

UHPLC–MS/MS

The UHPLC–MS–MS system consisted of Agilent triple quadrupole 6410 combined with Agilent 1200 LC system (Agilent Technologies, Santa Clara CA, USA). The 1200 LC system can tolerate pressures up to 600 bars and consisted of a degasser, a binary pump with a solvent selection valve, a thermostated well plate autosampler, and a column oven with a two column selection valve (Figure 3.2). The LC system was configured for rapid resolution, which includes reduction of dead volume by discarding the solvent mixer and reduction of tube diameter (126).

Figure 3.2

CEDIA

The Thermo Scientific Indiko benchtop analyzer is designed for routine clinical chemistry testing in small laboratory settings and specialty testing such as specific proteins, drug of abuse testing and therapeutic drug monitoring, including immunosuppressant drug monitoring (Figure 3.3)

Figure3.3

AUTOMATED ANALYZERS

Liquids (reagents, diluents and samples) are pumped through a system of continuous tubing. Serum/Blood samples are introduced in a sequential manner, following each other through the same network. Series of air bubbles at regular intervals serve as separating and media. The internal diameter of the tubing and the rate of flow determine the volumes of sample prior to mixing with the reagents and the turn around time of the result. An oil heating bath is used to promote color development or the completion of enzymatic reaction

Principle of detection:

Detection is made by spectrophotometer whose principle based on absorbency measuring through a continuous flow cuvet (cell). When there is no sample, the sampler probe is placed in distilled water to avoid blockages and precipitation. More sophisticated continuous flow analyzers use parallel single channels to run multiple tests on each sample.

Statistical methods

Patients were divided into 6 groups according to their ages (20-29, 30-39, 40-49, 50-59, 60-69, >70 years) and divided into 3 diseases types groups according to their diagnosis in compliance with DSM IV criterias (bipolar disorder, substance dependence, and alcohol dependence). Also prescribed drugs were divided into 5 goups according to their number of drugs (1-3, 4-6,7-9, 10-12, and 13 and up). Relationship between number of drugs and the other results were evaluated by Pearson correlation analysis.

All results are expressed as mean ± SD. The statistical significance of results was determined by using one-way analysis of variance (ANOVA), followed by Tukey's tests and post hoc LSD tests for multiple comparisons of group means.

Analysis of covariance (ANCOVA) was used to correct the influence of ages groups and drugs groups over other factors linked with the laboratory data. All analyses were performed using IBM SPSS statistics 20, (IBM Corporation 2011).

4. RESULTS

In thesis 1530 patients with depressive disorder and dependence cases and 12734 prescriptions given for these diseases at different time were reviewed between the dates January 2010 to December 2015.

Patient Characteristics; Demographics and characteristics of patients with depressive disorder and dependence are described in Table 4.1. The mean age for all patients was 35.23 ± 0.12 (Mean±Sem, respectively) years (range, 18-88 years). The mean age for male patients was 33.93 ± 0.13 (range, 18-88 years) and for female patients it was 37.94 ± 0.22 (range, 18-86) years. The average of total prescribed drugs by physicians was

6. 51 ± 0.26 (range, 1-23) drugs. For male, it was 6.69 ± 0.03 (range, 1-21) and for female it was 6.14 ± 0.04 (range, 1-23) drugs for these hospitalized patients.

Through these one thousand five hundred thirty of the patients; 40,6 % were between 20-29 years, 28.13 % between 30-39 years, 15.02 % between 40-49 years, 10.35 % between 50-59 years, 4.34 % were between 60-69 years, and 1.48 % were over 70 years.

Among all prescriptions that is mentioned 12734; 51.8% (6598 inpatients) were met DSM IV criteria for bipolar disorder, 4239 of 12734 (33.3%) were met DSM IV criteria for substance dependence and 1897 of 12734 (14.9 %) prescriptions met DSM IV criteria for alcohol dependence.

A total of 12734 prescriptions were evaluated for the study, 5885 of these (46.2%) were gathered with TDM data or results, 2405 (18.9%) were gathered with toxicological (CEDIA) results and and 4444 (34.9%) were gathered with routine biochemistry test results and then observed.

TABLE 4.1-Demographics and characteristic informations of patients

	MEAN	SEM	%	Min	Max
AGE					
-Male	33.93	0.134	-	18	88
-Female	37.94	0.217	-	18	86
-Total	35.23	.116	-	18	88
NUMBER OF DRUG					
-Male	6.69	0.032	-	1	21
-Female	6.14	0.044	-	1	23
-Total	6.51	.026	-	1	23
Prescription types or Diseases prescribed drugs					
-Bipolar Disorder	6598	-	51.8		
-Substance-Dependent	4239	-	33.3		
-Alcohol-Deperndent	1897	-	14.9		
-Total	12734	-	100		
Analysis or Laboratory					
-LC-MS-MS	5885	-	46.2		
-Immunoassay	2405	-	18.9		
-Biochemistry	4444	-	34.9		
-Total	12734	-	100		

TABLE 4.2-Demographic and characteristic informations of male patients

	MEAN	SEM	%	Min	Max
-AGE	33.93	0.134	-	18	88
-NUMBER OF DRUG	6.69	0.032	-	1	21
Prescription types or Diseases prescribed drugs					
-Bipolar Disorder	2957	-	34.4		
-Substance-Dependent	4032	-	46.8		
-Alcohol-Deperndent	1625	-	18.9		
-Total	8614	-	100		
Analysis or Laboratory					
-LC-MS-MS	3657	-	42.5		
-Immunoassay	2028	-	23.5		
-Biochemistry	2929	-	34		
-Total	8614	-	100		

The male-to-female ratio was 2.09:1. Patients were definitely from hospitalized patients, none of them were outpatients. Because of the high ratio between male-to female, we determined the electronic databases or EHRs of inpatients, separately.

Demographic characteristics of the 8614 male patients are shown in Table 4.2. The mean age for male patients was 33.93 ± 0.134 (range, 18-88 years) and for female patients it was 37.94 ± 0.217 (range, 18-86). 2957 of 8614 (34.4%) prescriptions of male patients were bipolar disorder, 4032 of 8614 (46.8%) were substance dependence, 1625 of 8614 (18.9 %) prescriptions were for alcohol dependence. The amount of substance dependence prescriptions in male patients were significantly more than in female patients.

TABLE 4.3-Demographic and characteristic informations of female patients

	MEAN	SEM	%	Min	Max
-AGE	37.94	0.217	-	18	86
-NUMBER OF DRUG	6.14	0.044		1	23
Prescription types or Diseases prescribed drugs			-		
-Bipolar Disorder	3641	-	88.3		
-Substance-Dependent	207	-	5.1		
- Alcohol-Deperndent	272	-	6.6		
-Total	4120	-	100		
Analysis or Laboratory					
-LC-MS-MS	2228	-	54.1		
-Immunoassay	377	-	9.2		
-Biochemistry	1515	-	36.8		
-Total	4120	-	100		

Demographic characteristics of the 4120 female patients are shown in Table 4.3.The distribution of diseases in female patients were in the following way; 3641 of 4120 (88.3%) female prescriptions were arising from bipolar disorder, 207 of 4120 (5.1%) prescriptions were about substance dependence and 272 of 4120 (6.6 %) prescriptions were about alcohol dependence. Female prescriptions for bipolar disorder were significantly two times higher than male however alcohol and substance dependence prescription rates were actually very low, relatively.

4.1.The relationship between the number of prescribed drugs and diseases (or diagnostic type)

The number of drugs for 12734 prescriptions of drugs were divided into 3 groups as diseases types (bipolar disorder, substance dependence, and alcohol dependence) according to DSM IV criteria and number of drugs were statically analyzed for each disease groups. Number of prescribed drugs significantly differed among the three groups, $F(2;11368)=256.852 = p < .00001$. The number of drugs were most increased in patients with alcohol dependence (Mean = 7.86±0.08) and less increased in patients with substance dependence (Mean = 6.51±0,03).

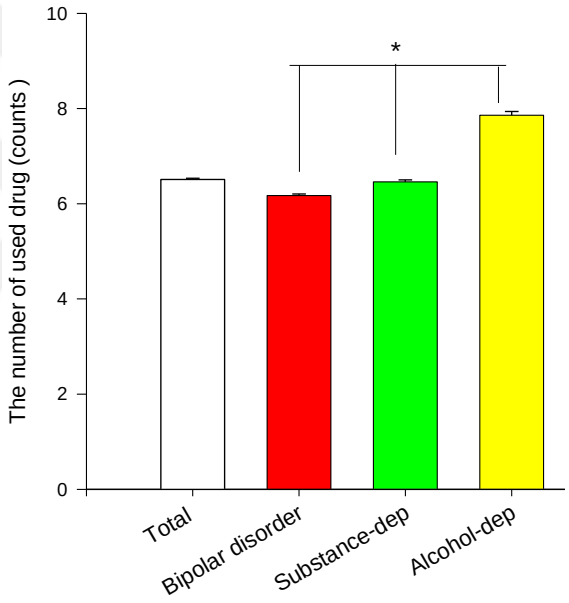

Figure 4.1- The changes in the number of drugs prescribed inpatients with bipolar disorder, substance-dependence and alcohol-dependence. Values are mean ± SD. '*' among groups represent significant differences ($p < 0.0001$) by Tukey post hoc test. One-way ANOVA has shown a significant difference ---- $F(2;11368)=256.852$;----- $p<0.0001$ post hoc Tukey -----

4.2.The relationship between the number of prescribed drugs and the age groups

To test an association between the age groups and the number of prescribed drugs in this study, bivariate Pearson correlation coefficients were used. At the beginning of the statistical analysis, the ages of patients were separated to 6 different groups. We found that, when the ages of patients were separated proportionally to age groups, the age groups were positively and significantly correlated with the number of prescribed drugs (figure 4.2). Linear plot of the age groups on the number of prescribed drugs in this study ($rp = -0.245$; $p < 0.001$) was not shown.

The number of prescribed drugs significantly differed among the 6 age groups $F(5,11365) = 144304$, $p < .01$. The number of drugs more increased in over 70 groups (9.3±0.15, Mean±SEM) and little increased in 20-29 age group (5,97 ± 0,034, Mean±SEM).

These Electronic health data suggests that the number of drugs had increased with age in this study.

The Tukey post hoc test indicated that the number of drugs of all age groups significantly differed from each other, respectively ($p < .0001$).

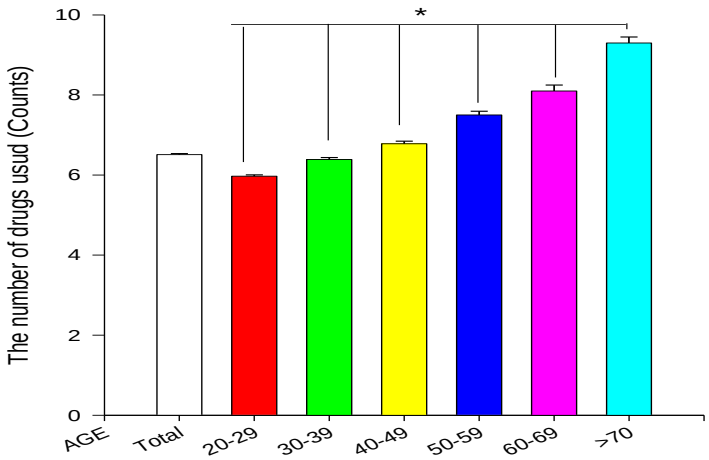

Figure 4.2 -The effects of age groups on the number of prescribed drugs. * The different letters among groups represent significant differences by one-way ANOVA (F (5: 11365)=144.304; P< 0.001).Each data point represents Mean ± SEM of(*p<0.01), post hoc Tukey, p<0.0001.

There are also a relationship between the number of drug and age groups (Pearson correlation analysis; age groups x number of prescribed drugs),r=-0.245,p<0.0001)

4.3.The relationship between the number of prescribed drugs and rutine biochemical parameters

To test an association between the number of prescribed drugs and the biochemical parameters such as serum fasting blood sugar, AST, ALT, creatinine, and UREA in all patients; bivariate Pearson correlation coefficients were not used because of the numerous prescriptions. If such a big database were analyzed by pearson correlation analysis, most probably, it could give incorrect results. As you see in Table 4.4; while p was significant, coefficient is very low.Therefore, it was decided to be generated proportionally groups for the number of prescribed drugs in prescriptions. 5 different drugs or polypharmacy groups were generated as 1-3 drugs included (or used) group, 4-6 drugs included group, 7-9 drugs included group, 10-12 drugs included group and over≥13 drugs included another group.

Table 4.4 - Stepwise multiple regression analysis of the relationship between the number of prescribed drugs and rutine biochemical parameters (Serum Fasting Blood Sugar, AST, ALT, creatinine, and UREA) in all patients.

(*) p <0.05, (**) p<0.01

		Fasting Blood Glucose ***mg/dL***	***Alanine Aminotransferase (ALT)*** ***IU/L***	***Aspartate Transaminase (AST)*** ***IU/L***	***Creatinine*** ***ml/min***	***UREA*** ***mg/dL***
The number of prescribed drugs	*Pearson Correlation*	**0,125****	**0,032***	**0,047****	**0,086****	**,077****
	Sig. (2-tailed)	<0.0001	0,043	0,003	<0.0001	<0.0001
	n	2369	3893	3902	3221	3242
Diagnosis	*Pearson Correlation*	**0,100****	**0,129****	**0,239****	**-0,031**	**-0,106****
	Sig. (2-tailed)	<0.0001	<0.0001	<0.0001	0,062	<0.0001
	n	2567	4244	4256	3521	3541
Age	*Pearson Correlation*	**0,309****	**-0,023**	**0,065****	**0,046****	**0,333****
	Sig. (2-tailed)	<0.0001	0,14	<0.0001	0,006	<0.0001
	n	2567	4244	4256	3521	3541

While the effects of the number of prescribed drugs in prescriptions were investigated on biochemical parameters; the other factors such as age, gender and diagnosis are thought to be confounding factors. At the beginning of the statistical analysis, the diagnosis, the gender and the number of drugs prescribed "fixed Factors", the age is considered as a covariance for the conducted ANCOVA tests. The conclusion of this test was continued. Therefore, five different drugs or polypharmacy groups were generated as 1-3 drugs prescribed (or used) group, 4-6 drugs prescribed group, 7-9 drugs prescribed group, 10-12 drugs prescribed group and over≥13 drugs prescribed group.

4.3.1.The effects of number of drugs in prescription on fasting blood glucose

There were no differences in fasting blood glucose levels among any of the drug groups. The number of drugs in prescription did not change the levels of fasting blood glucose [F(4,2344)=1,408;p=0,229]. Figure 4.3

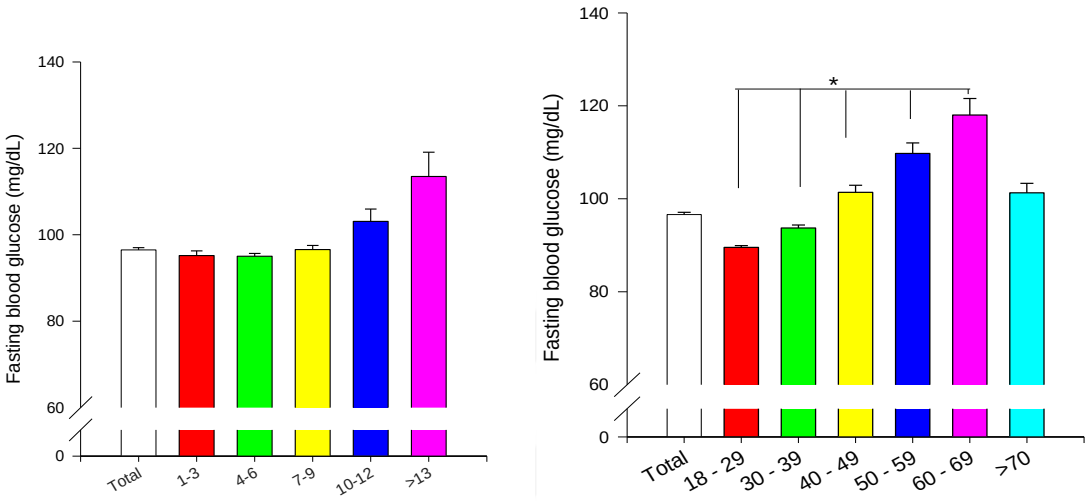

Figure 4.3-The effects of the number of prescribed drugs on fasting blood glucose (mg/dL). ANCOVA showed that the number of drugs did not have effects on the levels of fasting blood glucose(F (4, 2344) =1,408; p=0,229).Each data bar represents Mean ± SEM.

Figure 4.4- The effects of age groups on fasting blood glucose. ANCOVA showed that the age groups have significant effects on the fasting **blood** glucose (F(4,2344)=86,08;p<0,01).Each data bar represents Mean ± SEM.

4.3.1.1. The effects of age on fasting blood glucose

There were significant differences in fasting blood glucose levels among age groups (F(4,2344)=86,08; p<0,01). Years of age increased the levels of fasting blood glucose. As it is seen above (Figure 4.4), glucose levels appeared to be rised in 18-29 age group to 60-69 age group, but not over 70 years.

4.3.1.2. The effect of gender on fasting blood glucose

There were no differences in fasting blood glucose levels among any number of drug groups[F(1,2344)=0,68;p=0,41]. Data not Shown

4.3.1.3. The effects of diagnosis on fasting blood glucose

There were significant differences in fasting blood glucose levels among the diagnosis groups F(2,2344)=7,343;p=0,001). Tukey post hoc test indicated that the fasting blood glucose levels significantly increased in diagnosis of substance dependence groups compared to other diagnosis groups (Mean ± SEM) respectively). However, this significant increase in substance groups may be associated with the results of age related increase in fasting glucose, because the fasting glucose levels in substance dependence group did not change. (one way Anova, data not shown).

4.3.2. The effects on the levels of alanine aminotransferase (ALT)

The effects of number of drugs, age, diagnosis and gender on ALT levels were also analyzed by ANCOVA and all results are presented and summarized below. There were not any effects of the number of drugs (F(4,3868)=1,99;p=0,093) and age groups F(1,3868)=2,226;p=0,557) on ALT levels, however there were some effects of gender F(1,3868)=11;p=0,01) and diagnosis (F(2,3868)=12,898;p<0,0001) on ALT levels.

Despite significant findings related to gender and diagnosis, an additional analysis was not performed due to the insignificant effect of number of drugs.

Table 4.5-The effects of number of drugs, age, diagnosis and gender on ALT levels

Groups		**F Values for ANCOVA**	**P**
Number of drug		F(4,3868)=1,99	p=0,093
Gender		F(1,3868)=11	p=0,001
Age		F(1,3868)=2,226	p=0,557
Diagnosis		F(2,3868)=12,898	p<0,0001
Number of drug x Age		F(4,3868)=0,91	p=0,064
Number of drug x Diagnosis		F(8,3868)=0,418	p=0,911
Number of drug x Gender		F(4,3868)=0,927	p=0,447

4.3.3. The effects on the levels of aspartate transaminase (AST)

As you see in Table 4.6, there were not any effect of the number of drugs (F (4,3877)=1,171;p=0,322) and age (F(1,3877)=3,588;p=0,058) on the levels of AST. However, there were significant effects of gender (F(1,3877)=9,489;p=0,002) and diagnosis (F(2,3877)=12,898;p<0,0001) of the patient groups on the levels of AST. For this reason, additional analysis performed to determine whether there were interactions between the number of drugs and age or diagnosis or gender. ANCOVA indicated that there was a significant interaction between the number of drug and diagnosis (F(8,3877)=1,967; p=0,0470) , but not gender.

Table 4.6- The effects of number of drug, age, diagnosis and gender on the levels of AST

Groups	**F valuesfor ANCOVA**	**P**
Number of drug	F(4,3877)=1,171	p=0,322
Gender	F(1,3877)=9,489	p=0,002*
Age	F(1,3877)=3,588	p=0,058
Diagnosis	F(2,3877)=12,898	p<0,0001*
Number of drug x Age	F(4,3877)=1,635	p=0,163
Number of drug x Diagnosis	F(8,3877)=1,967	p=0,0470**
Number of drug x Gender	F(4,3877)=0,265	p=0,901

The effects of the number of drugs on levels of AST in diagnostic patients groups (bipolar disorder patients group, substance-dependent patients group and alcohol-dependent patients group) are shown in Figure 4.5 A, B, C.

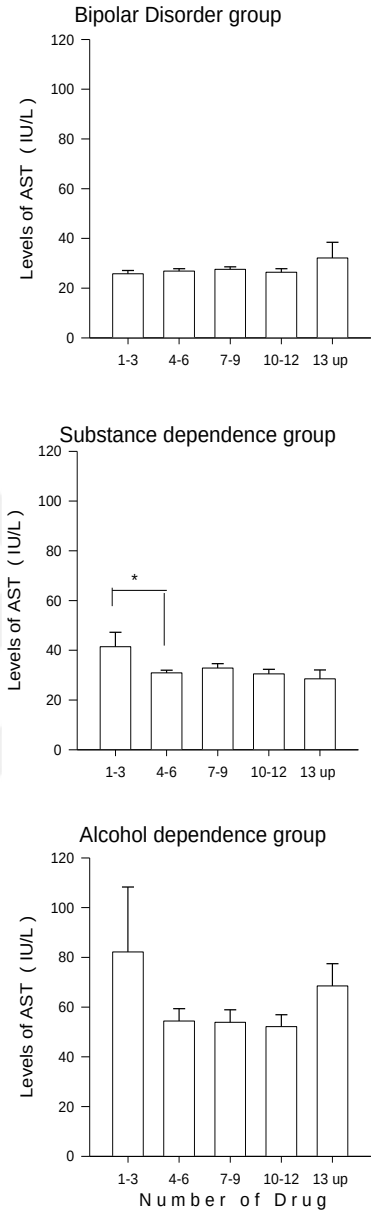

Figure 4.5 A,B,C- The effects of number of drugs on levels of AST in diagnostic patients groups. (A) bipolar disorder patients group (F(4,2086)=0,479;p=0,751), (B) substance-dependent patients group (F(4,1187)=2,613;p=0,034) and (C) alcohol-dependent patients group (F(4,614)=1,552;p=0,186), respectivlely).Each data bar represents Mean ± SEM. '*' between 1-3 and 4-6 drug groups represent significant differences ($P < 0.05$) by Tukey post hoc test.

4.3.4. The effects on the level of creatinine

As you see in Table 4.7, there were not any effect of the number of drugs (F (4,3196)=1,098;p=0,356) on the levels of creatinine. However, there were significant effects of gender (F(1,3196)=162,653;p<0,0001), age (F(1,3196)=19,246;p<0,0001) and diagnostic (F(2,3196)=28,773; p<0,0001) patients groups on the levels of creatinine. So, to determine whether there was an interaction between the number of drug, diagnosis, gender and age were analyzed statistically by ANCOVA. ANCOVA indicated that there was a significant interaction between the number of drug and gender (F (4,3196)=5,776; p<0,0001) , but not diagnosis and age.

Table 4.7 - The effects of number of drug, age, diagnosis and gender on the levels of creatinine.

Groups		**F valusfor ANCOVA**	**P**
Number of drug		F(4,3196)=1,098	p=0,356
Gender		F(1,3196)=162,653	p<0,0001*
Age		F(1,3196)=19,246	p<0,0001*
Diagnosis		F(2,3196)=28,773	p<0,0001*
Number of drug x Age		F(4,3196)=1,246	p=0,289
Number of drug x Diagnosis		F(8,3196)=0,993	p=0,439
Number of drug x Gender		F(4,3196)=5,776	p<0,0001**

To determine a relationship between the levels of creatinine and the number of used or prescribed drug in male and female patients groups, bivariate Pearson correlation coefficients were calculated. In male, Pearson correlation coefficients between the number of prescribed drugs and creatinine levels was r=-0,27 (p>0.05). In female, Pearson correlation coefficients between the number prescribed drugs and creatinine levels was r=-0,209 (p>0.05)

4.3.4.1.The effects of the number of drugs on levels of creatinine in gender groups

The effects of the number of drugs on levels of creatinine in gender groups (male and female patient groups) are shown in Figure 4.6A and B. ANOVA showed that the number of drugs have significant effects on levels of creatinine in male (F(4,2217)=3,25;p=0,01) and female (F(4,994)=14,199;p<0,01) patients groups. In male group, the creatinine level of 7-9 drugs prescribed patient group significantly differ (a decrease) from 10-12 drugsprescribed patients groups (P < 0.05, by Tukey post hoc test). In female group, the creatinine levels of 1-3 drugs group significantly differ from 4-6, 7-9 and 13 and upper number of drugs used groups. (Hereafter named 13 and up drugs group). And also the level of 13 and up drugs group differ than 7-9 and 10-12 drugs groups (P < 0.05, by Tukey post hoc test).

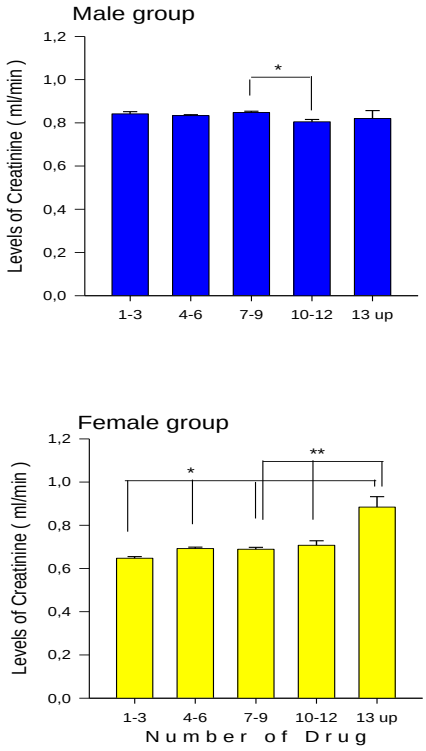

Figure 4.6- The effects of the number of drugs on levels of creatinine in gender groups; (A) male and (B) female patients groups.ANOVA showed that the number of drugs have significant effects on levels of creatinine in male (F(4,2217)=3,25;p=0,01)and female (F(4,994)=14,199;p<0,01)patients groups. Each data bar represents Mean ± SEM. In male group, 7-9 drugs group significantly differ from 10-12 drugs groups and in female group, 1-3 drugs group significantly differ from 4-6, 7-9 and 13 and up drugs group(P < 0.05) by Tukey post hoc test.

4.3.5. The effects on the levels of urea

The effects of number of prescribed drugs, age, diagnosis and gender on the levels of urea in patients were shown in Table 7. The levels of urea interact with the number of drug, age, diagnosis and gender. ANCOVA indicated that there were significant effects of the number of drugs ($F(4,3217)=10,149$; $p<0,0001$) gender ($F(1,3217)=27,404$; $p<0,0001$), age ($F(1,3217)=192,477$; $p<0,0001$), and diagnosis ($F(2,3217)=66,344$; $p<0,0001$) on the levels of urea. Moreover, there were also significant interactions between the number of drug and age ($F(4,3217)=11,259$;$p<0,0001$) or diagnosis ($F(8,3217)=3,535$; $p<0,0001$) or gender ($F(4,3217)=2,428$;$p=0,046$).

4.3.5.1. The effects of number of drugs on the levels of urea in male and female groups

We evaluated separately the effects of gender, age, diagnosis and number of drugs on the levels of urea. Firstly, the effect of number of drugs on the levels of urea in male patients groups were analyzed and we observed significant differences ($F(4,2241)=9,874$;$p<0,0001$) among the drug groups (Figure 4.7 A). There were significant differences in 1-3 drugs group when compared to 4-6 ($p<0,01$) and 7-9 ($p<0,01$) drug groups by Tukey post hoc test. The urea levels of 13 and up drugs group also differ significantly when compared to 7-9 ($p<0, 01$) and 10-12 ($p<0,01$) drug groups by Tukey post hoc test.

Table 4.8 - The effects of number of drug, age, diagnosis and gender on the levels of urea.

Groups	**F values for ANCOVA**	**P**
Number of drug	F(4,3217)=10,149;	p<0,0001
Gender	F(1,3217)=27,404;	p<0,0001
Age	F(1,3217)=192,477;	p<0,0001
Diagnosis	F(2,3217)=66,344;	p<0,0001
Number of drug x Age	F(4,3217)=11,259;	p<0,0001
Number of drug x Diagnosis	F(8,3217)=3,535;	p<0,0001
Number of drug x Gender	F(4,3217)=2,428;	p=0,046

Secondly, in female patients groups, the effect of number of drugs on the levels of urea were analyzed and we observed significant difference (F(4,991)=11,615;p<0,0001) among the drug groups (Figure 4.7 B). 13 and up drugs group significantly differ from the other all drug groups (P < 0.05) by Tukey post hoc test.

To determine a relationship between the levels of urea and the number of used (or prescribed) drug in male and female patients groups, Pearson correlation coefficients were calculated. In male, Pearson correlation coefficients between the number prescribed drug and urea levels is r=-0,028 (p>0.05). In female, Pearson correlation coefficients between the number prescribed drug and urea levels is r=0,156 (p<0,0001).

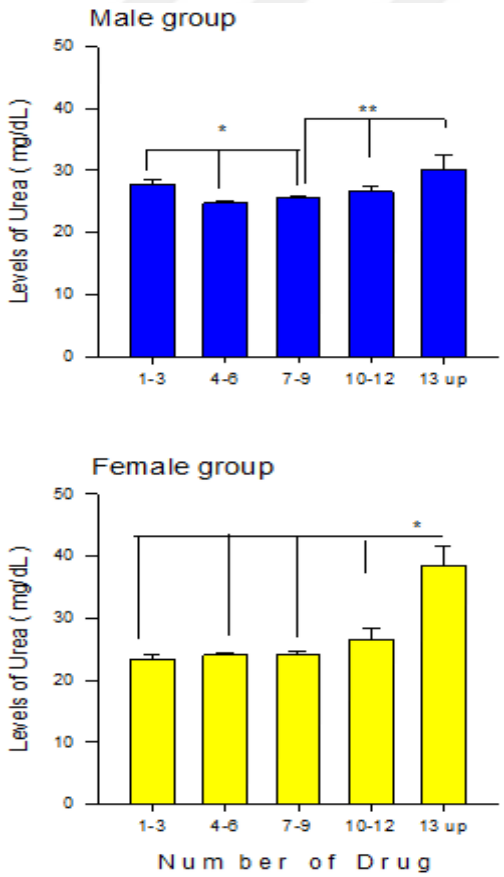

Figure 4.7- The effects of the number of drugs on levels of Urea in gender groups; (A) male and (B) female patients groups.ANOVA showed that the number of drugs have significant effects on levels of urea in both male F(4,2241)=9,874;p<0,0001)and female (F(4,991)=11,615;p<0,0001) patient groups. Each data bar represents Mean ± SEM. In male group, 1-3 drugs group significantly differ from 4-6 and 7-9 drugs groups and 13 and up drugs group differ significantly from7-9 and 10-12. In female, 13 and up drugs groupsignificantly differ from the other all drug groups (P < 0.05) by Tukey post hoc test.

4.3.5.2. The effects of number of drugs on the levels of urea in diagnostic patient groups

The effects of the number of drugs on levels of urea were determined in diagnostic patients groups (bipolar disorder patients group, substance-dependent patients group and alcohol-dependent patients group) they were shown in Figure 4.8 A, B and C. The variation of the number of drugs produced significant difference on levels of urea in patients with bipolar disorder (Figure 4.8).

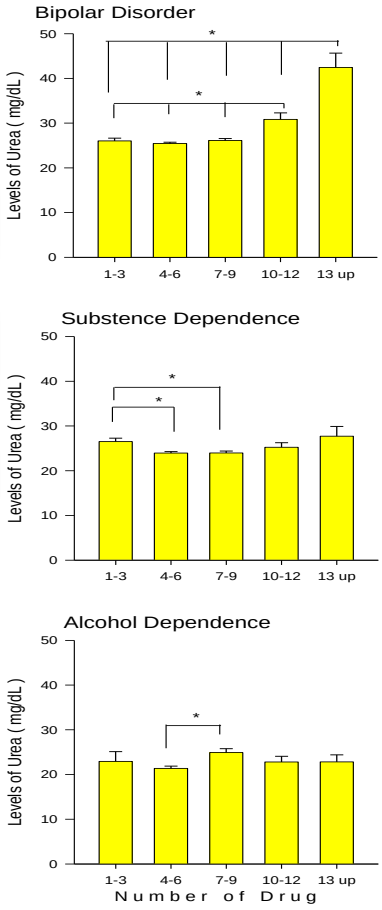

Figure 4.8 - The effects of the number of drugs on levels of urea were determined in diagnostic patients groups; (A) bipolar disorder patients group, (B) substance-dependent patients group and (C) alcohol-dependent patients group. ANOVA showed that number of drugs have significant effects on levels of urea in bipolar disorder patients group $F(4,1774)=28,369$; $p<0,0001$), substance-dependent patients group $F(4,979)=3,85$;$p=0,004$) and alcohol-dependent patients group $F(4,474)=2,745$;$p=0,028$). ($F(4,991)=11,615$;$p<0,0001$) patients groups. Each data bar represents Mean ± SEM. In bipolar disorder patients group, 13 and up drugs group and 10-12 drugs groups significantly differ from the all other drug groups ($P < 0.01$). In substance-dependent patients group, 1-3 drugs group significantly differ from 4-6 and 7-9 groups ($P < 0.01$). In alcohol-dependent patients, 4-6 drugs group significantly differ from 7-9 groups ($P < 0.009$) by Tukey post hoc test.

4.3.5.3. The effects of number of drugs on the levels of urea in age groups

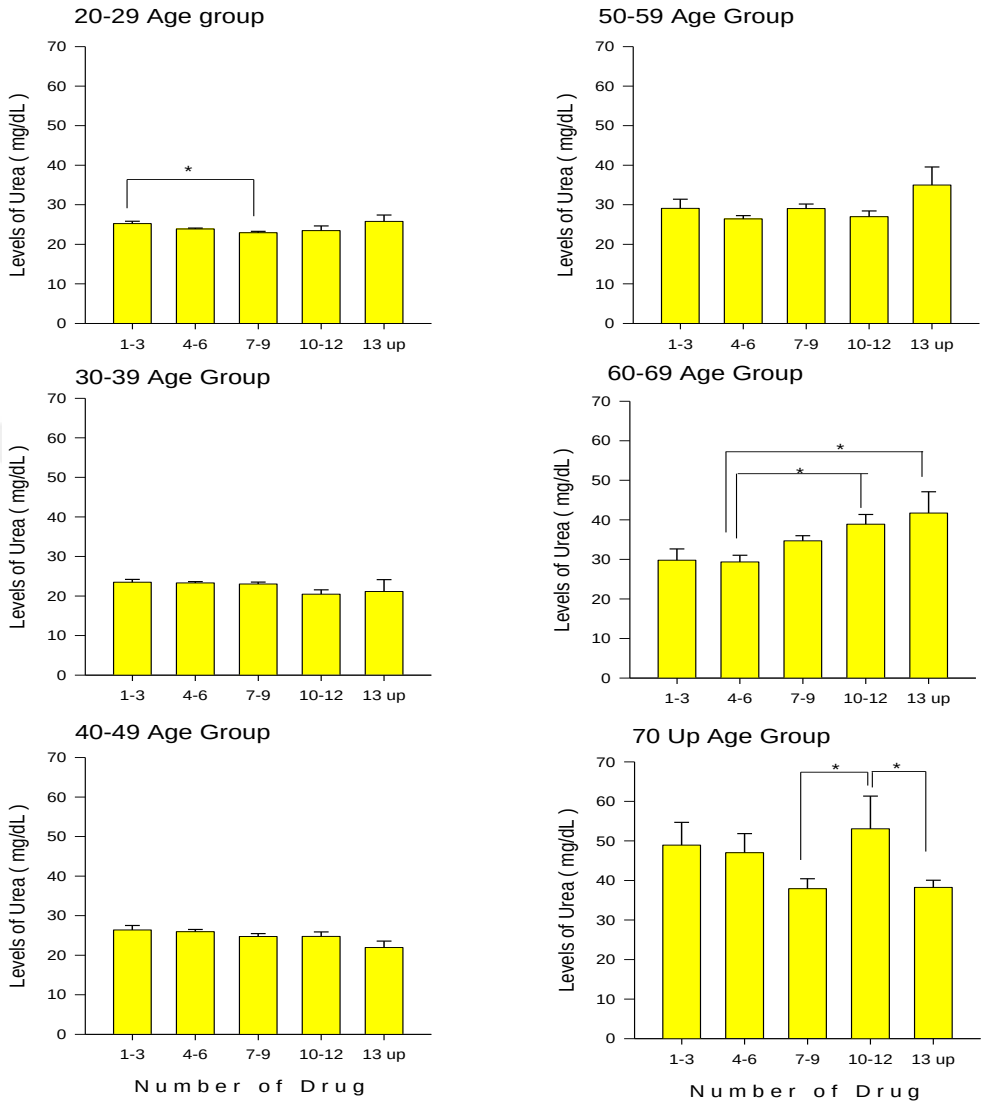

Figure 4.9 - The effects of the number of drugs on levels of urea were determined in age groups; (A) 20-29 age patient group, (B) 30-39 age patientgroup and (C) 40-49 age patient group. (D) 50-59 age patient group (E) 60-69 age patients group (F) greater than 70 age patient group. ANOVA showed that the number of drugs have significant effects on levels of urea in 20-29 age group F (4,1256)=3,376;p=0,009), 60-69 age group (F(4,352)=4,313;p=0,002) and 70 and upper ages of patients group (F(4,61)=2,568;p=0,046). Each data bar represents Mean ± SEM. In 20-29 age group, 1-3 drugs group significantly differ from 7-9 group ($P < 0.01$). In 60-69 ages group, 4-6 group significantly differ from 10-12 and 13 and up drugs group($P < 0.01$). In 70 and upper ages of patients group, 7-9 drugs group significantly differ from 10-12

drugs group (P < 0.02) and 10-12 group significantly differfrom 13 and up drugs group(P < 0.01) by Tukey post hoc test.

4.4. The Effects of Polypharmacy on the Levels of Drug Concentrations or TDM

During prescription, the ratio of routinely use of TDM were 58.5% for bipolar disorder, 61.8 % for substance dependence and 50.09 % for alcohol dependence.

Table 4.9 - The frequencies of Therapeutic Drug Monitoring (TDM) along with drug types and non TDM requests in three different patient or disease groups during treatment.

Bipolar Disorder Patients			**Substance-Dependent Patients**			**Alcohol-Dependent Patients**		
DRUG TYPE	F	%	DRUG TYPE	F	%	DRUG TYPE	F	%
Non-TDM	2740	41,5	Non-TDM	1618	38,2	Non-TDM	932	49,1
1 AP	539	8,2	1 AP	279	6,6	1 AP	123	6,5
1 AP 1 AE	431	6,5	1 AP 1 AE	299	7,1	1 AP 1 AE	104	5,5
2 AP	429	6,5	1 DS	271	6,4	4 DS	74	3,9
2 AP 1 AE	407	6,2	2 AP	260	6,1	1 AP 1 AD	74	3,9
1 AP 1 AD	298	4,5	4 DS	210	5	3 DS	70	3,7
1 AE	184	2,8	5 DS	198	4,7	1AE	65	3,4
1 AP 1 AD 1AE	160	2,4	2 AP1DS	174	4,1	1AD	62	3,3
1 AD	159	2,4	3 DS	168	4	5DS	59	3,1
4 DS	155	2,3	2DS	155	3,7	1DS	51	2,7
3 DS	137	2,1	1AE	106	2,5	2AP	48	2,5
5 DS	119	1,8	6DS	94	2,2	2AP1AE	43	2,3
2 AP 1 AD	109	1,7	1 AP 1 AD	54	1,3	2DS	39	2,1
2 DS	80	1,2	3 AP	39	0,9	1AD1AE	31	1,6
1 AD 1 AE	80	1,2	1AP1AD1AE	34	0,8	1 AP1AE1AD	31	1,6
3 AP	78	1,2	2AP1AD	31	0,7	6DS	23	1,2
3 AP 1 AE	71	1,1	3AP1AE	31	0,7	3AP	11	0,6
1 DS	57	0,9	2AP1AD1AE	27	0,6	1AD2AE	10	0,5
2 AP1AD1DS	57	0,9	1AP2AE	22	0,5	7DS	6	0,3
6 DS	55	0,8	7DS	19	0,4	1AP1DS	6	0,3
1 AP2AE	53	0,8	1AD	19	0,4	1AP1DS1AE	5	0,3
2AD	25	0,4	2AP1DS1AE	19	0,4	2AP1DS1AE	4	0,2
1AP2AD	21	0,3	1AP1DS1AE	14	0,3	2AD	3	0,2
2AE	20	0,3	2AP1AD1AE1DS	13	0,3	2AP1DS1AE1AD	3	0,2
2AP2AE	20	0,3	1AD1AE	11	0,3	2AE	2	0,1
1AP1AD2DS	17	0,3	2AP2AE	10	0,2	1DS1AE	2	0,1
1AP2AD1DS	16	0,2	2AE	7	0,2	1AP1DS2AE	2	0,1
7DS	14	0,2	4AP	7	0,2	1AP1DS1AD	2	0,1
3AP1AD	14	0,2	1DS1AE	5	0,1	1AP1DS2AD	2	0,1
1AD2AE	7	0,1	1AP1DS	4	0,1	2AP1AD1AE	2	0,1

2AD1AE	7	0,1	1AP1DS1AE	4	0,1	3AP1AE	2	0,1
2AP1AD2DS	5	0,1	1AP1AE	3	0,1	1AD1DS1AE	1	0,1
4AP	5	0,1	1AP1AD1AE1DS	3	0,1	1AP1DS1AD1AE	1	0,1
1AP2DS	4	0,1	2AP1DS	3	0,1	1AP2AD	1	0,1
2AP2AD	4	0,1	3AP1AE1AD	3	0,1	2AP2AE	1	0,1
3AP2DS	4	0,1	4AP1AE	3	0,1	2AP1AD	1	0,1
3AE	3	0	-	-	-	2AP1AD1DS	1	0,1
1AP1AD2AE	3	0	-	-	-	-	-	-
2AP1AD1DS	2	0	-	-	-	-	-	-
3AP1AD1AE	2	0	-	-	-	-	-	-
4AP1AE	2	0	-	-	-	-	-	-
2AD2AE	1	0	-	-	-	-	-	-
1AP2AD2DS	1	0	-	-	-	-	-	-
2AP1AD3DS	1	0	-	-	-	-	-	-
2AP1AD1DS1AE	1	0	-	-		-	-	-
TOTAL	**6598**	**100**	**TOTAL**	**4217**	**100**	**TOTAL**	**1897**	**100**

Antipsychotic, AE: Antiepileptic, AD: Antidepressant and DS: Dependence substance

The effects of number of prescribed drugs on the levels of serum drug concentrations

Relationship between the number of prescribed drugs and serum concentration levels of drugs or substance dependencies were evaluated in this part of the study. The number of drugs were separated to 5 different groups; as first group included 1-3 drugs prescribed (or used) , second group included 4-6 drugs, third group included 7-9 drugs, fourth group included 10-12 drugs and the last group included the usage of more than 13 drugs. The effects of these drug groups on serum concentrations of drugs or substance dependencies were analyzed by one way ANOVA test whether there were significantdifferences among drug groups. We observed significant effects of number of drugs on therapeutic drug monitoring or serum concentration levels in seven drugs whose blood levels monitored by LC-MSMS. Serum concentration levels of Aripiprazole, Bupropion, Clomipramine, Pregabaline, Sulpiride, Valproic Asit and Zuclopenthixol were significantly changed in relation to number of concurrent drug usage of the patients. ($F(4,807)=2.557$; $p=0.038$) (Table-4.9) the others did not represent any differences.

On the other hand, the number of concurrent drugs produced significant differences on serum concentration levels of some drugs of abuse. These are;

Benzodiazepine, Phencyclidine, Ecstasy and Opiate, monitored by CEDIA Immunoassay methods. (F(4,807)=2.557; p=0.038) (Table-4.10). The other drugs of abuse beyond mentioned did not demonstrate any significant difference.

Table 4.10 - The effects of number of drugs (or polypharmacy) on serum concentration levels of therapeutic drugs and drugs of abuse were shown below. The significant association between the number of drugs and serum concentration levels for each drug were analyzed by ANOVA .

Name of Drug		**Sum. of Squares**	**df**	**Mean Square**	**F**	**Sign.**
Aripiprazole	Between Groups	139969	4	34992,24	2,557	0,038
	Within Groups	1,10E+07	807	13684,21		
Benzodiazepine	Between Groups	1,47E+07	4	3670162	5,077	<0.0001
	Within Groups	9,25E+08	1280	722887		
Bupropion	Between Groups	7713,35	4	1928,338	2,959	0,021
	Within Groups	121193,9	186	651,58		
Clomipramine	Between Groups	149863,3	4	37465,84	3,876	0,007
	Within Groups	551016,8	57	9666,961		
Phencyclidine	Between Groups	46,801	4	11,7	2,913	0,021
	Within Groups	5141,713	1280	4,017		
Ecstasy	Between Groups	87646,44	4	21911,61	2,922	0,02
	Within Groups	1,11E+07	1477	7498,997		
Opiates	Between Groups	476173,1	4	119043,3	6,792	<0.0001
	Within Groups	2,66E+07	1517	17527,91		
Pregabaline	Between Groups	47,777	4	11,944	3,484	0,009
	Within Groups	538,196	157	3,428		
Sulpiride	Between Groups	882204	4	220551	4,505	0,002
	Within Groups	1,38E+07	281	48957,44		
Valproic Acid	Between Groups	12403,55	4	3100,888	8,444	<0.0001
	Within Groups	416790,5	1135	367,216		
Zuclopenthixol	Between Groups	4530,196	4	1132,549	2,719	0,029
	Within Groups	334031,3	802	416,498		

THEEFFECTS OF POLYPHARMACY ON BLOOD LEVELS OF THE DRUGS

4.4.1. The effects of polypharmacy on serum concentration levels of aripiprazole

Aripiprazole plasma concentration levels changed significantly in drug groups and these changes were in this way; an increase in 4-6 and 7-9 drugs groups ($F(4,807)=2.557$; $p=0.038$). Post hoc LSD test for Aripiprazole showed a significant decrease in 1-3 drugs group when compared 4-6 and 7-9 drugs groups (post hoc LSD test; $p<0,015$).

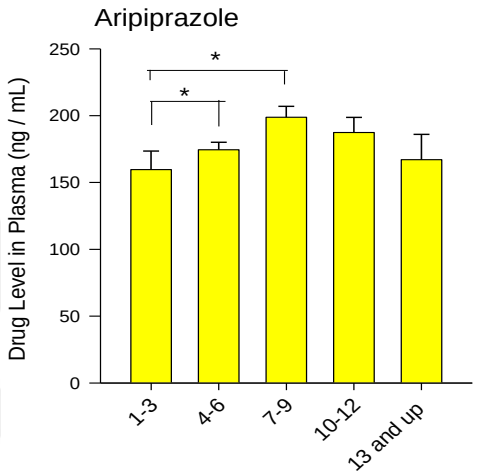

Figure 4.10- The effects of the number of drugs on Aripiprazole concentration were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on Aripiprazole concentration levels in drug groups ($F(4,807)=2.557$; $p=0.038$). (*) The patients group used 1-3 drugs significantly differ from these 4-6 and 7-9 drugs groups .(post hoc LSD test; $p<0,015$)

4.4.2. The effects of polypharmacy on serum concentration levels of bupropion

Bupropion plasma concentration levels significantly changed in drug groups and these changes were in this way; a decrease in 7-9 and 13 and up drugs group.F (4,186)=2.4257; p=0.0340). Post hoc LSD test for bupropion showed decreases in 7-9 and 13 and up drugs group. These changes were probably associated with other factors, not related to the number of prescribed drugs, poly pharmacy.

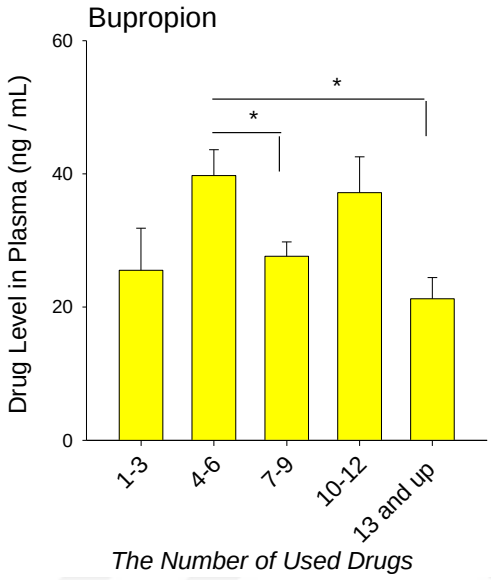

Figure 4.11- The effects of the number of drugs on Bupropion concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant decreasing effects on Bupropion concentration levels in drug groups (F (4,807) = 2.557; p=0.038). (*) 4-6 drugs used patients group significantly differ from 7-9 (post hoc LSD test; p<0,004) and 13 and up drugs group(post hoc LSD test; p<0,034).

4.4.3. The effects of polypharmacy on serum concentration levels of clomipramine

Clomipramine plasma concentration levels significantly changed in drug groups and these changes were in this way; a decrease in 4-6, 7-9, 10-12 and 13 and up drugs group ($F(4,57)=2.2357$; $p=0.049$). Post hoc LSD test for Clomipramine showeda significant increasein plasma concentration levels of 1-3 drugs group when compared with other drug groupsthat showed declining trends. (post hoc LSD test; $p<0,004$ for 4-6 drugs group, $p<0,001$ for 7-9 drugs group, $p<0,001$ for 10-12 drugs group, $p<0,023$ for 13 and up drugs group). These decreases may be significant for polypharmacy.

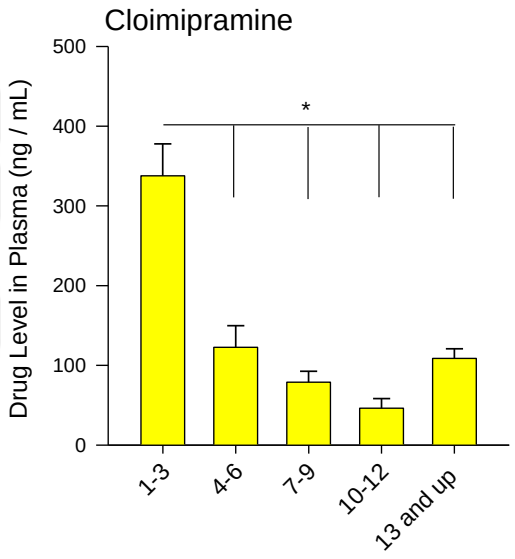

Figure 4.12 - The effects of the number of drugs on Clomipramine concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant decreasing effects on Clomipramine concentration levels in drug groups ($F(4.57)=2.2357$; $p=0.049$). (*) 1-3 drugs group differ significantly from the all other drug groups (post hoc LSD test; $p<0,004$ for 4-6 drugs group, $p<0.001$ for 7-9 drugs group, $p<0.001$ for 10-12 drugs group, $p<0.023$ for 13 and up drugs group).

4.4.4. The effects of polypharmacy on serum concentration levels of pregabaline

Pregabaline plasma concentration levels significantly changed in drug groups and these changes were in this way; an increase in 7-9, 10-12 and 13 and up drugs group ($F(4,157) = 2.411$; $p=0.0345$), except 4-6 drugs used group. Post hoc LSD test for pregabaline showed that the increased plasma concentration levels may be due to the wide range of drug usage. (Post hoc LSD test; $p<0,026$ for 4-6, $p<0,047$ for 13 and up, $p<0,002$ for 7-9, $p<0,032$ for 10-12 drugs groups, respectively). This increase may be related with polypharmacy.

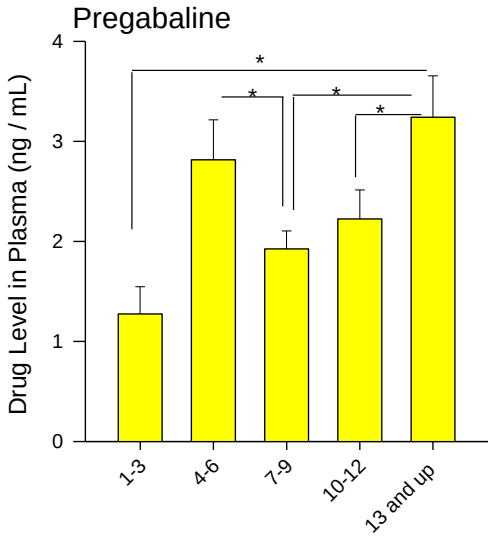

Figure 4.13 - The effects of the number of drugs on Pregabaline concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on Pregabaline concentration levels in drug groups ($F(4,157)=2.411$; $p=0.0345$). (*) 1-3 drugs group significantly differ from 4-6 and 13 and up drugs group (post hoc LSD test; $p<0,026$ for 4-6 drugs group and $p<0,047$ for 13 and up drugs group, respectively). 7-9 and 10-12 drugs group significantly differ from 13 and up drugs group ($p<0,002$ for 7-9 drug group, $p<0,032$ for 10-12 drug group, respectively).

4.4.5. The effects of polypharmacy on serum concentration levels of sulpiride

When the number of prescribed drugs increase, Sulpiride plasma concentration levels were also increased significantly in all drug groups (F(4,281)=3.6787; p=0.01). Post hoc LSD test for Sulpiride showed that regular rising of sulpiride plasma concentrationsbegan significantly in 4-6 drugs group. There was not significant increase between 1-3 and 4-6 drugs group, but 10-12 and 13 and up drugs group were significantly higher than 1-3 and 4-6 drugs groups (post hoc LSD test; p<0,04 for 10-12, a p<0,002 for 13 and up drugs group, p<0,034 for 4-6 , p<0,007 for 7-9 drugs groups). These increases in Sulpiride plasma concentration levelsmay be significant for polypharmacy.

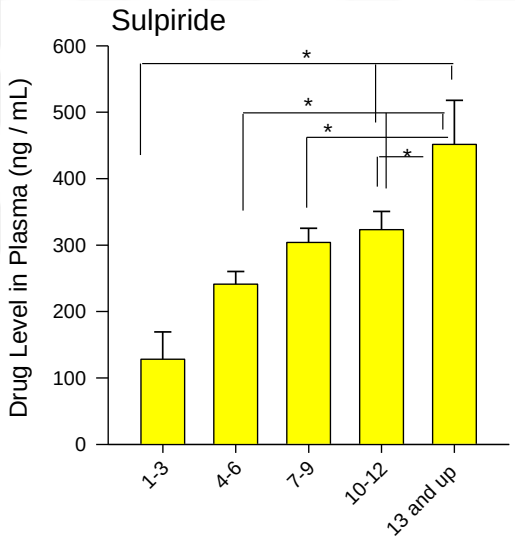

Figure 4.14 - The effects of the number of drugs on Sulpiride concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on Sulpiride concentration levels in all drug groups (F(4,281)=3.6787; p=0.01). (*) 1-3 drugs used patients group significantly differ from 10-12 and 13 and up drugs group(post hoc LSD test; p<0,04 for 10-12 drugs group and p<0,002 for 13 and up drugs group, respectively). 4-6 and, 7-9 drug groups significantly differ from 10-12 and 13 and upper amount of drugs used group (p<0,034 for 4-6 drug group, p<0,007 for 7-9 drug group, respectively). 10-12 drugs group significantly differ from and 13 and up drugs group (p<0,027 for 10-12 drugs group).

4.4.6. The effects of polypharmacy on serum concentration levels of valproic acid

The effects of number of drugs on valproic acid plasma concentration levels were analyzed by ANOVA in drug groups and significant changes were in this way; significant decrease in 7-9 and 10-12 drugs group. ($F(4,1136)=5.4787$; $p=0.001$). Post hoc LSD test for valproic acid showed that plasma concentration levels significantly decreased in 7-9 and 10-12 drugs used groups. (post hoc LSD test; $p<0,01$ for 7-9, $p<0,002$ for 10-12 drug group, respectively), but did not decrease in 13 and up drugs group. These decreased valproic acid plasma concentration levels were not marked decreases, so, these were not related with polypharmacy.

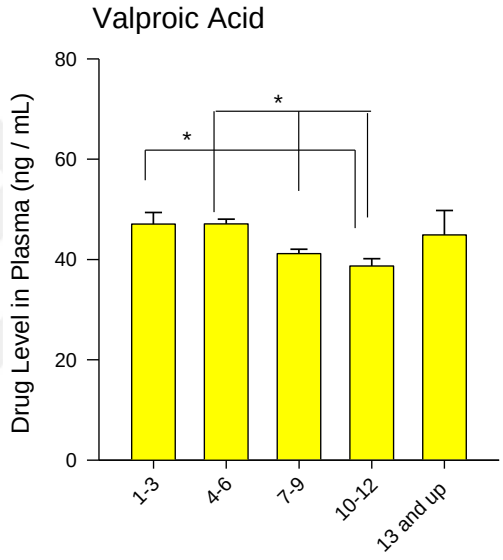

Figure 4.15 - The effects of the number of drugs on Valproic Acid plasma concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant decreasing effects on Valproic Acid concentration levels in drug groups ($F(4,1136)=5.4787$; $p=0.001$). (*) 1-3 drugs used group significantly differ from 7-9 and 10-12 drugs group (post hoc LSD test; $p<0,01$ for 7-9 drug group and $p<0,002$ for 10-12 drugs group, respectively). 4-6 drugs group significantly differ from 7-9 and 10-12 drugs groups ($p<0,001$ for 7-9 drug group, $p<0,001$ for 10-12 drug group, respectively).

4.4.7. The effects of polypharmacy on serum concentration levels of zuclopenthixol

Zuclopenthixol plasma concentration levels were increased continually according to the number of concurrent drugs, there were a significant increase between 1-3 drugs group and the other drug groups (F (4,802)=2.2297; p=0.028). Post hoc LSD test for Zuclopenthixol showed that plasma concentration levels significantly increased in 4-6, 7-9, 10-12 and 13 and up drugs group (p<0,018 for 4-6, p<0,002 for 7-9, p<0,015 for 10-12, p<0,039 for 13 and up drugs group, respectively). These increases may be related with polypharmacy, but the number of subjects were insufficient.

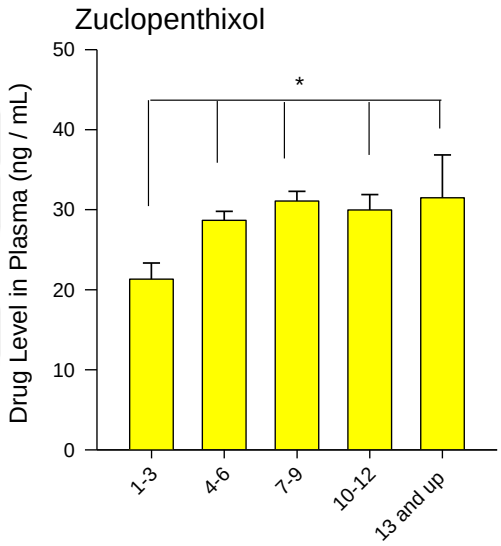

Figure 4.16 - The effects of the number of drugs on Zuclopenthixol concentration levels were determined from patients requested TDM and prescription groups quantified by LC-MSMS. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on Zuclopenthixol concentration levels in drug groups (F(4,802)=2.2297; p=0.028). (*) 1-3 drugs group significantly differ from the other all drug groups (post hoc LSD test; p<0,018 for 4-6 drug group, p<0,002 for 7-9 drug group, p<0,015 for 10-12 drug group, p<0,039 for 13 and up drug group).

4.4.8. The effects of polypharmacy on serum concentration levels of benzodiazepine

Benzodiazepine plasma concentration levels increased significantly in 7-9, 10-12 and 13 and up drugs groupwhen compared with 1-3 and 4-6 drugs groups (F(4,1280)=12.2677; p=0.01). Post hoc LSD test for benzodiazepine showed significant increases between 7-9 and 13 and up drug groups (p<0,001 for between 7-9 and 13 and up drug group) and between 10-12 and 13 and up drug groups (p<0,013 for between 10-12 and 13 and up drugs groups, respectively). This increase may be significant for polypharmacy or metabolisms of drugs.

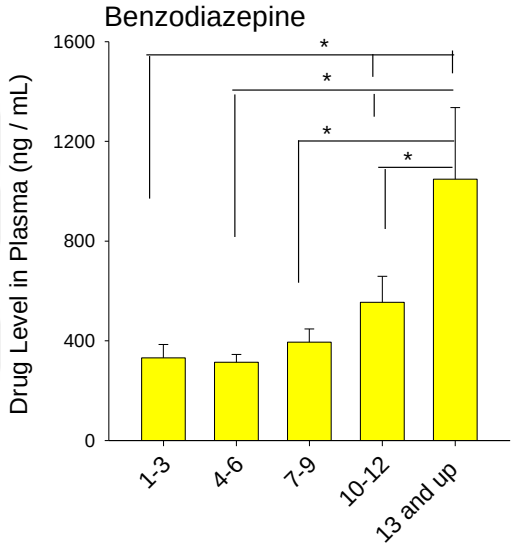

Figure 4.17 - The effects of the number of drugs on benzodiazepine concentration levels were determined from patients requested TDM and prescription groups quantified by CEDIA immunoassay. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on benzodiazepine concentration levels in drug groups (F (4,807) = 2.557; p=0. 038). (*) 10-12 and 13 and up drugs group significantly differ from 1-3 drugs group (post hoc LSD test; p<0,04 for 10-12 drugs group and p<0,001 for 13 and up drugs group, respectively). 10-12 and 13 and up drugs group significantly differ from 4-6 drugs group (post hoc LSD test; p<0,013 for 10-12 drug group and p<0,001 for 13 and up drug group, respectively). 13 and up drugs groupsignificantly differ from 7-9 drugs group (post hoc LSD test; p<0,001 for 13 and up drug group, respectively). And also 13 and up drugs groupsignificantly differ from 10-12 drugs group (post hoc LSD test; p<0,019 for 13 and up drug group).

4.4.9. The effects of polypharmacy on serum concentration levels of phencyclidine

Phencyclidine plasma concentration levels seems like a declining trend in drug groups, as we observed significant reduction in 7-9 and 10-12 drug groups when compared with 4-6 drugs group (F(4,1281)=4.8127; p=0.042). This was not related with polypharmacy.

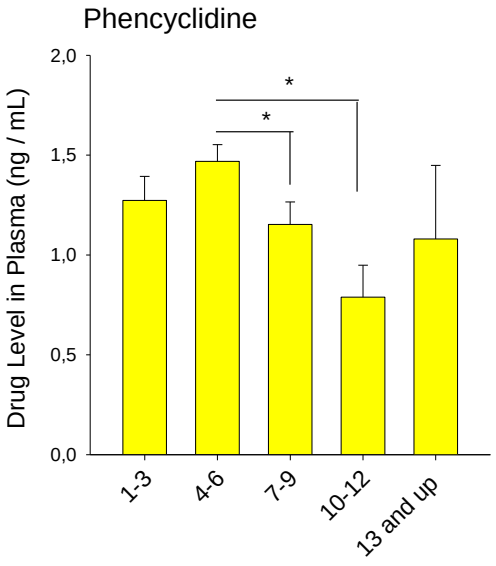

Figure 4.18- The effects of the number of drugs on phencyclidine concentration levels were determined from patients requested TDM and prescription groups quantified by CEDIA immunoassay. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant decreasing effects on phencyclidine concentration levels in drug groups (F (4,807) = 2.557; p=0. 038). (*) 4-6 drugs group significantly differ from 7-9 and 10-12 drugs groups (post hoc LSD test; p<0,0224 for 7-9 drug group and p<0,005 for 10-12 drug group, respectively).

4.4.10. The effects of polypharmacy on serum concentration levels of ecstasy

Ecstasy plasma concentration levels significantly had an increasing trend in all drug groups, except 1-3 drugs group (F (4, 1477)=2.923; p=0.034). However, there were significant increases between 4-6 and 7-9 (post hoc LSD test; p<0,047 for between 4-6 and 7-9 drug group) and between 4-6 and 13 and up drugs group (post hoc LSD test; p<0,043 for between 4-6 and 13 and up drugs group). There was a positive correlation between the number of drugs and ecstasy concentration levels, but not for all drug groups.

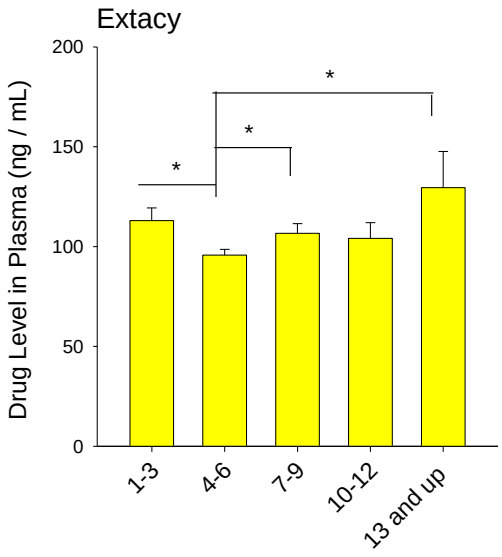

Figure 4.19 - The effects of the number of drugs on ectasy concentration levels were determined from patients requested TDM and prescription groups quantified by CEDIA immunoassay. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on ectasy concentration levels in drug groups (F (4,807) = 2.557; p=0. 038), except 1-3 drugs group. (*) 7-9 and 13 and up drugs group showed significant increases than 4-6 drugs groups (post hoc LSD test; p<0,047 for 7-9 drugs group and p<0,043 for 13 and up drugs group, respectively).

4.4.11. The effects of polypharmacy on serum concentration levels of opiate

Opiate plasma concentration levels showed significant increase among the drug groups (F(4,1517)=5.8787; p=0.001). There were significant increase between 1-3 drugs used patients group and 7-9, 10-12 and 13 and upper amount of drugs used groups (post hoc LSD test; p<0,01for 7-9, p<0,01 for 10-12, and p<0,01 for 13 and up drug groups). There were also significant increase between 4-6 drug group and 7-9, 10-12 and 13 and up drugs group(post hoc LSD test; p<0.01for 7-9, p<0.01 for 10-12, and p<0.01 for 13 and up drugs group. 7-9 drugsgroup showed significant increase than 13 and up drugs group (post hoc LSD test; p<0.01 for 13 and up drug group). There were positive correlations between number of drugs and opiate concentration levels in all drug groups.

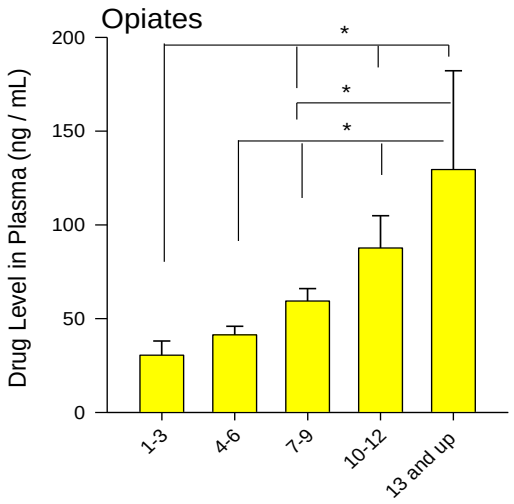

Figure 4.20 - The effects of the number of drugs on opiate concentration levels were determined from patients requested TDM and prescription groups quantified by CEDIA immunoassay. Each data bar represents Mean ± SEM. ANOVA showed that numbers of concurrent drugs have significant increasing effects on opiate concentration levels in all drug groups (F(4,1517)=5.8787; p=0.001). (*) 1-3 drugs group showed significant increase than 7-9, 10-12 and 13 and up drugs group(post hoc LSD test; p<0.01for 7-9, p<0.01 for 10-12, and p<0.01 for 13 and up drug groups). (*) 4-6 drugs group showed significant increase than 7-9, 10-12 and 13 and up drugs groups(post hoc LSD test; p<0.01for 7-9, p<0.01 for 10-12, and p<0.01 for 13 and up drug groups. (*) 7-9 drugs used group showed significant increase than 13 and up drug group. (post hoc LSD test; p<0,01 for 13 and up drug group).

5.DISCUSSION AND CONCLUSION

Current study data provide further evidence for the high rates of complex polypharmacy in BD and dependence therapy and extend findings about those patients in hospitals. Polypharmacy has been one method which physicians have been using in difficult circumstances since a long time; however, its appropriateness by electronic inpatients record (EIR) has come under scrutiny in this study. EIRs have been analized to check the covered harmfull effects of number of prescribed medications on biochemicals parameters and the blood concentration levels of therapeutic medications of inpatients. Our analysis of electronic databases related with bipolar disorder and dependent patients revealed some positive associations among polypharmacy and the other specifications such as types of diseases, age groups, biochemical parameters and the TDM levels. Additionally, the role of number of drugs on age portions and diseases types examined. However, the potential value of EIRs remain limited, in otherwords not explored sufficinetly.

Enrolled prescribed medications are highly controlled in managed care, whereas non-prescription medications are not. The lack of information about non-prescription medications makes it very difficult to trace polypharmacy under managed care environments. The actual occurrence of polypharmacy may be higher than that reported, since many people do not inform their doctors about regularly used non-prescription drugs.

5.1. The Relationship Between the Number of Prescribed Drugs and Diseases or Diagnostic Type

A total of 12734 prescriptions evaluated in this study. 51.8% (6598 inpatients) were bipolar disorder, 33,3 % (4239) were substance dependence and 14,9 % (1897) were alcohol dependence prescriptions. The number of prescribed drugs in patients with alcohol dependence (7,86±0,078) were the highest when compared to patients with bipolar disorder (6,17±0,034) and substance dependence (6,46±0,042). Despite a growing armamentarium of psychotropic medications for the treatment of BD (American Psychiatric Association, 2002), morbidity and mortality rates remain high.

Anxiety disorders, personality disorder, and alcohol or drug dependence are particularly common comorbidities (127).

A retrospective chart review study by Weinstock L. M. Et all, has shown that the rates of polypharmacy (i.e, ≥ 4 psychotropic medications) and patterns of psychotropic medication use in adults with bipolar disorder (BDI; N=230) since psychiatric hospital admission. In this study, patients reported taking an average of (5.94± 3.78) total medications, and an average of (3.31 ± 1.46, Mean± SD) of them were psychotropic medications (128). Use of all remaining medications (i.e. Lithium, anticonvulsants, antipsychotics, stimulants, hypnotics) did not differ as a function of episode polarity. Author noted that, there were no differences in patterns of specific medication use between those with and without a comorbid anxiety disorder, cardiometabolic illness.

Certain chronic physical conditions are also common in the bipolar population, such as cardiovascular and metabolic disorders. For example, obesity affects half of the patients with bipolar disorder (129). These conditions may reflect patiens' lifestyle and behaviors associated with bipolar disorder, and they can have significantly increased therapy expectancy (130). Therefore, average number of prescriptions in our study almost doubled (6,17±0,034) when both psychotropic and non-psychotropic medications were taken into account. For emphasizing the medication burden of Bipolar disorder patients; effects of their ages and the complex interaction between mental and physical health needs have to be mentioned.

Though BD and dependence were not associated with increased polypharmacy, alcohol dependence was associated with increased polypharmacy in the current study. Alcohol is the most commonly abused substance in patients with BPD. According to a community-based study about lifetime prevalence of alcohol-related disorders, the ratio was 46% in bipolar patients, which is only 14% when compared with the whole population.

5.2. The Relationship Between the Number of Prescribed Drugs and the Age Groups

The number of prescribed drugs increased remarkable among the age groups as expected in overall patients. This is a clinical reality, so it is not surprising that the usage of complex polypharmacy for BD and dependence increased dramatically over the years (131). For example, the percentage of treatment regimens containing 3 or

more psychotropic medications during discharge increased 13 fold between the years 1974-1996 at the NIMH Psychiatry Branch (132). More recent data from an Ambulatory Medical Care Survey has continued similar trend, in reference to this study, the increasing medication prescribing rate was approximately 40 % over this 10 year period, and there was greater than 2-fold increase in the number of people prescribed 3 or more psychotropic medications (133).

Although there are many examples of "rational polypharmacy" (134) and evidences regarding some benefits about certain multi drug regimens, increased usage of drugs does not appear to be contributing to decreased rates of illness chronicity or functional impairment. It should also be noted that; these increased number of prescribed drugs have been applied in the absence of any clinical trial demonstrating the efficacy of combined BD or dependence treatment consisting a range of medications. A lack of formal evidence that supports complex polypharmacy for BD may account for the substantial variability in prescribing and poor adherence to published guidelines (135) for BD treatment that have been reported in the literature.

Dols A et all. reported that lifetime alcohol dependence (24.8%) and abuse (13.9%) were more frequent and lifetime substance dependence (8.9%) was somewhat more prevalent in bipolar patients (136). In the same research, 31.7% of patients were on six or more medications, including both psychotropic and nonpsychotropic medication, hence fulfilling the criteria for polypharmacy. Although the prevalence of bipolar disorder seems to decline with age (137), the absolute number of bipolar elderly will increase drastically in the coming decades due to aging of the total population. And also, patients with bipolar disorder are predisposed to other psychiatric disorders at elevated rates. Therefore, the increased in number of drug usage due to age in this research is associated with increased use of medications, which is consistent with some prior reports in both psychiatric data.

5.3. The Relationship Between the number of Prescribed Drugs and Rutine Biochemical Parameters

Laboratory EIR test results yield valuable data that can be utilized for diverse purposes in observational studies, including those; extracting information about clinical

events, or seeking data sources for constructing polypharmacy and pharmacovigilance evaluation (138,139).

When a big database such as our EIR was analyzed by Pearson correlation analysis, in a high probability, it could give incorrect results. Despite the fact that Pearson correlation may found statistically significant association between the number of prescribed drugs and the biochemical parametres in all patients, analyzing big databases such as our EIR with Pearson could give incorrect results. For this reason Pearson correlation coefficients were not used.

Our results show that fasting blood glucose levels did not change as a result of increasing number of drugs. However, fasting blood glucose levels changed due to the increasing age.

Due to aging effect; decreases in the concentration of circulating hormones such as estrogens, androgens, dehydroepiandrosterone, and growth hormone are seen in the endocrine system and it has been shown that 40% of individuals from 65 to 74 years of age and 50% of persons above 80 yearspresent glucose intolerance or diabetes mellitus (140). Several studies have found that a high percentage of the elderly possesses a greater insulin resistance.

You could consider polypharmacy as one of the myriad of geriatric syndromes such as frailty, cognitive impairment, depression, injurious falls and urinary incontinence (141). These co-morbidities increase the challenges of controlling hyperglycaemia in older adults group.

Ageing reduces the glucose counter-regulatory and symptomatic response to hypoglycaemia, particularly in the presence of a longer duration of diabetes. So, the prevalence of diabetes mellitus increases with age. A local large-scale population-based epidemiological study using World Health Organization (WHO) diagnostic criteria reported that the prevalence of type 2 diabetes was 26% in people aged 65 to 74 years, compared with approximately 10% in those aged 35 to 64 years (142,143). Another local study of elderly subjects, using a fasting plasma glucose (FPG) level of >7.8 mmol/L (140mg/dL) for diabetes screening, showed a prevalence of 15% in people aged 60 to 80 years and 17% in those older than 80 years (144). These levels would be higher if an oral glucose tolerance test was performed. These data are similar to those found in our studies. (WHO diagnostic criteria for diabetes mellitus were 7 mmol/L (125 mg/dL) for the upper limit of FBG).

On the other hand, polypharmacy correlated with advancing age, this also increases the hypoglycaemic risk. The prevalence of iatrogenic hypoglycaemia tends to increase with advancing age (145). However, there are not any significant evidence for association of the number of drug or polypharmacy with blood glucose levels in our results.

5.4. The Effect of Gender on Fasting Blood Glucose

We tested the effects of gender on fasting blood glucose, after adjusting values with the number of drug, age and diagnosis as covariates eventually, there were no gender x fasting blood glucose interaction in male and female patient groups. However, Mendoza-Núñez VM, et all showed that there were indirect signs between hyperglycemia and gender (146). And it has been demonstrated that there has been a close relationship among leptin and insulin resistance. This findings may be related with obesity, but not gender.

5.5 The Effects of Diagnosis on Fasting Blood Glucose

Our data showed that; fasting glucose levels increased significantly in patients groups with substance dependence, there were not any difference in BPD and alcohol dependence patients groups. This significant increase in substance dependence groups may beassociated with theresults of age related increase. However, the fasting glucose levels not changed by aging in substance dependence group.

5.6. The Effects on the Levels of Alanine Aminotransferase (ALT) and Alanine Aminotransferase (AST)

Most of the drugs that cause drug-induced liver injury (DILI) do so in an unpredictable or so-called idiosyncratic fashion. Periodic screening of liver biochemistries, particularly serum ALT, is recommended for many drugs that have been associated with liver injury (147). However, the efficacy of serum ALT monitoring during drug treatment for preventing severe DILI remains controversial. Up to now, it has been estimated that more than 600 drugs and chemicals have been associated with significant liver injury (148).

Data analysis regarding ALT data showed that there were not any effect of number of drug and age on ALT levels, however there were some effects of gender and

diagnosis both on ALT and AST levels. We checked whether there were any interaction between the number of drug and gender, or the number of drug and diagnosis. Despite significant findings related to gender and diagnosis, ALT and AST data did not indicate any changes due to the insignificant effect of number of drugs or insignificant interactions between the number of drugs and other groups.

In clinical trials, detection of milder liver injury that may be a sign of a problem about the drug can be understandable by elevations of some biochemical markers. Conventionally it is defined as an increase more than 3 times the upper limit of the normal range of ALT level, a serum alkaline phosphatase level that is more than twice against the upper limit of normal, or a total bilirubin level more than twice against the upper limit of normal (148). In the current study there were not any changes related to number of drugs in the ALT levels.

On the other hand, our data showed that the mean of serum AST levels was higher in patients with alcohol dependence group than the other disease groups. This is thought to be due to the longer half life of mitochondrial AST released in response to alcohol and the coexistence of the deficiency of pyridoxal-6-phosphate in alcoholics, which is a cofactor for the enzymatic activity of ALT (149). In acute hepatocellular injury, serum AST levels usually rise immediately, next reaches a higher level than ALT initially, due to the higher activity of AST in hepatocytes. Within 24 to 48 hours, particularly, if ongoing damage occurs, ALT will become higher than AST, because of its longer plasma half-life. In chronic hepatocellular injury, ALT is commonly elevated more than AST; however, in alcoholic liver injury AST is often higher than ALT (150,151), just as seen in our results.

5.7. The Effects on the Level of Creatinine

The measurement of creatinine concentrations in plasma samples illustrates the filtration capacity of the glomerulus, also known as the glomerular filtration rate (GFR.) Creatinine is freely filtered by the glomerulus and these characteristics make creatinine a useful endogenous marker for creatinine clearance. Therefore, if the GFR is decreased, as in renal disease or toxicity, creatinine clearance via the renal system is on the line. The reduced GFR will then lead to an increase in plasma creatinine concentration. Despite our data regarding creatinine showed significant changes in

gender, age and diagnosis groups, creatinine levels increased according to the number of drug in a dose dependent manner in female group. The same increase were not observed in male group; however the mean creatinine level was higher than female patients group. Plasma creatinine levels may not be affected until significant renal damage has occurred (152). The normal creatinine clearence test value is 110-150ml/min in male and 100-130ml/min in female (153). This difference between male and female groups confirmed our data or results to be eligible for literature.

However, increased creatinine levels in female groups may be related with polypharmacy. Among older adults, nondisease-specific problems such as polypharmacy commonly co-occur with reduced glomerular filtration rate and elevated creatinine levels (154). Identification of nondisease-specific problems may provide informations like increased creatinine or decreased renal function risk independent from kidney functions. Our data may be related with aging, but the interaction between the number of drug and age groups was not significant. So, increased creatinine may have demonstrated female patients' sensitiveness. They could be more sensitive to amount of concurrent medication. Our findings may have important clinical implications. Polypharmacy were common among older adults with chronic kidney disease.

5.8. The Effects on the Level of Urea

According to our findings, urea is affected by all variables such as the number of drugs, gender, diagnosis and age. Which means, there are significant interactions between all of them. As known, urea is major nitrogenous end product of protein and amino acid catabolism, produced by liver and distributed throughout intracellular and extracellular fluid.

When the number of medications increases, plasma urea level was also increased in male and female patients. This finding showed that urea is susceptible biochemical test parameters to evaluate polypharmacy in male and female. However, the finding also showed that mean level of urea is also different in male and female patients. The concentration of urea depends on protein intake, the body's capacity to catabolize protein, and adequate excretion of urea by the renal system (155). The body's dependency on the renal system to excrete urea makes it a useful analyte to evaluate renal function. Increased blood urea nitrogen (BUN) is associated with kidney disease

or failure, blockage of the urinary tract by a kidney stone, congestive heart failure, dehydration, fever, shock and bleeding in the digestive tract. Low levels are seen in trauma, surgery, opioids, malnutrition, and anabolic steroid use (156).

In addition, several studies indicated that polypharmacy is indirectly associated with acute renal failure (ARF) (157,158). The mortality rate of patients that hospitalized for ARF is approximately 45 %, and almost 30 % of patients with ARF require renal transplantation (159). Further assessments of the association between ARF and polypharmacy would be important in clinical practice.

When the number of medications increases, blood urea level was also increased in bipolar disorder in our results. Long-term Li treatment may cause impairment in renal concentrating ability, some of which may originate from the effects of Li on vasopressin on hypothalamic level, and a decrease in glomerular filtration rate (160). Li may be a risk factor for Li-induced renal impairment, which has a progressive effect in nature. Additionally, valproate-induced encephalopathy has been increasingly reported and several risk factors have been proposed. The underlying mechanism could be risperidone's interference with valproate's binding to albumin, raising free valproate levels, which would impair the urea cycle and reduce ammonia conversion, leading to a hyperammonemic encephalopathy (161). Valproate and risperidone treatment and Li may have indirectly increased BUN or urea levels in bipolar disorder patients.

Therefore, the increased urea levels in our findings may directly or indirectly associated with Li and risperidon treatment in bipolar disorder. To demonstrate or determine this relationship between polypharmacy and urea, we need further researches in special patient groups.

5.9. The Effects of Polypharmacy on Blood Levels of the Drugs

5.9.1. The effects of polypharmacy on the levels of aripiprazole plasma concentrations.

Aripiprazole plasma concentration levels increased in 4-6 and 7-9 drug groups in the study. These levels were in therapeutic ranges (159, 69±13, 86 and 198, 87±8, 05 ng/ml). Eryilmaz et all. reported; while the patients were on a stable dose of aripiprazole 20 mg/day, measured plasma concentrationlevel was254.88±133.65 ng/ml by a liquid chromatography-mass spectrometry method in a routine TDM setting (162). With

reference to this data, aripiprazole plasma concentration levels werelowerthan in routine mono therapeutic aripiprazole usage (162). The same research group showed that concurrent treatment with valproate resulted in changes on the total aripiprazole plasma levels by 23%. A lower total aripiprazole plasma concentration levels during co-medication with valproate may be related with other drugs or polypharmacy.

Another study was reported that the mean concentration/dose ratios of aripiprazole were higher in patients with mutated alleles for CYP2D6 than in those without mutated alleles. This finding showed that CYP2D6 genotypes play an important role in controlling steady-state plasma concentrations of aripiprazole in Asian subjects. However, it was reported that dosage of the aripiprazole was not adjusted according to age, gender, race, and smoking or hepatic or renal impairment status during treatment (163).

5.9.2. The effects of polypharmacy on the levels of bupropion plasma concentrations.

In our study, bupropion plasma concentration levels increased in 4-6 drugs group. This increase was not in a dose dependent manner, so it may be a nonspecific increase owing to the comments below:

Bupropion is an atypical antidepressant that is biotransformed in humans to its major active metabolite hydroxybupropion by cytochrome P450 2B6 (CYP2B6), this increase may be related to be an evidence of pharmacokinetic changes. It was reported that co-administration of bupropion with an inhibitor of CYP2B6 could have been resulted in serious drug interactions that leads to bupropion related adverse effects such as seizurebecause of its elevated concentrations. (164). Numerous clinically relevant drugs have been shown to inhibit bupropion hydroxylation in vitro, including the thienopyridine antiplatelet agent ticlopidine (165,166). A recent study found a greater than 100-fold variability in microsomal CYP2B6 activity among different individuals (167).

CYP2B6 activity has also been shown to be highly inducible in primary human hepatocytes by several known inducers, including clotrimazole, phenobarbital, phenytoin, and rifampin(168). Of course, there are some drugs currently known to be metabolized by CYP2B6 include the antidepressant bupropion (166), the long-acting

opioid (S)- methadone(169), the MAO-B inhibitor selegiline (170), the serotonin reuptake inhibitor sertraline(171) and some other drugs not related with our diseases.

Despite the increasing number of clinically relevant CYP2B6 substrates and inhibitors, relatively little information exists regarding the extent of CYP2B6 inhibition in commonly used drugs. To assess concurrent used drugs as potential offenders via CYP2B6 drug-drug interactions is not possible because EIR data is inappropriate or insufficient for invitro evaluation of its inhibition.

5.9.3. The effects of polypharmacy on the levels of clomipramine plasma concentrations.

Clomipramine plasma concentration levels decreased in a dose dependent manner by the increasing number of concurrent drugs or polypharmacy. This decrease actually may be an evidence for the action of polypharmacy. A common feature for all TCAs is alarge interindividual variability of the serum concentrations of the respective drug (172). Poor or ultrarapid metabolizers of CYP2D6 and CYP2C19 may have tricyclic plasma concentrations outside the recommended therapeutic range, thereby increasing the risk of treatment failure or side effects (173,174). Clomipramine is demethylated by CYP2C19 to pharmacologically active metabolites (173). Both CYP2D6 and CYP2C19 metabolism influence plasma concentrations, the effectiveness and tolerability of tricyclics(175). The CYP2C19 gene is highly polymorphic; more than 30 known allelic variants and subvariants have been identified(176) and founded high ratio in Caucasian populations. Recently a researcher group reported that ultrarapid metabolizers are ~5–30% of patients, extensive metabolizers are ~35–50% of patients and intermediate metabolizers are ~18–45% of patients, according to phenotypes (173). Therefore, this decrease takes into consideration both clinical outcomes and observed tricyclic plasma concentrations based on genotype/phenotype characteristics.

5.9.4. Theeffects of polypharmacy on the levels of pregabaline plasma concentrations.

Pregabalin plasma concentration levels increased in a dose dependent manner in all polypharmacy groups, except 4-6 drug used group. Pregabalinehas been used in treatment of general anxiety disorder (177) and in the relapse prevention of alcohol-dependent subjects (178). Ethanol withdrawal in humans and animals is characterized

by CNS hyperexcitability that results in both physical and 'affective' signs of dependence. So, the effect of pregabalin appears to be correlated strongly with the degree of hyperexcitation of the presynaptic neurone. It does not bind to plasma proteins, it has an eliminatory half-life of 6 hours and is primarily (92%) excreted renally (179). It exhibits few drug–drug interactions, does notinhibit cytocrome P450 enzymes, nor do these enzymes alter its pharmacokinetics. Because of its minimal protein binding and lack of hepatic metabolism, probability of drug interactions appears to be low. However, our data indicates that comedication with enzyme inhibiting drugs or mainly renal excreted drugs can moderately increase PGB serum concentrations.

5.9.5. The effects of polypharmacy on the levels of sulpiride plasma concentrations.

Whenever the number of prescribed drugs increased, sulpiride plasma concentration levels increased in a dose dependent manner in this study. Approximately, the mean (of SEM) plasma concentration of 1-3 drugs and 13 and upper amounts of drugs used group are 128,16 ± 41,24 ng⁄ml and 451,55 ± 66,28 ng⁄ml, respectively. In the literature, at 50, 100 or 400 mg daily doses for treatment of depression or schizophrenia, the plasma concentration of sulpiride are 35.5, 90.1 and 330.5 ng/mL respectively (180). Very little metabolism occurs and renal excretion appears to be predominant, resulting in the accumulation of sulpiride in patients with renal dysfunction (181). About 70–90% of an intravenous dose and 15–25% of an oral dose is excreted unchanged in the urine (182). Another word, Its usual half-life is 6–8 h and 92% excreted as unchanged form in the urine. Owing to sulpirides'rapid renal elimination exposure, the increase of sulpiride plasma concentration may be based on the decrease of clearance and or the ratio of drug extraction. Due to polypharmacy, the renal extraction of sulpiride was reduced, thus its plasma concentration was increased in a dose dependent manner.

5.9.6. Theeffects of polypharmacy on the levels of valproic acid plasma concentrations.

Valproic acid (VPA) is mainly used to treat migraine, bipolar disorder, psychotic disorder, several types of anxiety disorder including panic disorder, social phobia, posttraumatic stress disorder and alcohol dependence and withdrawal. In our study, the increase of drug number tended to decrease VPA plasma concentration levels, except 13

and upper amount of drug groups. This decrease can be explained in two ways; one of them is the increase of VPA clearance, the other one is the increase of VPA metabolization.

VPA has complete bioavailability (96%Y100%) resulting from various formulations (183) and is eliminated almost completely by hepatic metabolism. The hepatic clearance depends on the free fraction (Fu) and the intrinsic clearance (CLint). The accepted therapeutic range of VPA steady-state concentration for general psychiatric conditions is 45 to 100 mg/L (184). In our study, the mean VPA blood concentration levels are lower than this values (39 to 47mg/L). VPA binds to plasma proteins at the rate of 78% to 94%, mainly to albumin, and exhibits a concentration-dependent degree of binding, in accordance with the saturate of protein binding in the usual therapeutic range (45-100 mg/L) (185). Therefore, the unbound steady-state drug plasma concentration (Cfree) increasesare lesser when compared shortly after the dosage increase. In case of additive drug usage, unbound drug plasma concentration (Cfree) decreases proportionately, due to extraction of free drug and competition with other drug for plasma protein. The decrease in plasma VPA levels by drug number maybe related with the increase of free VPA, in the study. VPA is metabolized by the liver through at least 3 main pathways, these are; glucuronidation, 50%; oxidation, 40%; and cytochrome P450, 10% (186). Generally, total VPA clearance (CLtotal) is 1.0 to 1.1 L/h in patients with epilepsy using other antiepileptic drugs (186). The decrease in the levels of VPA plasma concentrations may be related with enzyme induction. Linear pharmacokinetics rule may not apply to VPA because of the protein-binding saturation or metabolization.

5.9.7. The effects of polypharmacy on the levels of zuclopenthixol plasma concentrations.

The increase of number of drugs were increased plasma concentration levels of Zuclopenthixol. CYP2D6 is at least partially responsible for zuclopenthixol metabolism (187). CYP3A4 also have an additional contribution for metabolism of zuclopenthixol (188). Many co-prescribed psychotropic agents are substrates, inhibitors or inducers of CYP enzymes, especially CYP2D6 and CYP3A4 (189). All of these raise the potential for drug–drug interactions.

Many interactions are caused by the inhibition or induction of the human cytochromes P450 (CYP), the main enzymes responsible for drug metabolism. In psychiatric patients, the serum concentration of orally administered zuclopenthixol increased with co-prescription of the CYP2D6 /CYP3A4 inhibitor fluoxetine and the CYP2D6 inhibitors paroxetine and levomepromazine and decreased with co-prescription of the CYP3A4 inducer carbamazepine (190,191). The increase in concentration of orally administered zuclopenthixol were associated with the dose of co-prescribed fluoxetine, paroxetine and the serum concentration of co-prescribed levomepromazine (192). Ketoconazole and quinidine together abolished zuclopenthixol disappearance, but not need clinically a dose-corrected oral zuclopenthixol serum concentrations (187). In light of this knowledges, the increase of Zuclopenthixol plasma concentration may be related with the inhibitor effects of other co-administrative drugs on CYP2D6 and CYP3A4 enzymes.

5.9.8 The effects of polypharmacy on the levels of benzodiazepine plasma concentrations.

Benzodiazepine is mainly used for the management of seizures and epilepsy in alcohol detoxification and also it is used for the treatment of panic disorder and ethanol withdrawal (193). In the study, benzodiazepine plasma concentration levels increased due to increase of the number of drugs. Benzodiazepines (BZDs), as one of the clinical drugs, are recommended in first-line and should not be continued for more than 4 weeks (194). The data which is shown by graphics presents BZ levels during treatment periods as mentioned.The cut off concentration of BZD immunoassay is 200 ng/mL, and values over 200 ng/mL are designated as positive, and values below 200 ng/mL are designated as negative (194,195). It may be false negative due to the immunoassay methods.

BZD is mainly metabolized by cytochrome P450 (CYP) 3A4 and is also partially metabolized byCYP2C19 and CYP2B6 to yield an active metabolite (N-desmethyl-diazepam) (196).The number of concurrent drugs increase the inhibitor or inducer impacts on cytochrome P450 (CYP) enzymes. This increase may be significant for polypharmacy or metabolisms of drugs.Without no doubt, this will increase the benzodiazepine plasmaconcentration levels in patients.

5.9.9. The effects of polypharmacy on the levels of phencyclidine plasma concentrations.

As known, phencyclidine has been used as an abuse drug. Low to moderate oral doses (5–20 mg) of phencyclidine produces an acute, confused state that may last 6 hours. The analytical method choice for the determination of PCP in biological fluids like blood, serum, plasma and urine are gas-chromatography-mass spectrometry or immunoassay (197). Unfortunatelly, immunoassay includes production of false-positive results due to problems of cross-reactivity and false-negative results due to inadequate sensitivity of the assay (198). In our data, the levels of phencyclidine concentration were between 0.8 and 1.8 ng/mL in all groups and this concentration of phencyclidine were to be under the cut off concentrations. The cut off concentration of phencyclidine is 25ng/mL for CEDIA immunoassay methods (199). Therefore, the effects of polypharmacy on phencyclidine concentration level was not added to discussion. The screening test initially detects the presence of drug and (or) drug metabolite(s) at or above a stated administrative cutoff concentration, then the GC-MS procedures should be corrected it, by using separate cutoff values, in the end specifically confirms the presence of the drug.

5.9.10. The effects of polypharmacy on the levels of ecstasy plasma concentrations.

There was a positive correlation between the number of drugs and ecstasy concentration levels, but not for all drug groups. Extasy concentration levels were observed to be under the cut off concentration values (200). Therefore, the effects of polypharmacy on opioid and extasy concentrations were not included to discussion.

5.9.11. The effects of polypharmacy on the levels of opiate plasma concentrations.

Serum opiate concentration levels in all drug groups presented significant increase among the determined drug groups. There are positive correlations between number of drugs and serum opiate concentration levels. However, opioid concentration levels were observed to be under the cut off concentration values (201). And sure, false-positive results needed to be taken into account in terms of cross-reactivity when using immunochemical methods (202). The producer of the cloned enzyme donor immunoassays (CEDIAs) has published a cross-reactivity guide (203). It presents an

overview over compounds that give false-positive results in samples spiked with the potential cross-reactant over a range of clinically achievable concentrations (204).

CONCLUSION

In thesis we have attempted to expose the prescription patterns for the treatment of bipolar disorder, dependence and alcohol dependence in hospital in Turkey, whereby we composed the state of polypharmacy, related biochemical parameters, therapeutic drug monitoring and demographic features of inpatients in several ways. According to thesis, inpatients with alcohol dependence use more drugs when it is compared with any other diseases. Furthermore drug usage is highest among people in their late years; as consistent with the literature.

Fasting blood glucose seemed to be influenced by age and number of drugs is not associated with fasting blood glucose, ALT and AST levels. However, there were significant correlations between AST and age and diagnosis. It is also observed that creatinine levels was increased by increased concurrent drug usage particularly in females. Lastly, urea has been associated with all the variables; especially it has been higher due to the increased number of drugs in males. Urea levels tended to rise according to the number of drugs in bipolar patients especially in 60-69 age groups. Aripiprazol plasma levels increased until concurrent usage of 9 drugs, also pregabaline, sulpiride, benzodiazepine and opiate concentration levels increased due to the increasing number of drugs.

Taken as a whole, this thesis is meant to be an analysis of the current clinical implication of polypharmacy adapted to Turkish population while a lot of rising clinical concerns about the problem of ‘polypharmacy’ worldwide. My goal has been to contribute awareness of the potential pitfalls of polypharmacy and drug interactions in our country, in order to avoid harm to patients with advanced incurable illnesses. And my goal is also to focus on re-evaluating for the necessity of starting any new drug during prescription.

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7. APPENDICES

7.1 Ethical Approval from Uskudar University Ethical Committee

Ethical approval of the study was accepted by; Uskudar Univesity Clinical Researchs Ethical Committee (report date: February 16, 2015, Number: B.08.6.YÖK.2.ÜS.0.05.0.06/2015/41).

8. CURRICULUM VITAE

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