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ASSESSMENT OF ADVERSE REACTION EXPERIENCES OF DENTISTS FOR COMMON ANALGESICS IN DENTAL APPLICATIONS

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To my unique family!

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ABBREVIATIONS AND SYMBOLS

ADR	:	Adverse Drug Reaction
AIFD	:	Araştırmacı İlaç Firmaları Derneği (Association of Research-Based Companies)
ASA	:	Acetylsalicylic Acid
ATC1	:	Anatomical Therapeutic Chemical1
Bn	:	Billion
BPS	:	British Pain Society
CNS	:	Central Nervous System
COPD	:	Chronic Obstructive Pulmonary Disease
COX	:	Cyclooxygenase
CYP	:	Cytochrome P
FDA	:	Food and Drug Administration
GDP	:	General Dental Practitioner
GI	:	Gastrointestinal
HIV	:	Human Immundeficiency Virus
IASP	:	International Association for the Study of Pain
IMS	:	Intercontinental Marketing Services
IUD	:	Irrational Use of Drug
ISoP	:	International Society of Pharmacovigilance
MHRA	:	Medicines and Healthcare Products Regulatory Agency
Mn	:	Million
NAPQI	:	N-acetyl-p-benzoquinonimine
NSAID	:	Non-steroidal antiinflammatory drug
tNSAID	:	tranditional Non-steroidal antiinflammatory drug
OTC	:	Over The Counter
RUD	:	Rational Use of Drug
SSRI	:	Selective Serotonin Reuptake Inhibitor
TCA	:	Tricyclic antidepressant
TDA	:	Turkish Dental Association

TİK-6	:	Türkiye İlaçla Tedavi Kılavuzu-6 (Turkey Medication Guideline-6)
TL	:	Turkish Lira
TUFAM	:	Turkish Pharmacovigilance Center
US	:	United States
WHO	:	World Health Organisation
$	:	Dollar

ÖZET

Bilgin E. Diş Hekimliği Uygulamalarında Sık Kullanılan Analjezikler Açısından Diş Hekimlerinin Yan Etki Tecrübelerinin Değerlendirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Farmakoekonomi ve Epidemioloji Yüksek Lisans Tezi. İstanbul, 2014.

Amaç: Bu tezin amacı diş hekimliğinde sıklıkla kullanılan analjeziklerin (parasetamol, steroid olmayan anti-inflamatuar ilaçlar (NSAIDs) ve opioidler) önemli yan etkilerini vurgulamak ve diş hekimlerinin bu konudaki tecrübelerini değerlendirmektir.

Materyal & Metod: Anahtar kelimeler kullanılarak ulusal ve uluslararası literatür taraması gerçekleştirilmiştir. Bu bağlamda Yeditepe Üniversitesi Bilgi Merkezi üzerinden Pubmed, Sciencedirect, Ulakbim vb. birçok veri tabanına ulaşılmıştır. Ayrıca herkesin online olarak erişebileceği yayınlar taranmış ve bazıları tez içerisinde kullanılmıştır. Bunun yanında, Türkiye'de ve uluslararası alanda, sağlık otoritelerinin resmi internet siteleri taranarak, konuyla ilgili kısımlar değerlendirilmiştir. Dünyada yayınlanan IMS (Intercontinental Marketing Services) verileri kullanılarak değerlendirmeler yapılmıştır. Buna ek olarak, 2007-2012 arasında Türkiye'de analjeziklere ait IMS verileri çalışmada kullanılmıştır. Analjeziklerin yan etkilerinin daha iyi ele alınması açısından RxMediaPharma (2014) ve Türkiye İlaçla Tedavi Kılavuzu-6 (TİK-6)'dan yararlanılmıştır. Araştırmanın amacına uygun olarak, Türkiye'nin önemli bir üniversitesinin diş hekimliği fakültesinde akademisyen olarak görev alan ve diş hekimleri açısından önemli bir sivil toplum örgütü olarak nitelendirilen bir kurumun, yönetim kurulunda bulunan diş hekimleriyle odak grup görüşmesi metodu kullanılarak, elde edilen bulgular değerlendirilmiştir.

Bulgular: Diş hekimlerinin ağrı kesicilerle alakalı olarak çok fazla yan etki tecrübesi yaşamadıkları ancak yan etki ile karşılaştıklarında farmakovijilansın temel parçalarından biri olan yan etki bildirimi konusunda hiçbir bilgilerinin olmadığı görülmüştür.

Sonuç: Diş hekimleri gerek Sağlık Bakanlığı gerekse de ilaç firmalarının gerçekleştireceği organizasyonlarla farmakovijilans sistemi ve ürün güvenliği ile alakalı sürekli eğitimler almalı ve alınan eğitimler ışığında hastalar yönlendirerek (broşür, poster veya direk bilgi vererek) güvenli ilaç kullanımı konusunda bütünlük sağlamalıdır. Buna ek olarak diş hekimleri yıllık gerçekleştirdikleri kongrelerde veya hazırlanacak e-eğitimlerle kendilerinin bilgilerini hep taze tutmalılardır. Ayrıca bu tezin alanında ilk olması sebebiyle, daha çok araştırmanın gerçekleştirilmesi gerekmektedir.

Anahtar kelimeler: İlaç güvenliği, Yan Etki, Diş Hekimliği Uygulamaları, Farmakovijilans, Analjezikler

ABSTRACT

Bilgin E. Assessment of Adverse Reaction Experiences of Dentists for Common Analgesics in Dental Applications. Yeditepe University Institute of Health Sciences Pharmacoeconomics and Epidemiology Master Program. Istanbul, 2014.

Purpose: The main aim of the study is to emphasize important adverse reactions of analgesics (paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids) commonly used in dentistry and to assess experiences of the dentists regarding the issue.

Material & Method: National and international literature has been searched by using keywords. Concordantly, Pubmed, Sciencedirect, Ulakbim and other databases have been reached on Yeditepe University Information Center. Moreover, publicly available publications have been reviewed and some of them have been included into the study. In additional, national and international health authorities' web sites have been evaluated with regards to analgesics' adverse reactions and related guidelines and announcements. IMS (Intercontinental Marketing Service) data that have been published on in the world have been viewed. Furthermore, sales information of analgesics between 2007-2012 in Turkey have been extracted from IMS Programme. Web-based programme which is called RxMediaPharma (2014) and Turkey Medication Guideline-6 (TİK-6) have been use to provide better understanding in reference to adverse drug reactions (ADRs) of analgesics. In line with the purpose of the study, focus-group interviews have been performed with two dentist groups. First group works as an academician in one of the important dentistry faculty in Turkey and the second group of dentists are members of substantial non-profit organization of dentists.

Findings: Dentists as one of the most significant stakeholders of pharmacovigilance do not have much experience against ADRs of analgesics but dentists encounter any ADRs they do not know about reporting of ADRs which is one of the most significant part of pharmacovigilance

Conclusion: Dentists should be trained via organizations arranged by Ministry of Health and pharmaceutical companies. By this way, dentists can direct their patients (brochures, posters or direct information) better in line with drug safety. In addition, one session in congress of dentistry should be separated for pharmacovigilance and drug safety to keep their information updated and e-learning should become available for dentists that do not participate to congresses. Finally, further studies are needed to evaluate ADR experiences and behaviors of dentists with regards to analgesics because this study is the first for related field.

Keywords: Drug Safety, Adverse Reaction, Dental Applications, Pharmacovigilance, Analgesics

1.INTRODUCTION AND AIM

Pain is the huge health problem for the world. It has been calculated that 20% of people suffer from pain and 10% of people is diagnosed with chronic pain every year, globally (1). According to result of National Health Interview Survey in United States (US), people suffered from lower back pain (28%), severe headache or migraine (%16), neck pain (15%) and pain in the face or jaw (8%) respectively in line with their rates for three months. Among people who had persistent pain experienced difficulties in their functionality and quality of life (2). Besides, the prevalence of acute pain especially headache is supposed to be approximately 100%. Thus, it is thought that nearly all people may suffer from sort of pain throughout their life (3).

Pain can be expressed as one of the most common symptoms to visit clinicians by patients. For example, pain is the second common complaint in Italy that leads to visit clinicians. Concordantly, pain prevalence of inpatients has been evaluated as %91.2 in Italian hospitals (4). If pain is controlled insufficiently, adverse effects will be observed on physical and psychological functions as well as quality of life. Many surveys demonstrated that up to 90% of patients could reach sufficient pain relief in terms of pharmacological treatment but the rate loses its meaning when the treatment is applied in routine practice (5).

On the other hand, dental pain can be reflected one of the major kind of pain types in which frequent experience of pain is seen in patients. Pain is an extensive apprehension for dentistry (6). It has been provided that nearly 22% of people in US meet at least one type of orofacial pain and dental pain occupies the most widespread of the population at the rate of 12.2% which means more than 22 million (Mn) people (7).

In Turkey, pain related complaints are not different from worldwide statistics largely. Erdine et al. (2001) reported that prevalence of pain is 63.7% in adults and chronic pain consists 76.6% of it. Moreover, pain occurred in the region of head, lower back, lower extremities and abdomen are the most common respectively (8).With related to dental pain, Muglali et al. (2008) demonstrated that pain was the most

common complaint (38.4% of 307 patients) of people that attended to Ondokuz Mayıs University Dentistry Faculty (9).

High frequency and inadequate control of pain bring pain management into prominence. From the point of view, unplanned visits to dentist is mostly associated with pain and generally a dentist encounters at least one or two patients suffer from pain nearly every working day. Dental pain can be caused by any diseases and conditions as well as after treatment by a dentist. Thus, dentists should reveal the source and nature of the pain and treatment strategies should be performed in line with the source and the nature (10). In such situations, dental pain is related to non-odontogenic factors and it may not be decreased by tooth extraction or clear away of dental caries. Many patients reported that developing of new pain or increase of existing pain is observed after dental treatment so some of patients look for a solution to relief pain. Moreover, they can apply unnecessary and expensive treatment that worsen the case. Borromeo et al. (2012) suggested that unnecessary suffering from pain may be related to gap of healthcare professionals including dentists, pharmacists, physiotherapists, occupational therapists and nurses (11).

Management of pain is always crucial in dentistry. Non-opioid analgesics; paracetamol (acetaminophen) and NSAIDs (i.e. ibuprofen, naproxen, flurbiprofen) are frequently used for the treatment of dental pain. Opioid analgesics (i.e. hydrocodone, oxycodone, meperidine, propoxyphene, pentazocine, tramadol) are also efficient in the management of moderate to severe dental pain even if not frequently preferred (12). Patients with pain problem want to be given best analgesic and pain management strategy so dentists need to know the requests. Thus, knowing analgesics' mechanism of action and related techniques to relieve pain as well as their adverse reactions play an important role for decision-making (13).

Adverse reactions occupy one of the main principles for treatment strategies and every drug has adverse effects as well as medications used to treat pain. Thus, any drug can not be evaluated completely safe even if they are used commonly all over the world. Extensive use of analgesics to treat dental pain increases the risk of ADRs. Paracetamol

leads to serious ADRs called as “hepatotoxicity”. On the other hand, NSAIDs can cause irritation and bleeding in gastrointestinal tract that’s why cyclooxygenase-2 (COX-2) inhibitors were developed. However, serious cardiovascular effects have been observed with patients using COX-2 inhibitors. Besides, Hargreaves et al. (2005) suggested that opioids are strong analgesics but they lead to significant adverse reactions (i.e. respiratory depression). In such cases, dentists have to inform patients about not only for dose and dose interval of the drugs but also for adverse drugs reactions, drug interactions and other related circumstances should be explained to the patients. Thereby, quality of life, compliance of patient and success ratio of treatment will be increased (10,12).

Concerning drug-related adverse reaction or reactions, pharmacovigilance is coming into popular all over the world as well as in Turkey. According to World Health Organization (WHO) pharmacovigilance is defined as the science and activities to the detection, assessment, understanding and prevention of adverse effects or any other related drug problems (14). Within the scope of a pilot project in which WHO and Turkish Pharmacovigilance Center (TUFAM) have worked together, two major drug groups which were antibiotics (16%) and analgesics (12%) have been reported frequently to TUFAM in related to ADRs, respectively. However, overall reporting of ADRs to TUFAM have been conducted by mostly patients (57%) followed by pharmacist (31%), doctors (9%) and other healthcare professionals (15). When relevant rates are taken into account, dentists which can be considered as the group that provide insufficient reporting for ADRs and should improve their reporting habits especially analgesic products which are commonly used by dentists.

Another important subject with regards to analgesic treatment as well as for all treatment strategies is rational use of drugs (RUD). RUD covers all stakeholders for the treatment of any medical conditions. Based on WHO publication, half of medicines are taken by patients inappositely and half of patients do not achieve taking medications sufficiently. Moreover, there is another concern related to RUD called as Irrational Use of Drugs (IUDs). Many examples can be given to describe IUD like over-prescription of medicines, non-compliance of treatment guidelines, using more expensive drugs rather

than appropriate and cheaper one, overuse of medicines etc. In addition to the examples, IUD may lead to resource depletion, increase ADRs and lose patients' trust in front of clinicians and authorities (16).

From the point of analgesics, their usage have been increased for last 30 years in both developed and developing countries. In Turkey, irrational use of non-prescribed and prescribed analgesics have been observed. Thus, irrational use of analgesics can be described as a major health problem (17). Yapici et al. (2011) evaluated the behaviors of 300 people about drug usage. As a result of the study, analgesics were the most commonly retained drug group at home (18). In fact, possibility of irrational use of any drug increase if it is the most frequently held at home. Thus, based on information from the study, rate of irrational use of analgesics may be high.

In the light of all the facts mentioned before, the aim of the study was to determine adverse reaction profiles of commonly used analgesic drugs in dentistry and to evaluate their usage within the scope of RUD and pharmacovigilance activities and to comment of all safety-related subjects regarding to frequently used analgesics in dentistry with the help of information obtained from the interviews with dentists.

2. GENERAL INFORMATION OF PAIN

2.1. Definition of Pain

Pain phenomenon has many definitions that are available in lots of literatures. However, the most common definition of pain has been described by International Association for Study of Pain (IASP) as " an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage or both" (19). Based on the definition, subjective and psychological particulars of pain become prominent. Moreover, IASP definition also points out that pain is pain and it has not to be associated with nociception (20). In 2001, the Joint Commission on Accreditation of Healthcare Organizations presented the connection between untreated pain and negative physiologic and psychological effects (21).

Concordantly, Rhudy et al. (2000) examined the effect of anxiety and fear on pain and as a result, alteration of pain via emotional status was found out (22).

Pain is affected by many variables like gender, age, culture, history of pain experiences and emotional factors as joy, grief, fear, excitement, beliefs and behaviors and etc. (23). Thus, pain should be managed according to its definition and any other related-points like emotional perspective. If healthcare professionals ignore the definition of pain and its subjective meaning, unintended consequences would probably occurs in patients.

2.1.1. Classification of Pain

Several categorizes can be used with related to pain classification (24). Location, duration, frequency, underlying cause and intensity are common parameters using classification of pain. Thus, clinicians may encounter a complex classification of pain and that is why they can be confused and use different classification systems independently from each other. However, healthcare professionals have to take into consideration all points (e.g. time, anatomy, intensity, patient, pathology) to relieve pain successfully (21). One of classification system (Aydın, 2002) based on duration, mechanism and location with some information is demonstrated as following Table 1 (25).

Table 1: Classification of pain

Pain Classification According to	Types of Pain
Duration	*Acute Pain* - Always nociceptive - Indicates harmful aspects for the body
	Chronic Pain - Lasts longer than 3-6 months - Generally nociceptive and needs medical intervention
Mechanism	*Nociceptive Pain* - A response as a result of tissue damage *Neuropathic Pain* - Occurs as a result of dysfunction or primer lesion of nervous system - Characterized with spontaneous pain

Mechanism	*Deafferentation Pain* - Usually have burning sensation - Occurs at peripherical or nervous system lesions *Reactive Pain* - Includes myofascial pain *Psychosomatic Pain* - Expression of psychosocial problems as pain
Location	*Somatic Pain* - Sharp and sudden - Joint, muscle and bone pain are the examples (exclusion of viscera) *Visceral Pain* - Pain in viscera - Can be generalized and difficult to localize *Sympathetic Pain* - Vascular pain, coxalgy and complex pain syndromes are the examples.

2.1.2. Culture on Pain

Cultural background is very substantial point in the management of pain. Cultural differences between healthcare professionals and patients may lead to failure of the treatment. Due to the increased cultural interactions among societies around the world as well as increased pain complaints as one of the most common reason to seek healthcare professional demonstrate the importance of regarding subject.

First of all, pain comes out associated with cultural and social properties within many societies because pain exists from birth of human being and interacts with many stimuli. Based on the interactions, brain constitutes cultural structure and leads to understand the cases within its structure (26).

Culture affects many things in human life but also influence the beliefs regarding to prevention and the treatment of diseases which are the main two constitutes of successful care. When considered in details, culture impresses individuals' experiences and responses to pain including when and how to ask treatment (27). Interested particular of culture in pain treatment can be taught as important for each stakeholder

because a patient wants to take a treatment culturally acceptable and cultural patterns of healthcare professionals may also influence treatment options. Thus, healthcare professionals should be aware of the differentiation and should not provide stereotype treatment pathways to any patients. They should know how a patient thinks about his pain firstly.

Besides to effects of culture on pain management it may also affect its way of expression and interfere with pain assessment. If a patient is grown in a stoical family or culture, expression of pain will be a problematic state. It may come from the words in early childhood as “boys do not cry” or “get up you are okay”. Because of the fact that investigation of each culture is need to complete pain assessment (28). Moreover, the anthropologist, Carolyn Sargent shared following words in 1984; “between death and shame, death has the greater beauty”. Carolyn Sargent investigated the expression of pain in an ethnic group and as a result, pain were described as shameful sign of weakness mostly. Concerning cultural attitudes to pain, Mieko Hobara at the New York State Psychiatric Institute demonstrated that Japanese men and women are less likely to express pain than American men and women. Moreover, Sangeetha Nayak and his colleagues found that expression of pain for students in India is less acceptable than their counterparts in US (29).

Eventually, healthcare professional and clients have to be taken into consideration when culturally sensitive pain treatment is performed (30). D’Archy provided the interventions of a healthcare professional (nurse) as following points in cultural aspects in 2009 (31):

- Listen and explore the meaning of patient’s pain
- Determine the culture of patients and do not assume every member of a culture is same.
- Be sensitive against patient’s culture in which limit pain management is observed.
- Tell the importance of pain assessment and reporting.

- For foreign patients, special tools & techniques will be needed. Translator or translated tools or techniques will be helpful for the assessment.
- Be sensitive against spiritual or religious approaches of cultures to pain.
- Consider folk remedies. They can be common for some cultures in pain relief.
- Showing main purpose to treatment in which is culturally sensitive.

2.1.3. Pain Studies in Turkey

In Turkey, there are many studies regarding the pain characteristics associated with many factors. Among the studies, one of the most comprehensive studies has been conducted in 1999 between February-October. Erdine et al. (2001) provided the pain prevalence of adults in Turkey through the study. 15 cities were included from 5 different demographic regions of Turkey and 3001 people were addressed 28 questions. As a result, pain prevalence of adults has been found as 63.7% and chronic pain consisted 76.6% of it. Moreover, prevalence increased with age and was higher in females, urban society and western region of Turkey. Based on chronic pain statistics, chronic pain was evaluated as frequent in Western and Middle Anatolia, urban areas, 35-44 years and females. Within the scope of body regions, head (34.4%), lower back (14.1%) and lower extremities (12.0%) were the most painful regions respectively. When considering headache, it was frequent in females, urban society and Western and Middle Anatolia Region. However lower-extremity pain was evaluated more frequent in males and rural society (8). As a part of this study, Ozkan et al. (2009) has designed a cross-sectional study to evaluate prevalence of analgesics use in adults and associated factors. It was the first study as the most comprehensive and nationwide. In line with the purpose of aim of study, the prevalence of analgesic use was very high (73.1%) and its prevalence and patters showed alterations according to socio-demographic factors. According to results, prevalence of analgesic use was higher in female, 45-54 years, rural areas and northern region of Turkey. On the other hand, non-prescribed analgesic use was higher in 55-65 and people with lower-middle socioeconomic status (17).

Another study has been conducted to find out prevalence of pain and pain treatment in adults with 250 participants in 2009 between April – June. Kuru et al. (2011) demonstrated that pain prevalence of participant was 92.8% and 5 different body

regions were determined with related to most common causes of painful conditions as shoulder, lower back, neck, dorsal and knee. The highest prevalence belongs to shoulder pain but in terms of pain level, lower-back pain was the first. In addition, region of knee was the most frequent cause to prevent working. On the other hand, individuals chose 4 different methods to relive their pain. However, a clear majority of individuals (38%) had nothing to relieve their pain. Thus, the results of the study are indicated in following Table 2 (5).

Table 2: Methods preferred by individuals in pain relief

NSAIDs and/or analgesic drugs	33%
Physical treatment or rehabilitation	22.7%
Other pain relieving methods	4.1%
Surgery	1.2%
No treatment	38%

In another study, to evaluate the relationship between pain and pain belief and socio-demographic/economic characteristics in adults, Kocoglu and Ozdemir (2011) performed a cross-sectional study with 131 individuals between 18-65 years. As a result, 78.6% of individuals had pain experience within last year and 38.8% of the individuals suffering from chronic pain. Moreover, age between 30-65 years, graduation from elementary school and lower education level were determined as risk factors for lifetime pain suffering while being female and married for last year experience of pain and age between 30-65 years and lower income for chronic pain. On the other hand, with related to pain source and results, organic and psychological levels of beliefs were determined as similar but the increased perception of psychological beliefs were described within lower-income group (32).

When considering all mentioned data before, the prevalence of pain is very high levels in Turkey and there are many associated factors in the background of it. Examples of the factors include gender, age, marrial status, level of income and residence of individuals. In addition, different pain perception of individuals can be another factor in terms of lower and/or no medication use or overuse of medication that may cause undesired drug reactions. Thus, healthcare professionals play an important role to relive patients' pain adequately with the understanding of associated

characteristics of individuals. Moreover, patients' and healthcare professionals' education is one of the key elements of pain management. By this way, pain can be managed appropriately that lowers the prevalence of pain and unwanted situations with regards to medication and other-human related factors can be eliminated.

2.2. Pharmacology and Dentistry

Two areas regarding drug use have to be interested by dentists. One of the areas including the drugs used in dentistry because of their therapeutic effects and gaining maximum advantages while lessen disadvantages. The circumstance will be only observed when the dentist has knowledge of therapeutical use and adverse reactions of drugs. However, second area consists the awareness of prescription of drugs by physicians for their patients or their administration (over-the-counter drugs) by themselves that can cause alterations in patients' physiology. Moreover, the alterations may interfere dental procedures, may be significant or can change the approach to the patient. Thus, knowledge about the agents that cause such alterations may be required as well as their adverse reactions (33).

On the other hand, unfamiliar drugs to patients should never be used by dentists and their treatments have to be started after the assessment of all drugs have been taken by patients before. However, it should be note that basic knowledge of pharmacology is not enough but anybody may remember everything regarding all drugs (33). For this reason, physicians should improve their knowledge and educate themselves on pharmacology to provide pharmaceutical therapy in terms of high safety and low adverse reactions to their patients.

Pharmacology knowledge of dentists may be taken into account within following directions. Dentists have many reasons to have postgraduate education in clinical pharmacology. Examples of reasons include administration of local anesthetics, prescription of analgesics and antibiotics and so on. Based on populations, polypharmacy has been observed with older ones and dentists' knowledge of drug interactions and adverse effects that lead to unintended conditions are very important. From the point of younger patients, increased use of psychotropic medications as well

as herbal and nutritional medications affect patients' status and drug interactions. As a consequence, continuous learning of dentists about clinical pharmacology is crucial for related healthcare professional. (34).

Considering the other part called as undergraduates dentistry should have necessary properties to overcome new dental materials and techniques before starting their practices in dentistry or other sciences like dentistry. Concordantly, pharmacology education plays an important role. A good dentist should prescribe suitable drugs, recognize patients medical status with the help of currently taken medications and evaluate any adverse reactions that are caused by drugs on patients' health properly. By this way, pharmacology lessons help the students to accomplish many medical conditions with regards to their patients as well as writing rational prescriptions (35). In addition, Gregson et al. (2012) demonstrated that in practice, technical aspects of dentistry may be over emphasized than medical assessment and pharmacology and claimed that if educational model of faculties includes the two concepts consistently and reinforce the concepts, students can improve their knowledge and abilities in the areas as to be motivated (36).

Besides, thoughts of the two groups mentioned above regarding to pharmacology were reflected the study performed by Turkish Dental Association (TDA). In 2008, one of the study series of TDA mentioned the insufficient general medical information that included internal diseases, pharmacology, emergency aspects and inadequate first-aid knowledge. As a part of the study, 5.6% of the students (n=161) thought that they were given insufficient theoretical pharmacology courses. In an another part of the study, 3.6% of students (n=394) want to be given more pharmacological information. From the point of dentists, only 2.7% of dentists (n=183) want to get more information about pharmacology (37). According to results, knowledge of pharmacology has been come out as a problem both in students and dentists.

As a general perspective, all healthcare professionals have to be aware completely for recent trends in line with their specialty to provide their patients potent and accomplished treatment. Thus, they have to refresh their knowledge about drugs that are

used throughout the treatment and their interactions (38). Local anesthetics, antibiotics and analgesics are the most frequently prescribed drugs in the field of dentistry. All related drugs have intrinsic characteristics and it is very significant to administer accurate dose and recognize their adverse effects. Although short-term solutions and surgical procedures are the main causes of dental prescription, dentists need to know related drugs and the rules of prescription. In addition, there are many clues in such countries where dentists do not have sufficient pharmacological knowledge and make prescription mistakes frequently (39).

For the reasons, all clinicians as well as dentists include postgraduates and undergraduates should update and improve their knowledge and educate themselves on pharmacology to provide better pharmaceutical management of patients in terms of high efficacy and safety.

2.2.1. Treatment Approaches to Pain in Dentistry

Pain is frequent among societies and the case demonstrates the importance of the treatment approaches. Better and preplanned approaches may increase clinical outcomes of pain treatment positively.

Evaluation of patients suffering from pain have not been performed adequately. Pain frequently comes to mean analgesics and they are given to patients in such conditions. Moreover, pain is not an objective case and it is very difficult to treat patients with pain because pain shows varieties from patient to patient. Thus, the main thing in the beginning of the treatment is to believe patients' expressions against pain (40).

When considering the dentistry side, people have many reasons to visit a dentist such as regular check-ups, painful problems, planned treatment etc. Among the reasons, pain may be expressed as the most common reason for unplanned visit to dentists and a dentist may encounter at least one or two patients suffering from pain. Different diseases or conditions related to dental or nearby structures may cause dental pain. In addition, pain can be observed after dental treatment. Thus, dentists should reveal the

source and nature of pain and should organize the treatment strategy or strategies based on the two parts (10).

For the management of dental pain, '3-D' principle is a good choice to relive it. It consists diagnosis, dental treatment and drugs. The first and the most important step of 3-D principle is diagnosis. The step provides information about the reasons of pain and identifies the factors related to the reasons. The stage can be expressed as "information gathering" exercise. Clinicians take information about medical and dental history of patients and discuss with patients. Moreover, some tests should be appropriate to confirm the diagnosis but clinicians should choose the tests related to the complaints. As a result of the acts, clinicians provide exact diagnosis but it should not be forgotten that knowledge of varies diseases and conditions of dental clinician is very important to diagnostic processes. In such aspects, diagnosis can not be really completed because the reason that cause of pain is not identified. If the cause of pain is not resolved, fully recover of patients will not be seen and their medical conditions can go into bad situation such as conversion of acute pain to chronic type. However, the diagnosis is completed and the reason is identified, dental treatment can be started. By this way, the symptoms generally can be resolved in a rapid way. Moreover, the drugs are used to relieve painful conditions in which they are really required. Otherwise, the drugs should be used limitedly and as an adjunct in dental therapies (10).

Moreover, Scully and Felix (2006) provided six key points with regards to the diagnosis of orofacial pain as seen in Table 3 (41).

Table 3: Six key points to diagnose orofacial pain

Key point	Description
Location	Clinicians should ask patients to take information whether the pain is localized or diffused.
Character	Clinicians should know the character and severity of pain such as sharp, dull, aching, throbbing or shooting by asking and some tools can be used to assess pain severity. Moreover, pain can interfere sleep patterns and it can be useful to evaluate severity.

Duration	Duration may aid to perform exact diagnosis. For example, exposed dentine causes transient pain but pain comes from pulpitis lasts for a long time.
Frequency and periodicity	Clinicians specify the times or the circumstances in which pain occurs. As an illustration, severity of temporomandibular pain may be more than usual on waking.
Precipitating, aggravating and relieving factors	Sometimes, it can be required to ask whether some factors such as temperature, biting, alcohol etc. affect the pain. For example, heat can make pain difficult.
Associated features	In such states, other properties like swollen face in dental abscess may be helpful to diagnose.

Approach to pain is also crucial for children. They react to the pain differently from each other and under 4 years of children are more sensitive to pain and also are not available to dialogue in comparison with older ones and teens. Watching their behaviors and listening to their words are substantial for pain evaluation and facial expressions like crying, complaining and body movements are another important diagnostic criteria. Moreover, pain occurred from previous dental visit may cause fear or behavioral problems (42). In conjunction with pain in children, pain which is occurred after dental treatment applications is also an important factor to affect satisfaction of pediatric patients as well as mouth and dental health of children badly (43).

Unfortunately, many clinicians believe that children do not feel the pain as much as adults so they make nothing of the treatment of postoperative dental pain. For the reasons, clinicians should make a suitable plan to control of pain in children. Primarily, a local anesthetic that have enough action time should be used to start treatment and if pain is expected followed by dental applications, information about postoperative analgesics should be given to parents (43). Thus, communication skills of dental team are very important and they should work together via communication with parents and children to shape future attitudes of children (42).

There are also responsibilities of clinicians other than dental practitioners in pain management. Some patients may visit medical practitioners to show dental problems but it is not frequently observed. The reasons related to the conditions are listed below (44):

- Inadequate time to seek dentist
- Dentists are not always available
- Economical factors of dental treatment
- Fear of pain

- Low level of information regarding the scope of dentistry and responsibilities of dentists
  - Recognizing the pain as not related to dental or oral origin
  - Searching opioids for some dependent patients

General population of medical practitioners do not have much information as dentists but they feel responsible to relive patient pain. Thus, they can prescribe medications to treat patients' pain and other associated factors. In addition, medical practitioners suppose their patients' to visit dentists as soon as possible but if they suffer from severe pain analgesics and other medications rational to patients' health status can be indicated. However it shouldn't be forgotten that some interventions from medical practitioners may interfere dentists' diagnosis and cause a delay of treatment (44).

In brief, pain management is not a easy process as might be expected. The treatment approaches should be based on patients' needs and status (ie, age, gender, pregnancy, polypharmacy etc.) and meet the expectation of patients in pain relief. In terms of health practitioners, they must respect the pain expressions of individuals, handle the underlying causes of pain and use both non-pharmacologic and pharmacological applications.

2.2.2. Pharmacological Treatment of Pain in Dentistry

Dental practice contains an important concern which is called as pain control (33). Sermet et al. (2005) indicated that pain management has been described as one of the

important parts by now for dental pain and also provided that medications commonly used for dental pain consist nonopioid analgesics as paracetamol and NSAIDs (i.e. ibuprofen, naproxen, flurbiprofen) while opioid analgesics such as hydrocodone, oxycodone, meperidine, propoxyphene, pentazocine, tramadol are occasionally used in moderate to severe dental pain (12). Thus, better use of analgesics to solve pain problem exhibits a great importance for both dentists and patients (33).

Analgesics are generally divided into two groups as non-opioids and opioids (45). Instead of opioid and non-opioid terms, narcotic and non-narcotic terms may be used interchangeably. The main difference of two analgesic groups is their mechanism of actions. Non-opioid analgesics including paracetamol and NSAIDs interfere prostaglandin synthesis and they have a limit (ceiling) in their analgesic effects. On the other hand, morphine represents opioid analgesics and they have no limit for analgesic effect. They can be administered until pain sensation is disappeared or limiting side effects occurs (46). In addition to the information, non-opioid analgesics are effective to relieve pain in such conditions but not severe ones. Although they are ineffective to severe conditions, dental pains are mostly controlled by non-opioid analgesics. It is especially significant because non-opioid analgesics are safer than opioid analgesics (33).

In detail, paracetamol is one of the most frequently used drugs in the world. Different from other analgesics, it shows antipyretic and analgesic effects due to the inhibition of prostaglandins in peroxide-rich environments like hypothalamus and spinal cord. Besides, inhibition of COX-3 enzymes in brain plays an important role to exert its analgesic effect. However, paracetamol does not have any anti-inflammatory action because of no effect on COXs (47). Moreover, paracetamol is very safe when it is used within acceptable limits and it is the first drug to consider as an analgesic to treat mild to moderate pain. For instance, because of its appropriate risk/benefit ratio, paracetamol is selected to relive acute postoperative pain for adults and children. It has also advantages in terms of side-effect profile as far as NSAIDs so paracetamol can be used if NSAIDs are contraindicated for patients but sometimes paracetamol and NSAIDs are used together to relieve pain (47,48). Unfortunately, paracetamol may lead to serious

adverse reactions because of over-dosing. It should not be administered more than 4 g in a day for healthy adults. Pain treatment may include 650-750 mg paracetamol for each tablet (47). Besides, in terms of severe pain, paracetamol is not good enough to relief by itself and for that reason its combination with opioid analgesics such as codeine or oxycodone may be considered (48). Furthermore, paracetamol is generally combined with codeine and the combination is frequently used in dentistry (10).

On the other side, NSAIDs have been used to relieve pain after the discovery of the mechanism of acetylsalicylic acid (ASA) 30 years ago. The drug group that includes NSAIDs is effective for all level of dental pain and inflammation (45). In addition, Haas (2002) expressed that clinical studies demonstrated NSAIDs are potent analgesics with regards to all level of dental pain and their mechanism of actions are associated with the inhibition of two enzymes known as COX-1 and COX-2 (48).

COX-1 enzyme is responsible to the synthesis of prostaglandins that protect gastric mucosa and regulates renal blood flow and thromboxanes that initiate thrombocyte aggregation. The effects of medications used to relieve pain is based on the inhibition of COX in connection with prostaglandin synthesis. Prostaglandins affect thrombocyte aggregation, inflammation and the formation of pain and fever (45). In addition, COX-2 is responsible for the synthesis of prostaglandins that induce inflammation. Conventional NSAIDs inhibits the two enzymes but there are also newly developed NSAIDs that are selective to COX-2 (48).

The other group of drugs named as opioid analgesics provide effective analgesia and have potential to cause dependence. They do not exert any antipyretic and anti-inflammatory effects and their analgesic effects are the consequence of the impact on central nervous system (CNS) (47). Opioids show their effects as agonist on kappa and/or mu receptors. Different from non-opioid analgesics, they have no ceiling effect and if the dose of opioid analgesics exert their effects at mu receptors are increased, analgesics effects of opioids will be improved. Even though their unlimited analgesic effects, side-effects related to opioids frequently prevents their usage for complete relief of severe pain (46).

Opioid analgesics can be useful to manage dental pain. They are taken into account when paracetamol and NSAIDs are not sufficient to treat it (48). In addition, opioid analgesics are frequently used in dentistry in combination with ibuprofen, aspirin or paracetamol and the combination of opioid analgesics and non-opioid analgesics can be more effective than the use of non-opioids alone (47,49). The situation is only available when appropriate dosage combinations are used. In addition, their use is limited because of adverse effect profiles in the treatment of moderate to severe pain. Because of the dose limiting, dental clinicians approach to the use of drug combinations. Thus, codeine is especially emphasized for oral combinations (47).

For the subject of their use, Alpaslan (2014) demonstrated some of analgesics as following Table 4 (50).

Table 4: Information of some analgesics about their use

Group of Analgesic	Name of the active ingredient	How it should be used?
Opioid Analgesics	Fentanyl	Before surgical processes, 0.05 mg – 1 mg
	Codeine phosphate	15 – 60 mg, orally, 4 times a day
	Morphine sulphate	Do not produce powerful analgesia when used orally Used twice a day based on the severity of pain
	Tramadol Hydrochloride	Orally, 50 – 100 mg, every 4 – 6 hours
NSAIDs	ASA	Conventional adult dose is 650 mg Orally, 325 – 1000 mg every 4 – 6 hours
	Metamizole	Single dose administration equals to 400 mg ibuprofen
	Diclofenac sodium	Orally, 50 mg, two or three times a day Do not exceed 150 mg (maximum dose)
	Diflunisal	Orally, 250 – 500 mg, every 8 – 12 hours
	Etodolac	Orally, 200 – 400 mg, three times a day Do not exceed 1200 mg

NSAIDs		
	Flurbiprofen	Orally, 50 – 100 mg, two – three times a day Do not exceed 300 mg (maximum dose)
	Ibuprofen	Orally, 400 – 800 mg, three-four times a day Do not exceed 3200 mg (maximum dose)
	Indomethacin	Orally, 150 – 200 mg, two-three times a day
	Ketoprofen	Orally, 25 – 50 mg, every 4-6 hours Do not exceed 300 mg (maximum dose)
	Lornoxicam	Orally, 8 mg, once or twice a day Do not exceed 16 mg (maximum dose)
	Meloxicam	Daily dose is 7.5 mg Maximum dose is 15 mg
	Naproxen sodium	Orally, 250 – 500 mg, twice a day
	Piroxicam	Orally, 20 mg, four times a day
	Celecoxib	Do not use instead of conventional analgesics in postoperative pain. May be choosen for chronic pain
Other Analgesics	Paracetamol	Orally, 325 – 1000 mg every 4 – 6 hours For children, 3 – 4 x 125 – 500 mg (6-12) For children, 3 – 4 x 125 mg (0-6)

As a consequence, non-opioid analgesics and opioid analgesics are used to relieve dental pain. Based on their efficacy, safety and other conditions, NSAIDs may be seen as a major group for the treatment. Furthermore, paracetamol and opioid analgesics can be considered as useful in such conditions related to dental pain especially combination technique to provide more analgesia or better treatment with less adverse reactions. However it should be note that patients as well as clinicians may encounter drug-related problems especially adverse drugs reactions. Thus, dental clinicians should taken into account the pharmacological properties and mechanism of actions of drugs and design an effective therapy to overcome it.

2.3. Rational Use of Analgesics

Attainability of medicines has increased all over the world so the position have caused irrational and misuse significantly. People use medicines by themselves, frequently without consulting their doctors. Based on the information, tendency for self-medication is increasing. In addition, drugs have useful effects as well as their negatives. In another word, drugs can be very efficient or beneficial tool for human being if used by accurate hands and if not it may be a dangerous one. Thus, drugs should be used suitable manner like its dose, route of administration, choice of drug, etc. so patients take intended effect but any changes on standards related to drugs can create lots of problems. Moreover, drugs used by patient may show physical, toxicological, chemical and physiological effects that brings acute or chronic trouble. One of Food and Drug Administration (FDA) Reports suggest the importance of drug causes death or related problems as following Table 5 (51).

Table 5: FDA statistics regarding drug related cause and death

US FDA reports that 12000 deaths and 15000 cases of hospitalization in US are due ADRs in 1987.
Nearly 98000 Americans die each year due to medical mistakes, out of which 7000 cases are due prescription errors
In US hospitals, medication errors cover nearly 25%-50% of all ADRs.
Drug related morbidity reduces quality of life and results in loss of work and loss of money
Drug related morbidity cost as much as 7 billion (Bn) US dollars

Based on statistics seen in Table 5, drugs may cause serious problems including material and moral things so long as they are used as inappropriate behaviors medically.

WHO explained RUD at the Nairobi Conference in 1985 as “where patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for and adequate period of time, and at the lowest cost to patients and their community. In the simplest term, RUD means right drug, accurate dose for the adequate duration and suitable to clinical needs of the patients at lowest cost (51,52). In

line with the information, Alpaslan (2014) provided following points with regards to RUD (50):

- Drugs whose efficacy and safety have been proved in terms of clinical and epidemiological studies should be chosen when physician write a prescription.
- New drugs are only prescribed when their benefits surpass over the drugs that are already available into the market.
- Cost-benefit relationship of drugs has to be evaluated. If drugs have close properties about it, drugs that have safe pharmacokinetic particulars and are produced by local and confidential manufacturer have to be prioritized.
- When current treatment options are not adequate in such cases, rational decision should be made based on comprehensive and objective data. Writing prescription do not be perceived like taking description from cook book and do not be endured on commercial concerns.

On the other hand, irrational drug use is significant problem in the world. According to WHO, more than half of all drugs are inappropriately prescribed, dispensed or sold and half of all patients do not reach suitable drugs. Irrational use of medicines cause loss of resources and many health problems. Excessive drug consumption per patient (poly-pharmacy), inconvenient self-medication, fail to comply dosing regimens, choice of much injectable administration instead of available oral formulation can be represented as irrational use of medicines (53).

In Turkey, ineffective, wrong and unnecessary drug use have increased and the state is need to control with strict approaches. Based on the statement which is existed on the official website of Ministry of Health, more than half of prescription with related to cost and unit have been found as irrational. As a result, one of two drugs have been prescribed unnecessarily or wrongly. In irrational drug use, antibiotics take the lead because they are best selling drugs (19%) in Turkey following by analgesics (12%) and rheumatic drugs (11%) respectively (54).

As an example of irrational drug use in Turkey, Yapici et al. (2011) conducted a survey-based study to indicate attitude and behavior of drug usage. Based on the results of the study, participants use drugs without consulting any medical doctors (26%) followed by using drugs with the advice immediate surroundings (17%). Moreover, 33% of participants take medications from pharmacies without any prescription and 37% of all participants hold their unused drugs at home in which analgesic medications come first (16). In addition, Akici et al. (2001) performed another study to investigate evaluation of rational drug use of general practitioners' in the management of elderly patients. Based on the interviews with patients, 75% of patients were not examined and it wasn't think as necessary to write prescription, general practitioners didn't tell anything about the diagnosis of 63% of patients, 77% of patients were not informed with regards to drug information (instructions of drug use) and general practitioners didn't mention about non-drug treatment to 91% of patients. Furthermore, the most commonly prescribed drug was anti-hypertensives (28%) followed by analgesics/anti-inflammatory drugs (17%) in the study (55).

On the basis of the information mentioned before, rational analgesic use has not been into a satisfactory level in Turkey. In this regards, clinicians as well was patients should pay attention to the subject. Clinicians should improve themselves about any subjects related to RUD and serve as a source to conduct their information into patients apprehensibly. In addition, patients take notice of the warnings from clinicians and do not change anything (drug product, dose, duration etc.) about the treatment and do not use a drug without any consultation.

On the other side, according to National Survey on Drug Use and Health in US presented that 6.4 Mn people who are at 12 or older used prescribed psychotherapeutic drugs for non-intentional reasons during previous month in 2005. 4.7 Mn of the population used analgesics followed by tranquilizers and stimulants. Non-therapeutical use of prescription drugs in the last month among young adults from 2002 to 2005 increased too much and the increment was principally related to pain reliever usage growingly within the years (56). Furthermore, during the past ten years, nonmedical use of prescription medications has remained significantly. In 2010, 2 Mn Americans

started nontherapeutic prescription analgesic use in the last 12 months, and 5.1 Mn of the population used prescription analgesic medication non-therapeutically in the last month. Nontherapeutic use of opioid analgesics caused in an approximate 425,00 emergency department visits in 2010, an increment of 156% from 2004. The morbidity and mortality rate related to nonmedical use of opioids are also rising. In 2010, because of overdoses in prescription opioid analgesics lead to many deaths more than 16,500 which is 4-fold increase than statistics available in 1999 (57).

The main idea of WHO documents, there are 5 recommendations for the rational use of analgesics to make treatment appropriate and effective. Five recommendations and also WHO analgesic ladder are presented as followings (58).

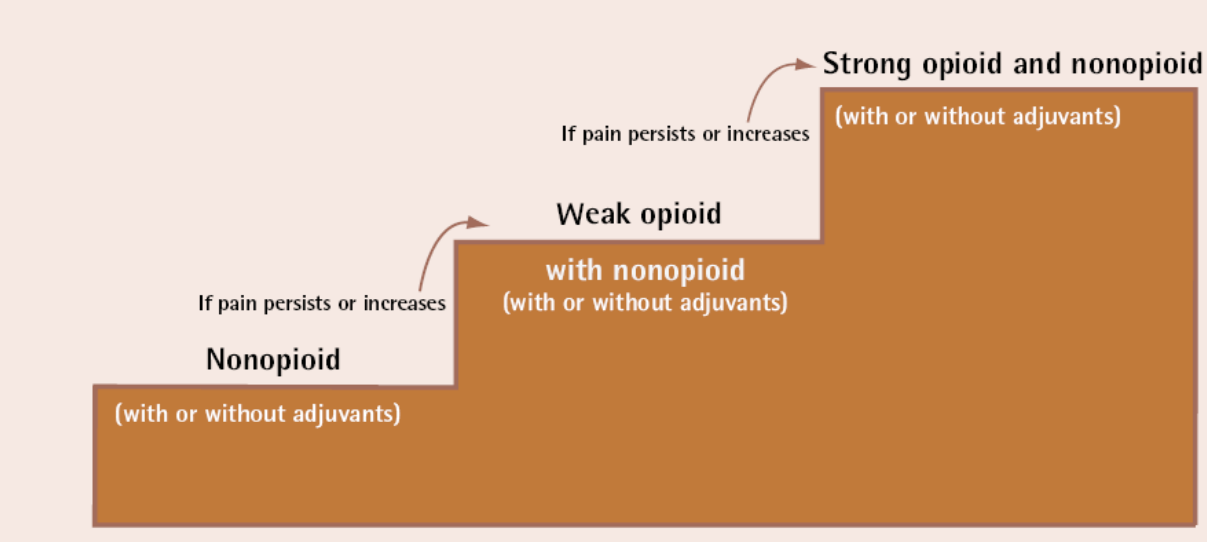

Figure 1: WHO analgesic ladder

1. Oral administration of analgesics:

Oral form of analgesics should be used as far as possible.

2. Analgesics should be given at regular intervals.

To solve pain problem of patient, medications should be taken into previously identified durations based on the pain level of patient. The dosage of medication should be fitted according to patient status.

3. Analgesics should be prescribed according to pain intensity as evaluated by a scale of intensity of pain.

It is very crucial point of treatment so prescription of analgesic medication should be performed after the evaluation of pain and clinical examination. Prescription should be based on patients' pain grade and not physician or any other medical staff's point of view about it. Moreover, patient story with regards to pain must be believed.

4. Dosing of pain should be adapted to the individual.

For treatment of pain, there is not any standardized dose. Every patient suffer from pain will show different response against treatment. The correct dose means any dose that provide enough pain relief. Thus, posology of medication should be arranged according to indication and side effects.

5. Analgesics should be prescribed with a constant concern for detail.

Organization of treatment is substantial for treatment of pain. Personal program can be useful to provide ideal treatment so that patients and people around patients will have adequate information about treatment intervals and administration method.

2.4. ADR and Drug Interaction

2.4.1. What is an ADR?

In 1964, one of famous justice, Potter Stewart indicated obscenity as "I know it when I see it". In contrast with the opinion, identification and understanding of ADRs are troublesome. It is an unhandled exception because many drugs have been developed and used over the years and lots of drug-related problems have occurred frequently. In addition, WHO described an ADR as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. Hence, ADRs are evaluated as undesirable events with regards to drug's administration, irrelevant to etiology (59).

2.4.2. What is Drug Interaction?

Drug interactions can be explained into 2 ways as pharmacokinetic, body's process over a particular drug, and pharmacodynamic, therapeutic effect and adverse effects of administrated drug. Any drug may decrease the excretion of another and effect its action. In addition, interactions can provide some advantages but can also raise possibility of

ADR. Other factors like as food, beverages, current substances in the body might also influence potency of medicine (60).

2.4.3. Classification of ADRs

The most wide-spread classification of ADRs consists two sections. One of classifications is dose-related ADRs also known as type A and the another one is non-dose related ADRs known as type B. Moreover, other groups exist as subclasses of type A and type B ADRs which are represented as. type C, type D, type E and type F ADRs. The classification of ADRs with characteristics and examples are tabulated in Table 6 (61).

Table 6: Classification of ADRs

Type of ADR	Characteristics	Examples
Type A (augmented)	Dose related Common Suggestive time relationship Related to pharmacological action of the drug Predictable Variable severity, but usually mild High morbidity Low mortality Reproducible	Nephrotoxicity caused by aminoglycosides Dysrhythmia caused by digoxin Constipation caused by chronic opioid use Anticholinergic effects of tricyclic antidepressants (TCAs)
Type B (bizarre)	Not dose-related Uncommon Not related to pharmacological action Not predictable Variable severity, proportionately more severe than type A	Tinnitus caused by small doses of aspirin Penicillin induced urticaria Respiratory syndrome caused by NSAIDs Anticonvulsant hypersensitivity syndrome reaction

	High morbidity High mortality Not reproducible	
Type C (chronic)	Uncommon Related to cumulative dose Long term exposure required	Hypothalamic-pituitary adrenal axis suppression by corticosteroids
Type D (delayed)	Uncommon Usually dose-related Seen on prolonged exposure to a drug or exposure at a critical time	Teratogenesis Carcinogenesis Tardive dyskinesia caused by antipsychotic medication
Type E (end of use)	Uncommon Occurs soon after withdrawal of a drug	Opiate withdrawal syndrome Rebound hypotension on clonidine withdrawal
Type F (failure of therapy)	Common May be dose related Often caused by drug interactions	In effectiveness Tolerance Tachyphylaxia

2.4.4. Epidemiology of ADRs in Clinical Practice

Many epidemiological studies have been performed to show frequency of ADRs with healthcare costs in clinical practices. Drug-related admission to hospital, extension of hospital stay and emergency visits to the department are some of the consequences (62).

In France, estimated data proposed that reach up to 123,000 patients in a year visit to their clinicians with an ADR (63). Moreover, hospital admissions caused by drug-related problems are often (62). When looking at US and Canada, Australia and Europe, ADRs are the cause of hospital admissions with the percentage of 4.2 – 30, 5.7 – 18.8, 2.5 – 10.6, respectively (64). According to studies that have been performed on special populations such as pediatric and geriatric patients, 2.1 – 5.2% of ADRs in children cause hospitalization and seen ADRs up to 39% can be fatal in pediatric patients (65). As a consequence of one of national study in US, older patients applied to emergency

department for drug-related causes with 11.4 – 35.5 percentage distribution (66). Analogically, performed studies in Europe demonstrated that ADRs are experienced by up to 20% of ambulatory patients and nearly 10 – 20% of geriatric hospital admissions are found as drug-related (67,68). ADRs have many consequences and one of consequences is extension of hospital stay (69). With regards to it, a prospective study demonstrated that mean hospital stay of patients without ADR is 8 days and the duration increases to 20 days for patients with ADRs (70). Thus, drug-related adverse reactions can be considered as frequent in societies and their consequences not only cover health-problems but also economical issues.

2.4.5. Economic Burden of ADRs including Analgesic Group

Medicines cause morbidity and mortality and the economic burden lead by medicines have been presumed at $US30 Bn dollars per year and the amount could exceed $US130 Bn under worst-case scenario (71). Major agents that cause ADRs related costs are NSAIDs, anti-bacterial, anti-coagulant and anti-neoplastic. Financial burden arises from both prolonged duration of hospital stay and out-patient care as a result of ADRs. In hospital, wages, disposable goods and medications are the main cost of ADRs. Moreover, there are also in-direct costs of ADRs such as missing work day and/or occurrence of morbidity such as anxiety (62).

Many studies have been performed comprehensively to show pharmacoeconomic effect of ADRs related with non-steroidal anti-inflammatory drugs. Based on a review, NSAIDs reported with highest costs among non-opioid analgesics in line with toxicity. In addition, economical burden of chronic renal failure and acute exposure related to paracetamol was $US51.1 Mn. Another non-opioid analgesic, aspirin, causes gastrointestinal injury and acute exposure cost was calculated as $US458.6 Mn. Moreover, NSAIDs lead to ADRs such as acute and chronic renal failure and gastrointestinal injury and their acute exposure costs were $US1.35 Bn. Gastrointestinal injury caused by NSAIDs is the most frequent and expensive ADR and the most serious ADRs are hemorrhage or perforation of the esophagus, small bowel and colon. It has been propounded that for every spending each US dollar through NSAID treatment, $US0.35 is scarified to handle adverse reactions related to therapy (71). As a

consequence, ADRs are not only the main drug-related problem for treatments but also there are economical problems associated with ADRs. Clinicians have to be aware of economical burden of ADRs and take required measures to minimize the reactions.

2.5. ADRs of Analgesics

Clinicians need to recognize the probability of adverse reactions of analgesics to evaluate risk:benefit ratio. By the way of pharmaceutical companies or reference documents, list of adverse reactions can be achieved. However, interval details of the reactions are not applicable typically (13). Moreover, non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs have been used conservatively to treat mild to moderate cancer or non-cancer related pain. In addition, several safety concerns are caused by the medications that lead to inadequate pain relief (72).

On the other hand, common use and raised accessibility of over the counter (OTC) analgesics mirror that the drugs are safe for general population. However, it is significant to follow safety aspects with regards to direct ADR or interactions with other drugs, especially in patients at higher risks. For example, paracetamol can be utilized as a first choice for acute mild to moderate pain conditions based on its safety, efficacy and low cost but few adverse reactions or interactions with other drugs can be associated with paracetamol when used therapeutical doses (73).

2.5.1. ADRs of Paracetamol

Paracetamol is a non-opioid pain reliever that has narrow therapeutic index with suitable efficacy, tolerability, commonly usage and low cost. However, it may cause hepatotoxicity (13). Paracetamol is metabolized into its toxic metabolite which is called as N-acetyl-p-benzoquinonimine (NAPQI). NAPQI binds to glutathione and causing its depletion. As a result, hepatocytes produce danger signals then immune response is started causing inflammation and collateral tissue damage to the liver (72).

On the other hand, according to evidence related to high population level that can accidentally take toxic dose paracetamol leading to liver damage and FDA required warning labels on paracetamol products. In another study, FDA demonstrated that over

56,000 emergency room visit in a year was caused by paracetamol overdose and quarter of overdoses was unintentional. Besides, OTC-paracetamol products have label to warn drinkers (more than three drink) against paracetamol – alcohol combination which may harm the liver (74).

FDA described the risk factors of unintentional paracetamol overdose in adults and children are seen in Table 7 (73).

Table 7: Risk factors of unintentional paracetamol dose

Adults	- Failure by consumers to recognize the ingredients contained in OTC drug products and/or the potential for harm due to exceeding the recommended dose - The wide variety and availability of both OTC and prescription drug products that contain paracetamol (e.g., single ingredient, combinations, and multiple formulations) - The lack of consumer awareness for the potential to develop serious adverse events from taking 2 or more different products containing paracetamol concomitantly - The failure of prescription container labels to list paracetamol as an ingredient
Children	- Administering the wrong pediatric paracetamol formulation [i.e., subtituting the concentrated infant drops (80 mg/0.8 ml) for the less concentrated children's suspension (160 mg/5 mL) - Administering the adult instead of the age-appropriate children's formulation - Incorrectly calculating the weight-appropriate dose of paracetamol - Using the wrong dosing device (e.g., tablespoon instead of teaspoon, dropper versus syringe)

Besides to above information, prothrombin time of patients taking anticoagulants, paracetamol can cause prolongation of it. From time to time, it may cause urticarial or erythematous skin rash, fever or blood dyscrasias (10). In addition, with the help of

current data, paracetamol has suitable gastrointestinal tolerability. Randomized-controlled studies showed that frequency of gastrointestinal effects (i.e. abdominal pain, gastrointestinal distress, nausea, vomiting or dyspepsia) was found similar to placebo. Likewise, a meta-analysis from case-control studies verified that paracetamol was not related to increased risk of upper gastrointestinal bleeding at any dose (72).

Under the title of ADRs of paracetamol, following information (contraindications, list of ADRs, information about clinical situations need special attention) were prepared with taking information from Rx Media Pharma 2014 (75).

Terms with bold & larger letters indicate the situations in which the drug certainly must not be used.

Table 8: Contraindications of paracetamol

- Alcoholism
- Anemia
- **Hypersensitivity against paracetamol**
- Asthma
- Babies
- Children
- Infection
- Phenylketonurea
- Pregnancy
- Deficiency of glucose-6-phosphate dehydrogenase
- Hepatic disease
- Hepatitis
- Hypovolemia
- Immunosupression
- Bone-marrow depression
- Malnutrition
- Neutropenia
- Renal disease*
- Hypersensitivity against salicylates
- Lactation
- Smoking
- Neonates

*Renal disease is defined as a status of any illness related to kidneys regardless of its effects on renal function.

Table 9 shows the ADRs of paracetamol according to system organ classification.

Table 9: ADRs of paracetamol

Immune system disorders
• Anaphylactic shock • Anaphylactoid reactions
Renal and urinary disorders
• Interstitial nephritis • Oliguria • Renal papillary necrosis • Renal tubular necrosis • Renal insufficiency (unidentified)
Skin and subcutaneous tissue disorders
• Acute generalized exanthematous pustulosis • Angioedema • Skin rash (unidentified) • Skin itching • exploitative dermatitis • erythema • Contact dermatitis • Maculopapular rash • Purpura • Toxic epidermal necrosis
Electrolyte disorders
• Hypokalemia • Hypomagnesaemia
Gastrointestinal disorders
• Abdominal pain • Nausea and Vomiting • Diarrhea • Constipation • Trismus
General disorders and administration site conditions
• Fever • Peripheral edema • Fatigue
Hepato-biliary disorders
• Hepatic encephalopathy • Increased hepatic enzyme levels • Hepatic necrosis • Hepatic insufficiency • Jaundice
Blood and Lymphatic system disorders
• Agranulocytosis

• Anemia • Hemolytic anemia • Hemolysis • Hypoalbuminemia • Hypoprothrombinemia • Methemoglobinemia • Neutropenia • Pancytopenia • Thrombocytopenia • Thrombocytosis
Cardiac disorders
• Myocarditis • Sinus tachycardia
Musculoskeletal and connective tissue disorders
• Myalgia skeletal pain • Muscle cramps
Metabolism and nutrition disorders
• Myalgia skeletal pain • Muscle cramps
Psychiatric disorders
• Agitation • Anxiety • Sleeplessness
Nervous system disorders
• Headache • Encephalopathy
Respiratory, thoracic and mediastinal disorders
• Dyspnea • Hypoxia • Wheezing • Pleural effusion • Pulmonary edema
Vascular disorders
• Hypertension • Hypervolemia • Hypotension

Furthermore, there are some situations need special attention regarding to paracetamol use as below:

Table 10: Clinical situations need special attention for paracetamol

Lactation	CAN BE USED IN LACTATION PEROID **Paracetamol** is slightly excreted into milk. On the level, medication do not damage to babies.

Pregnancy	**All Pregnancy Period B (**paracetamol), C (paracetamol) **B:** Animal studies and well-controlled cross-sectional studies in pregnant women, have failed to demonstrate a risk. C: Potentially risky medicine, preferred based on benefit/risk ratio
Hepatic Impairment	**SHOULD BE AVOIDED TO USE** Paracetamol should be used carefully in patients with hepatic impairment or overdose history of the medicine. Paracetamol must not to be used for patients suffer from alcoholisim in the past. Patients that have stabil hepatic disease can use paracetamol for a transient (< 5 days) episodic pain at a therapeutic dose. Toxicity is proportional with dose. High dose administration must no to be used.
Renal Impairment	**DOSE HAVE TO BE DECREASED** **Paracetamol** is the required choice for treatment of transient (episodic) pain under renal impairment condition. Despite, chronic use should be avoided. Dose should be arranged according to clinical response and level of renal impairment but applicable dose recommendations are not available in such cases.

In brief, hepatotoxicity of paracetamol comes to the forefront. However, clinicians should take into considerations not only hepatotoxicity risk of paracetamol but also other adverse reactions including the occurrence of the reactions resulting from drug interactions. Furthermore, they should calculate risk:benefit ratio of paracetamol treatment based on patient individuals as well as all medications although paracetamol is considered as a safe medication all over the world.

2.5.2. ADRs of Non-steroidal Anti-Inflammatory Drugs

NSAIDs are one of the most commonly used medications in the world because of their effectiveness to treat pain and inflammation. Their treatment fields are included osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout, dysmenorrhea, dental pain and headache. Their mechanism of action is based on the inhibition of the pro-inflammatory enzyme, COX. NSAIDs can be classified as traditional NSAIDs (tNSAIDs) that inhibit both COX-1 and COX-2 and selective COX-2 inhibitors. Although, tNSAIDs provide effective pain and inflammation relief, they can cause serious gastrointestinal adverse reactions with chronic use that is why COX-2 selective NSAIDs were developed. However, significant apprehensions have been raised with related to cardiovascular toxicity of selective COX-2 inhibitors (76).

2.5.2.1. Gastrointestinal Adverse Reactions of NSAIDs

Gastrointestinal adverse effects are frequent for patients using NSAIDs and approximately at least serious 103000 gastrointestinal-related hospitalization and 16500 deaths per year have been reported in the US alone in 1997 (77). They included heartburn, nausea, vomiting, abdominal pain or dyspepsia as upper-gastrointestinal symptoms. As a result of the reactions, 5-15 % of patients unfortunately have to stop NSAIDs therapy. Moreover, there are many studies to show a relevant relationship between the use of NSAIDs and gastrointestinal mucosal injury and associated complications. Gastric erosion is developed nearly half of patients receiving NSAIDs and also peptic ulcer have been observed for long-term NSAID users in the proportion of 10-30%. Besides, increased risk of lower gastrointestinal reactions such as bleeding, perforation, obstruction, ulceration and symptomatic diverticular disease have been demonstrated associated with NSAIDs (78).

2.5.2.2. Cardiac Adverse Reactions of NSAIDs

There is an increased risk for hypertension, stroke, myocardial infarction and death related to both non-selective and selective-NSAIDs use. Lots of studies have been shown that risk of cardiovascular thrombotic complications with regards to higher dose and chronic use of NSAIDs increase up to fivefold. Guidances suppose that patients suffer from active ischemic heart disease, cerebrovascular disease and moderato-to-severe heart failure should avoid NSAIDs. There is a 1.7 fold increased risk for hypertension among people over 75. Hypertensive patients should be carefully monitored while taking NSAIDs (79).

NSAIDs related other adverse reactions are demonstrated in Table 11 (80).

Table 11: Other adverse reactions of NSAIDs

Hepatic ADRs	Increased hepatic enzyme levels Risk of hepatotoxicity (prolonged treatment, cirrhosis, active chronic hepatitis, congestive heart failure, impaired renal function)

	Toxic hepatitis, cholestatic jaundice, hepatic insufficiency
Renal ADRs	Decreased renal blood flow Decreased glomerular filtration rate (acute renal failure, papillary necrosis and nephrotoxicity) Decreased excretion of water & salt(retention) Persistent renal impairment, analgesic nephropathy and papillary necrosis (especially patient in risk groups)
Hematological ADRs	Slow hemostasis Prolonged bleeding Aplastic anemia Thrombocytopenia Agranulocytosis Blood dyscrasia
Pulmonary and Allergic ADRs	Bronchospasm (especially hypersensitivity against ASA) Angioedema Urticaria Asthma attack
Dermatological ADRs	Eruptions Exfoliative dermatitis Photosensitivity
CNS-related ADRs	Headache Dizziness Confusion Tinnitus Hallucination Depression Drowsiness
Joint-cartilage related ADRs	Impaired Glycosaminoglycan Increased loss of proteoglycan

In addition, based on FDA Medication Guidelines, NSAIDs-related adverse reactions and other medically important directions are expressed in Table 12 (81).

Table 12: Adverse reactions and important medical conditions related to NSAIDs

Serious adverse reactions	**Other adverse reactions**
Heart attack Stroke Heart failure from body swelling (fluid retention) Kidney problems including kidney failure Bleeding and ulcers in the stomach and intestines Low red blood cells (anemia) Life-threatening skin reactions Life-threatening allergic reactions Liver problems including liver failure Asthma attacks in people who have asthma	Stomach pain Constipation Diarrhea Gas Heartburn Nausea Vomiting Dizziness
Get emergency help right away if recognize following symptoms Shortness of breath or trouble breathing Chest pain Weakness in one part or side of body Slurred speech Swelling of the face or throat	**Stop taking NSAIDs if followings are observed** Nausea More tired or weaker than usual İtching Yellow skin or eyes Stomach pain Flu-like symptoms Vomit blood Blood in bowel movement or black and sticky tar Unusual weight gain Skin rash or blisters with fever Swelling of the arms and legs, hands and feet

Moreover, another FDA publication, following directions are explained in the way of question-answer style if patients take prescription or OTC NSAIDs (82).

Table 13: Questions and answers for patients taking OTC/prescribed NSAIDs

Questions	Answers
What are the risks of taking NSAIDs?	Like all drugs, there is the potential for an allergic reaction to NSAIDs. Symptoms may include hives, facial swelling, wheezing and skin rash. There is the potential for gastrointestinal bleeding associated with all NSAIDs. The risk of bleeding is low for people who use NSAIDs intermittently. The risk of stomach problems goes up for people who take NSAIDs every day or regularly, especially for people who are over 65, people with a histroy of stomach ulcers, and people who take blood thinners or corticosteroids (prednisone). Alcohol use can also increase the risk of stomach problems. Long-term continuous use of all NSAIDs, except for aspirin, may increase the risk of heart attach or stroke. Aspirin is a non-selective NSAID, but it has been shown in clinical trials to reduce the risks of cardiovascular events. All NSAIDs also carry the risk of potential skin reactions. Patients should be altered for symptoms such as the skin reddening, rash or blisters.
Which people are at the highest risk for cardiovascular adverse events associated with NSAIDs?	People who have coronary artery disease (known angina or who have had a heart attack), people who have high blood pressure, and people who have had a stroke are at the greatest risk. Also, people who have just had cardiovascular bypass surgery are at risk for heart attacks with use of NSAIDs.
Which COX-2 selective inhibitors have been taken off the market?	A company voluntarily withdrew a product contains rofecoxib in 2004 after finding out the results of a study that showed patients who took the product had a higher risk for heart attacks than patients who took a placebo.

Which COX-2 selective inhibitors have been taken off the market?	FDA asked a company to withdraw a product contains valdecoxib from the market in 2005 because the overall risk/benefit profile was unfavorable. An increased risk of cardiovascular adverse events has been shown for all COX-2 inhibitors, including products contain celecoxib which are still on the market in the United States. Based on available data, FDA determined that the benefit of the products outweigh the potential risks in properly selected and informed patients. FDA asked the company to include a boxed warning on the products contain celecoxib. The boxed warning highlights the potential for increased risk of cardiovascular events as well as serious, potential life-threating gastrointestinal bleeding.
What can consumers do to lower their risks with NSAIDs?	Tell your doctor about your complete medical history, including any history of cardiovascular disease or stomach ulcer. You can also ask your doctor what you can do to lesson the chance for stomach irritation such as taking medication with meal. Available scientific data don't suggest an increased risk of serious cardiovascular events for short-term, low-dose use of OTC NSAIDs. However be aware that the OTC labelling states that if you take an NSAID for longer than 10 days, you should see your doctor. The lowest effective dose should be used for the shortest time.

2.5.2.3. Drug interactions of NSAIDs

Drug interactions of non-steroidal anti-inflammatory drugs mostly include gastrointestinal and antiplatelet effects. One of drug interactions is related to ASA. Low-dose ASA is cardioprotective but evidence regards to concomitant use of ASA and such NSAIDs (particularly ibuprofen) suggests that usage can reduce cardioprotective particular of ASA and increase gastrointestinal risk. Besides, concomitant use of COX-2

inhibitors which provide gastroprotective effect and ASA which is used for cardiovascular prophylaxis result in partially or totally lost of benefits of COX-2 inhibitors. Gastrointestinal risk may be increased with combination of NSAIDs and warfarin or corticosteroids. Other possible interactions with NSAIDs are followings (13).

Table 14: Drug interactions of NSAIDs

Drugs	Results of interaction
Angiotensin Converting Enzyme Inhibitors	Decreased effects of angiotensin-converting enzyme inhibitors. Increased Risk of renal impairment and hyperkalemia
Anticoagulants	Increased warfarin levels (related to competition for protein binding)
Anti-diabetics	Increased effect of oral sulfonylureas
Corticosteroids	Increased risk of peptic ulceration (with bleeding and perforation)
Diuretics	Increased nephrotoxicity Decreased diuretic effects Increased serum potassium level
Methotrexate	Increased methotrexate level

In addition to related interactions, alcohol (ethanol) interacts with NSAIDs and leads to increased risk of fecal blood loss associated with gastrointestinal erosions and ulcers. Medicinal products contain NSAIDs have warning on their labels related to enhanced gastrointestinal toxicity with alcohol if 3 or more drinks are consumed per day. Another interaction have been shown between Selective Serotonin Reuptake Inhibitors (SSRIs) and NSAIDs. When the drug groups are taken concomitantly, upper gastrointestinal bleeding increases significantly (83).

When considering all data about ADRs of NSAIDs, cardiovascular and gastrointestinal adverse reactions are the most significant problems. Clinicians should follow all updated safety guidelines and provide suitable applications to their patients.

Moreover, they should evaluate patients' current medical status and decide to which NSAIDs have to be prescribed or used as an OTC medication by themselves.

2.5.3. ADRs of Opioids

Opioid analgesics have been used for many years because of their analgesic potential and they are thought as most frequently used pharmacological agents for moderate to severe pain. The medications are safe when they are used properly and under the supervision of physicians but it is necessary to understand benefits and risks relationship when they are prescribed (84).

Many organization like American Pain Society and the American Academy of Pain Management prepared many materials for clinicians. Beside the organizations, the European Association of Palliative Care Research Network has constituted recommendations for treating opioid-induced adverse effects (85).

If patient takes opioid for the first time, sedation, dizziness, nausea and vomiting are reported adverse reactions frequently. However, in the upcoming days, the effects ceases and do not further impair with opioid use. Another adverse effect, respiratory depression, may be problematic at the beginning especially patients are given large dose without any assessment but for regular and prolonged opioid administration, respiratory depression is usually not a problem. Cognitive impairment has a potential problem at the beginning but like as respiratory depression, patients taking regular opioid treatment do not encounter the problem. Typical opioid adverse effect, constipation does not disappear and persist throughout the treatment. It may cause serious medical problems (86).

Many studies have been performed to assess opioid adverse reactions. According to one of systematic review, 22% of patients suffer from chronic non-cancer pain stop opioid treatment because of adverse reactions. Another meta-analysis provided that adverse reactions were more frequent in patients taking opioids than others taking placebo and reactions included constipation, nausea, dizziness or vertigo, somnolence or drowsiness, vomiting, dry skin and itching or pruritus. Sedation and dry mouth were the

most common concerns of patient taking opioids based on an another survey. Confusion, urinary retention, myoclonus, dysphoria, euphoria, sleep disturbance, sexual dysfunction, respiratory depression, physiological dependence, tolerance and inappropriate secretion of vasopressin can be included as additional adverse reactions (87).

Based on IASP, major opioid-induced adverse reactions and their treatments options are included into the below (88).

Table 15: Adverse reactions and their treatments in opioid use

Side Effect	Treatment
Nausea and vomiting	Anti-emetics, metoclopramide, anti-cholinergics, opioid rotation
Pruritus	Antihistamines, opioid antagonists, propofol or serotonin antagonists, non-pharmacological treatments
Sedation	Discontinuation of other sedation medications; opioid rotation, psychostimulants, donepezil
Myoclonus	Opioid rotation, benzodiazepines, skeletal muscle relaxants
Delirium	Opioid rotation, haloperidol, benzodiazepines, anticholinesterase
Respiratory Depression	Naloxone (emergency cases only)
Constipation	Prophylactic treatment with a stool softener and bowel stimulant, non-absorbable laxative (lactulose, polyethylene glycol), metoclopramide, opioid antagonists
Long-term side effects	Abnormal pain sensitivity: reduce opioid dose? Hypogonadism: testosterone or estrogen replacement

Besides all information regarding adverse reaction of opioid therapy, British Pain Society (BPS) explained that 80% of patient taking opioids will encounter at least one adverse reactions and common adverse reactions are listed according to BPS as below (89).

- Constipation
- Nausea
- Somnolence
- Itching
- Dizziness
- Vomiting

2.5.3.1. Drug Interactions of Opioid Analgesics

Induction and inhibition of CYP 450 system leads to many interactions. Opioids' elimination mainly depends on hepatic metabolism that's why drug interactions consist the mechanism is very important. Antibiotics are frequently used with opioids for patients undergoing surgical process. On be half of antibiotics, erythromycin and rifampicin interactions have already been well-documented. Opioids' effect is increased with erythromycin but decreased with rifampicin. When H_2-receptor antagonists are analyzed, cimetidine can increase the effects of opioids via the mechanism that increases their duration of action but interactions related with ranitidin have not been well-documented. Other drugs like carbamazepine, phenytoin and the barbiturates may enhance the hepatic metabolism of opioids (90).

Based on TİK-6, interactions of opioid analgesics are presented in Table 16 (49).

Table 16: Drug interactions of opioids

Interactions with	Results
Alcohol	Increased hypotensive and sedative effects
Anesthetics	Inhibition of etomidate metabolism (fentanyl) Increased effects of iv general anesthetics and volalite liquid general anesthetics (Opioid analgesics)
Anxiolytics and Hypnotics	Increased sedative effects İnhibited metabolism of midazolam (fentanyl)
	Increased plasma concentration of alfentanil (Erythromycin)

Antibacterials	Decreased plasma concentration of ciprofloxacin (Opioid analgesics) Accelerated metabolism of alfentanil, codein, methadone,fentanyl and morphine (Rifampicin) Inhibition of oxycodone methabolism (telithromycin)
Antidepressant	Increased plasma concentration of methadone (Fluoxetine, fluvoxamine, paroxetine, sertraline) Increased seratonergic effect (Pethidin/Tramadol+Duloxetine) Increased seratonergic effect (Tramadol+Mirtazapine/Venlafaxine) CNS excitation or depression (Opioid + Monoamine oxidase inhibitors) CNS excitation or depression (Moclobemide+dextromethorphan/pethidin/fentanyl/morphine/other opioid analgesics Increased CNS toxic effects (Tramadol+ SSRI/TCAs)
Antiepileptics	Decreased plasma concentration of methadone (Carbamazepine) Increased effect of carbamazepine (Dextroprophoxyphene) Decreased effect of tramadol (Carbamazepine) Increased bioavailability of gabapentin (Morphine) Accelerated metabolism of methadone (Phenytoin)
Antifungals	Inhibition of buprenorphine metabolism (ketoconazole) Inhibition of alfentanil metabolism (fluconazole, itraconazole) Increased plasma concentration of alfentanil and methadone (Voriconazole) Increased plasma concentration of fentanyl (Triazoles)
Antihistaminics	Increased sedative effects (Opioid analgesics+sedating antihistaminics)
Anticoagulants	Increased anticoagulant effects of coumadins (tramadol)
Antipsychotics	Increased sedative and hypotensive effect Increased risk of ventricular arrhythmia (methadone + QT interval prolonged antipsychotics) Increased risk of convulsion (tramadol)

	Increased risk of ventricular arrhytmia (methadone+amisulpride)
Antivirals	Decreased plasma concentration of methadone (Abacavir, nevirapine,didanosine,efavirenz,fosamprenavir,nelfinavir, ritonavir) Increased plasma concentration of dextropropoxyphene (ritonavir) Increased plasma concentration of buprenorphine (ritonavir) Decreased plasma concentration of pethidin (ritonavir) Decreased plasma concentration of morphine (ritonavir) Decreased plasma concentration of tipranavir (buprenorphine) Increased plasma concentration of zidovudine (methadone)
Atomoxetine	Increased risk of ventricular arrythmia (Methanode+Atomoxetine) Increased risk of convulsion(Tramadol+Atomoxetine)
Barbiturates	Increased CNS effects of opiod analgesics Decreased plasma concentration of methadone (Phenobarbital)
Beta-blocker	Increased plasma concentratin of esmolol (Morphine)
Domperidon	Antagonistic against domperidon gastrointestinal effects (Opioid analgesics)
Dopaminergics	Toxic effect on CNS (Pethidin+Rasagiline) Hyperpyrexia and toxic effect on CNS (Pethidin+Selegiline) Do not use dextromethorphan anda rasagiline concomitantly Tramadol and selegiline have to be used carefully.
Serotonin Antagonists	Antagonistic effect on tramadol (Ondansetron)
Calcium Channel Blockers	Inhibition of alfentanil metabolism (diltiazem)
Muscle Relaxants	Increased sedative effects (Fentanyl/Morphine + Baclofen)
Memantine	Increased toxic effect on CNS (is not recommended to use with dextromethorphan)

Metoclopramide	Antagonistic effects to gastrointestinal problems
Ulcer Drugs	Inhibition of opioid analgesics metabolism (by Cimetidine)
Sodium oxybate	Increased effect of sodium oxybate (do not use concomitantly)

According to the information, opioids may cause serious ADRs for patients. On the other hand, they provide potent analgesia so clinicians should know how they can overcome opioid-induced adverse reactions and should weigh the benefits against the risk of the treatment. All other considerations (drug interactions, pregnancy etc.) for other analgesics (paracetamol, NSAIDs) should be also taken into account for opioid treatment.

2.6. Global Analgesic Market and Consumption in Turkey

Prevalance of acute pain, especially headache throughout human life is estimated to be approximately 100%. Regarding information suggests that nearly every people will sorrow from any kind of pain during their daily life. Because of the fact, analgesics are the most frequenly used drug for self-medication (3).

Non-opioid analgesics (paracetamol and aspirin), opioid analgesics (opioids), NSAIDs carry on to be the main structures of pain treatment. In recent years, many medications have been added especially, antidepressants, anticonvulsants and selective COX-2 inhibitors for treatment pathway of pain. However, emerging safety concerns of COX-2 class drugs in 2004 lead to decline in their marketing in support of NSAIDs and opioids (91).

Many pharmaceutical companies are still working to develop current analgesic agents. Such effort is also beneficial to reduce risks and costs as well as to increase efficacy and safety. In this sense, many drugs that have been recently approved are the reformulation of existing drugs. Even so many drugs have been reformulated or developed in analgesic market, opioids are still thought as the most potent drug class for serious pain and ranks as first place on market share (91).

In 2009, global pain market reached above US$50 Bn and US$27 Bn of it was compassed by seven economy (US, Japan, France, Germany, Italy, Spain and United Kingdom) in the world. Figure 2 shows total worth and marketing share of primary pain drug classes for related countries in 2009 as below (91).

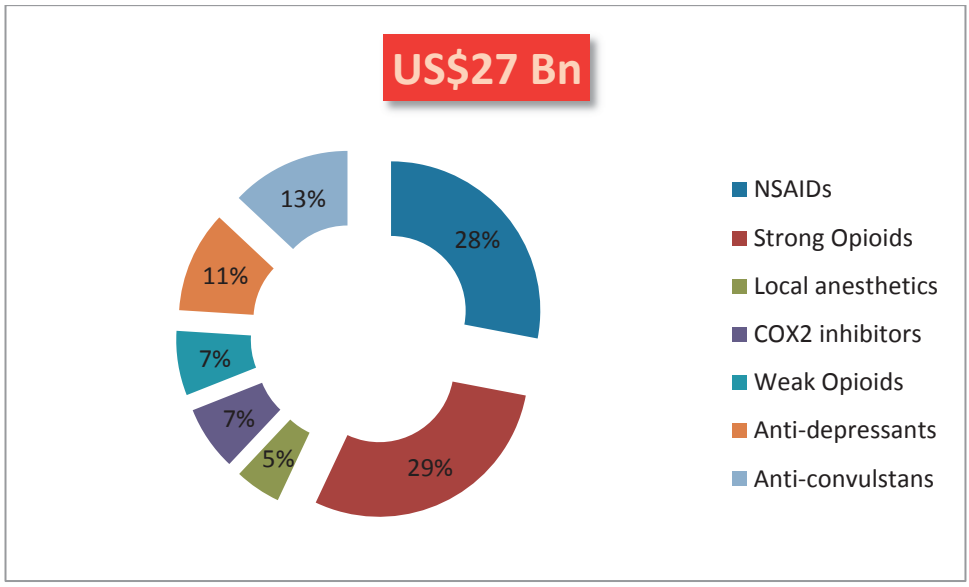

Figure 2: Total worth and marketing share of primary pain drug classes in 2009

Based on IMS Data, worthy information about therapeutic classes including pain medications between 2008 – 2012 with regards to their sales volume in the world is provided in following Table 17 (92).

Table 17: Sales volumes of top-20 therapeutic classes in 2012

	2012 Rank	2012 Sales (US$Bn)	2012 % Growth	2011 Sales (US$Bn)	2011 % Growth	2010 Sales (US$Bn)	2010 % Growth	2009 Sales (US$Bn)	2009 % Growth	2008 Sales (US$Bn)	2008 % Growth
Global Market		856.1	1.8	841.2	4.8	802.5	5.6	760.1	6.8	711.9	5.2
Oncologics	1	61.6	5.1	58.6	3.9	56.4	8.8	51.8	8.6	47.7	12.4
Pain	2	56.1	2.7	54.6	3.7	52.6	3.1	51.1	5.7	48.3	6.2
Anti Hypertensives	3	51.6	3.5	53.4	2.7	54.9	0.7	54.5	3.8	52.5	3.1
Antidiabetics	4	42.4	8.2	39.2	11.7	35.1	14.3	30.7	13.2	27.1	10.3
Mental Health	5	41.6	13.8	48.3	4.6	46.2	7.6	42.9	1.8	42.2	4.7
Respiratory Agents	6	39.7	1.4	39.2	7.5	36.5	8.6	33.6	10.7	30.3	6.1
Anti Bacterials	7	38.8	3.7	40.3	1.5	40.9	3.4	39.5	5.4	37.5	4.0
Lipid Regulators	8	33.6	14.2	39.1	3.9	37.7	4.8	35.9	4.9	34.2	1.0
Autoimmune	9	27.8	15.1	24.1	14.6	21.1	16.8	18.0	18.4	15.2	19.5

Diseases											
Anti Ulcerants	10	26.0	2.4	26.6	6.7	28.5	5.1	30.1	0.7	29.9	0.3
Other Cardiovasculars	11	19.2	8.6	17.7	9.1	16.2	8.3	15.0	8.5	13.8	6.3
Human Immundeficiency Virus (HIV) Antivirals	12	18.9	10.2	17.2	9.7	15.6	14.4	13.7	15.3	11.9	12.9
Nervous system disorders	13	18.8	4.8	18.0	5.6	17.0	0.6	17.1	15.6	20.3	9.2
Other CNS	14	16.7	4.5	15.9	4.8	15.2	6.6	14.3	5.4	13.5	-
Vitamins Minerals	15	13.9	3.7	13.4	6.4	12.6	6.1	11.9	9.0	10.9	8.3
Vaccines	16	13.8	3.9	13.3	13.7	11.7	8.1	10.8	1.0	10.9	0.7
Cough cold	17	12.7	2.4	12.4	6.1	11.7	-	11.7	10.7	10.5	6.6
Platelet Aggregation Inhibitors	18	12.6	23.3	16.4	4.4	15.7	3.8	15.1	9.2	13.8	10.8
Hospital Solutions	19	12.1	8.8	11.1	7.1	10.4	8.1	9.6	8.5	8.9	10.4
Anti virals excluding Anti-HIV	20	10.5	17.4	8.9	9.5	8.2	23.1	10.6	25.5	8.5	6.9

Table 17 shows that pain medications held the second place among top-20 therapeutic classes in 2012. During the period, their sales volume reached US$56.1 Bn and growth rate was calculated as 2.7% in 2012. When assessing with total market sales in 2012, sales ratio of pain therapeutics was 6.55%. Comparing to their values in 2008 and 2012 separately, sales volume of pain medications increased US$7.8 Bn in contrast to decline of global marketing share (from 6.78 to 6.55).

Another IMS report that was included Dispensed Prescriptions of top-25 active ingredients between 2008-2012 in US showed an increment about dispensed prescriptions from 3,870 Mn to 4,078 Mn (total increment was 208 Mn) in time (92). Furthermore, analgesic medications that were represented as hydrocodone/paracetamol, tramadol, oxycodone/paracetamol and ibuprofen showed 31.8 Mn raise of dispensed prescription that comes to mean approximately 15.29% of total dispensed prescription of top-25 active ingredients between 2008-2012. For the list, hydrocodone/paracetamol, an analgesic combination, took the first place with 135.3 Mn dispensed prescription based on 2012 value. Another active ingredients that are used as pain-relievers, like tramadol (21st with 37.3 Mn prescription), oxycodone/paracetamol (22nd with 36.6 Mn

prescription) and ibuprofen (25th with 33.4 Mn prescription) were also included into the list. Tramadol had the most increment among the analgesic on the list followed by hydrocodone/paracetamol and oxycodone/paracetamol combinations respectively.

Table 18: Top-25 medicines by dispensed prescription in US

Dispensed Prescriptions Mn	2008	2009	2010	2011	2012
Total US Market	3,870	3,953	3,997	4,028	4,078
Hydrocodone/paracetamol	125.5	129.4	132.1	136.7	135.3
Levothyroxine sodium	98.8	100.2	103.2	104.7	107.5
Lisinopril	77.2	83.0	87.6	88.8	90.8
Simvastatin	68.0	84.1	94.4	96.8	86.1
Metoprolol	79.7	76.9	76.6	76.3	78.1
Amlodipine	46.0	52.1	57.8	62.5	66.0
Omeprazol	35.8	45.6	53.5	59.4	65.7
Metformin	51.6	53.8	57.0	59.1	61.6
Salbutamol	50.1	54.5	55.1	56.9	61.5
Atorvastatin	58.5	51.7	45.3	43.3	54.9
Azithromycin	51.9	54.7	53.6	56.2	54.5
Amoxicilin	51.3	52.8	52.4	53.8	52.0
Alprazolam	43.3	45.3	47.7	49.1	49.2
Hydrochlorothiazide	48.5	47.9	47.8	48.1	47.7
Zolpidem	39.1	42.7	43.7	44.6	43.8
Furosemide	44.4	43.8	43.6	42.3	41.9
Fluticasone	24.2	28.0	32.8	36.7	41.4
Sertraline	33.7	34.8	36.2	37.6	39.2
Citalopram	22.6	27.3	32.2	37.8	38.9
Gabapentin	22.5	25.7	29.6	33.4	38.0
Tramadol	23.3	25.5	28.0	33.9	37.3
Oxycodone/paracetamol	33.5	36.0	36.3	37.3	36.6
Prednisone	27.1	27.8	28.7	33.7	34.0
Warfarin	34.9	35.7	35.6	33.9	33.8
Ibuprofen	28.5	30.3	31.1	32.6	33.4

Similarly with the previous report, further analyse in related to top-20 Therapeutic Classes by Dispensed Prescription in US was published via IMS (92). According to dispensed prescription value, antihypertensives had maximum prescription value with 656 Mn followed by pain section with 472 Mn in 2012. Prescription value of pain section increased in every interval between 2008-2012. Total increment of dispensed prescription of pain therapeutic class was 32 Mn within 5 years. It is realized that altough there was only 3 analgesics (2 of analgesics are in combination) on the list of top-25 medicines by dispensed prescription in US, pain therapeutic class held 2nd

position of top of dispensed prescriptions. Table 19 demonstrate overall list as following:

Table 19: Top therapeutic classes by dispensed prescription in US

Dispensed Prescriptions Mn	2008	2009	2010	2011	2012
Total US Market	3,870	3,953	3,997	4,028	4,078
Antihypertensives, Plain&Combo	653	654	657	653	656
Pain	439	449	459	465	472
Mental Health	293	301	309	320	329
Antibacterials	272	275	271	274	268
Lipid Regulators	238	249	255	255	255
Other CNS	173	179	184	188	189
Antidiabetics	166	169	172	173	174
Respiratory Agents	147	152	153	153	159
Anti-Ulcerants	139	146	147	150	157
Nervous System Disorders	128	135	142	148	156
Thyroid Preps	104	105	107	110	114
Hormonal Contraception, Systemic	94	93	91	90	91
Attention Deficit Hyperactivity Disorder	58	62	67	73	78
Vitamins&Minerals	68	73	78	77	76
Corticosteroids, Plain	49	51	53	55	58
Nasal Preparations, Topical	40	41	44	46	49
Corticosteroid, Topical, Plain & Combo	41	43	44	44	45
Other Cardiovasculars	50	47	46	45	44
Sex Hormones (Androgens, Oestrogens, Progestogens)	41	39	38	36	37
Vitamin K Antagonists	35	36	36	34	34

2.6.1. Analgesic Market in Turkey

To provide better understanding of analgesic consumption and market status in Turkey, IMS data (between 2007-2012) of analgesics and another drug group used to relieve pain called as NSAIDs was taken and evaluated as following tables and figures (93).

In Turkey, the following table shows top-10 selling (in units) active ingredients that are included into the products whose ATC Group is known as N02, in other words, called as analgesics in 2012. Especially, three active ingredients paracetamol, caffeine and dexketoprofen trometamol, were the most common included ingredients into

analgesic products (ATC Code: N02) in 2012. Moreover, development of the active ingredients in unit base starting from 2007 are also reflected into Table 20.

Table 20: Top-10 sales in units of active ingredients that are presented in analgesic products

Active Ingredient	Units Year/07	Units Year/08	Units Year/09	Units Year/10	Units Year/11	Units Year/12
ANALGESICS (N02)	117.689.132	120.853.322	122.454.810	117.126.299	132.343.233	134.705.457
PARACETAMOL	62.495.752	64.037.797	63.469.747	62.522.951	69.684.445	68.224.191
CAFFEINE	23.468.981	26.723.263	21.668.457	21.992.534	22.186.403	22.384.567
DEXKETOPROFEN TROMETAMOL	5.970.915	7.646.631	10.171.092	11.563.782	16.418.727	20.539.660
IBUPROFEN	15.313.845	17.409.449	20.515.606	18.114.958	20.702.704	19.988.237
ASA	15.115.480	16.719.758	13.335.315	10.888.613	11.007.871	11.875.040
METAMIZOLE SODIUM	12.777.789	10.427.825	10.711.324	9.160.425	9.455.920	9.070.509
PROPYPHENAZONE	6.633.294	7.337.160	7.714.493	7.779.798	8.343.053	7.877.202
ASCORBIC ACID	4.458.431	4.316.971	3.918.211	3.404.181	3.607.320	3.532.421
PHENOBARBITAL	3.775.964	3.501.225	3.600.912	3.220.492	3.252.811	3.121.270
ERGOTAMINE	2.726.817	2.821.430	2.825.249	2.763.941	2.750.089	2.716.840

On the basis of above Table 20, analgesic drugs include paracetamol had the highest sale in units all years between 2007-2012. Paracetamol (68.224.191 unit) was followed by caffeine (22.384.567 unit), dexketoprofen trometamol (20.539.660 unit), ibuprofen (19.988.237 unit) and ASA (11.875.040 unit) in 2012, respectively. Metazimole sodium, prophyphenazone, ascorbic acid, phenobarbital and ergotamine containing analgesic products had always performed last 5 rank of that list during related period. In 2007, ASA held the 4th position (15.115.480 units) but it had sharp decrease within 5 years and lapse-rate was found approximately %21,07. Dexketoprofen had the highest increment in period of that time from 7th to 3rd position. Unit sales of dexketoprofen increased with 14.568.745 units and rate of increase was calculated as nearly %244.

On the other hand, in line with Table 20, Figure 3 shows rise and fall of top-5 selling (in units) active ingredients (ATC Group: N02) between 2007-2012.

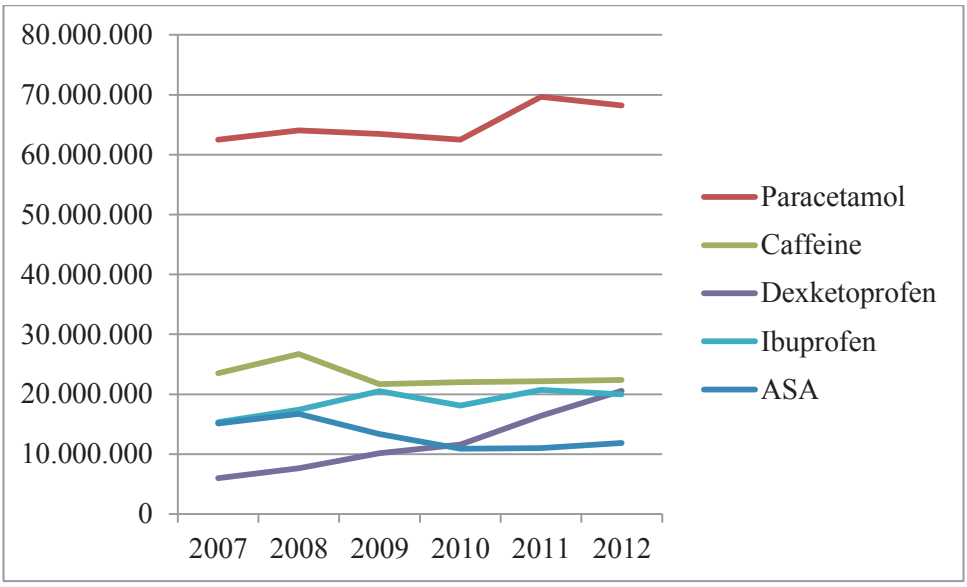

Figure 3: Top-5 active ingredients (in units) that were included into analgesic medications

In addition, total unit sales of analgesics between 2007-2012 was resulted as 117.689.132 units, 120.853.322 units (growth rate was %2.7) , 122.454.810 units (growth rate was %1.3), 117.126.299 units (growth rate was -%4.4), 132.343.233 units (growth rate was 13.0%) and 134.705.457 units (growth rate was 1.8%) respectively. Unit sales increased within all years except 2010. Following Figure 4 demonstrates rise and fall of unit sales of analgesics in the intervals.

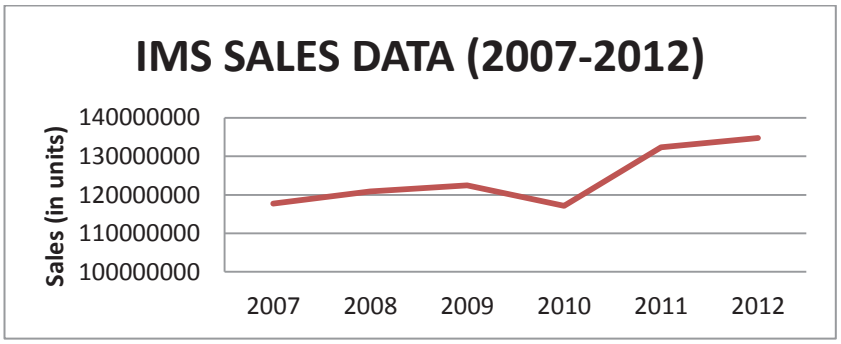

Figure 4: Unit sales graph of analgesic products (ATC Code: N02) between 2007-2012

From 2007 to 2012, use of analgesic drugs (ATC Code: N02) increased by 17.016.325 units and in percentage term, the increment was nearly 14.46%. Besides,

market share of Top 10 active substances related to analgesic drugs (ATC Code: N02) was determined according to unit sales in 2012 and showed as following Figure 5.

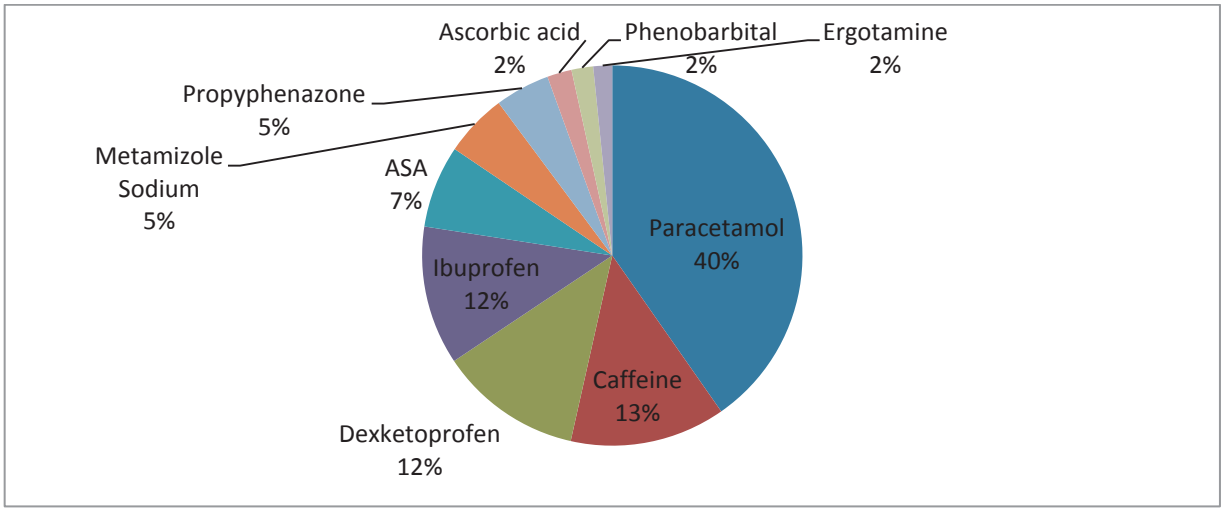

Figure 5: Market share (unit base) of top-10 analgesic active ingredients in 2012

Another statistic that is in line with the previous one shows top-10 sales volume of active ingredients that were included into analgesic formulations between 2007-2012 as below.

Table 21: Top-10 sales volumes (TL) of active ingredients that are presented in analgesic products

Active Ingredient	Sales Volume Year/07	Sales Volume Year/08	Sales Volume Year/09	Sales Volume Year/10	Sales Volume Year/11	Sales Volume Year/12
ANALGESICS (N02)	247.115.114	263.824.875	299.415.593	293.573.949	312.984.901	298.380.091
PARACETAMOL	101.270.779	107.355.974	114.532.876	114.028.144	127.348.406	123.596.952
DEXKETOPROFEN TROMETAMOL	46.278.998	55.027.857	76.366.932	78.317.272	79.704.947	74.219.021
CAFFEINE	45.624.840	55.168.897	52.366.102	55.411.989	57.375.599	56.618.902
IBUPROFEN	21.841.874	24.949.724	31.488.998	28.291.183	32.677.802	31.777.675
PROPYPHENAZONE	16.016.455	18.304.402	20.989.411	23.049.546	24.661.916	23.206.322
ASA	18.819.262	22.092.905	19.525.706	16.810.879	17.063.842	17.487.390
METAMIZOLE SODIUM	19.149.943	16.226.100	18.220.061	15.659.728	16.589.455	15.616.040
ASCORBIC ACID	9.866.431	9.482.615	8.965.203	8.500.004	9.007.543	8.799.207
ELETRIPTAN	5.704.223	5.259.811	5.126.552	6.423.026	7.454.083	7.839.749
ERGOTAMINE	6.306.827	6.671.835	7.376.020	7.786.721	7.860.889	7.817.753

When the value based sales were analysed, it has been seen that paracetamol was the leader active ingredient again included into analgesic formulation with 123.596.952 TL

sales volume for last six years. Dexketoprofen trometamol is the second in the value base with 74.219.021 TL sales volume in the Turkish market for the year 2012. The two active ingredients are followed by caffeine, ibuprofen, propyphenazone and the others respectively in 2012.

Total sales volume of analgesics between 2007-2012 was found as 247.115.114 TL, 263.824.875 TL 299.415.593 TL, 293.573.949 TL, 312.984.901 TL and 298.380.091 TL respectively. Based on results, paracetamol constitutes 41.4% of sales volume of analgesics in 2012.

Further information demonstrates that analgesics held 3rd position for overall unit sales among all ATC groups in 2012. Systemic antibacterials and antirheumatic system drugs were two major group that presented first 2 line of overall sales units respectively. Following table shows ATC groups that place first 10 line in overall unit sales in 2012.

Table 22: Top-10 ATC groups in terms of unit sales in 2012

ATC Group	Unit Sales 2007	Unit Sales 2008	Unit Sales 2009	Unit Sales 2010	Unit Sales 2011	Unit Sales 2012
J01 SYSTEMIC ANTIBACTERIALS	211.950.045	210.000.535	217.153.385	213.335.557	218.057.439	215.351.279
M01 ANTIRHEUMATIC SYSTEM	126.577.382	129.285.495	127.545.508	130.558.185	136.890.402	144.775.484
N02 ANALGESICS	**117.689.132**	**120.853.322**	**122.454.810**	**117.126.299**	**132.343.233**	**134.705.457**
R05 COUGH & COLD PREPARATIONS	100.147.981	103.298.506	120.549.614	110.360.638	130.150.154	119.790.438
A02 ANTACIDS-ANTIFLATULENTS-ANTIULCERANTS	64.746.098	70.009.832	68.214.551	75.992.306	82.684.204	85.701.864
C09 RENIN-ANGIOTEN SYSTEM AGENTS	40.116.638	45.649.431	49.362.792	55.479.408	58.866.630	62.409.079
V06 GENERAL NUTRIENTS	14.224.079	18.830.403	25.215.783	32.860.321	48.346.902	58.041.457
R03 ANTI-ASTHMA & CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PRODUCTS	26.930.874	29.970.228	34.494.659	39.062.249	44.244.195	45.708.664
B01 ANTITHROMBOTIC AGENTS	31.974.712	35.356.376	36.928.836	39.226.319	41.290.013	44.533.084
N06 PSYCHOANALEPTICS	32.022.317	36.526.947	37.070.634	40.130.109	42.758.205	44.286.069

On the other hand, analgesics held 15th position for overall sales volume through all ATC group in 2012. First three lines constituted with systemic antibacterials, anti-asthma & COPD products and drugs used in diabetes, respectively. The table below shows top-20 ATC groups that had highest sales volume in 2012;

Table 23: Highest sales volumes of top-20 ATC Groups in 2012

ATC Group	Sales Volume 2007	Sales Volume 2008	Sales Volume 2009	Sales Volume 2010	Sales Volume 2011	Sales Volume 2012
J01 SYSTEMIC ANTIBACTERIALS	1.548.392.643	1.556.488.692	1.846.430.225	1.719.968.401	1.595.644.454	1.428.671.884
R03 ANTI-ASTHMA & COPD PRODUCTS	549.289.938	648.881.116	810.644.490	869.017.076	894.120.212	739.411.156
A10 DRUGS USED IN DIABETES	490.771.860	583.054.095	696.902.227	694.942.478	681.445.186	685.391.645
A02 ANTACIDS-ANTIFLATULENTS-ANTIULCERANTS	503.693.538	583.723.313	618.182.937	699.041.585	714.460.720	672.709.541
L01 ANTINEOPLASTICS	476.793.018	533.709.931	653.851.439	651.365.172	627.010.416	654.825.284
C09 RENIN-ANGIOTENSIN SYSTEM AGENTS	747.187.132	815.961.230	916.862.749	826.104.390	730.345.872	618.477.009
G04 UROLOGICALS	271.730.556	311.120.390	361.960.704	404.144.809	500.318.069	543.327.038
M01 ANTIRHEUMATIC SYSTEM	447.969.165	437.371.971	481.491.574	512.126.166	527.492.898	530.798.290
R05 COUGH & COLD PREPARATIONS	306.666.333	343.261.602	447.906.674	431.449.400	497.861.844	431.181.388
L04 IMMUNOSUPPRESSANTS	158.363.798	208.483.108	283.523.635	307.533.076	332.340.965	354.095.096
N06 PSYCHOANALEPTICS	369.588.053	428.639.993	465.310.730	425.848.155	437.128.352	353.538.103
V06 GENERAL NUTRIENTS	109.157.141	134.287.185	177.307.127	217.706.630	283.734.504	346.990.822
N05 PSYCHOLEPTICS	297.033.543	317.119.355	363.964.084	377.218.021	361.697.855	320.352.180
S01 OPHTHALMOLOGICALS	196.886.566	235.400.691	279.561.998	291.074.769	297.948.402	318.793.606
N02 ANALGESICS	**247.115.144**	**263.824.875**	**299.415.593**	**293.573.949**	**312.984.901**	**298.380.091**
C10LIPID-REGULATORf/ANTI-ATHEROMATIC	352.996.755	406.664.800	478.805.413	448.709.801	435.584.097	275.280.640
N03 ANTI-EPILEPTICS	189.098.960	215.460.744	261.549.175	256.897.173	269.887.623	256.841.215
B03 ANTIANAEMICS	248.700.465	267.578.698	279.947.790	276.113.791	264.196.398	248.880.093
A11 VITAMINS	175.151.986	181.715.929	189.783.147	197.026.353	225.718.430	241.784.505
M03 MUSCLE RELAXANTS	167.773.971	189.774.199	209.459.775	221.578.518	244.130.268	231.181.847

Although analgesics presented 3rd line about unit sales in 2012, low prices of analgesics and national health policy systems lead to analgesics being 15th line of total sales volume in 2012.

Furthermore, evaluation of another drug group that is frequently used for pain called as NSAIDs, sales volume and sales in units is explained based on IMS data between 2007 – 2012 within following tables and figure.

Table 24: Top-10 sales in units of active ingredients related to NSAIDs

Active Ingredient	Units Year/07	Units Year/08	Units Year/09	Units Year/10	Units Year/11	Units Year/12
ANTIRHEUMATICS NON STEROIDAL PLAIN (M01A1)	126.299.465	128.851.151	126.858.383	129.440.717	135.578.897	142.901.572
DICLOFENAC	28.998.958	31.437.046	34.258.213	36.137.089	42.259.711	47.905.171
FLURBIPROFEN	22.871.317	22.657.555	20.962.507	22.868.454	21.328.901	21.497.219
NAPROXEN	16.932.685	14.942.510	14.868.681	14.388.588	14.794.834	17.834.993
ETODOLAC	7.675.391	9.140.678	13.742.372	16.493.454	16.016.362	15.269.989
TENOXICAM	7.716.577	8.511.136	5.758.758	7.102.182	7.576.995	8.240.768
ETOFENAMATE	8.123.577	8.565.666	7.617.267	6.494.171	6.549.361	6.876.073
ACEMETACIN	2.511.457	3.303.605	3.692.456	3.645.658	4.100.815	4.747.348
IBUPROFEN	2.691.120	2.968.318	2.918.954	2.799.004	3.313.465	3.413.315

KETOPROFEN	2.807.085	3.293.968	3.728.827	3.504.996	3.243.561	3.220.757
MELOXICAM	11.482.876	7.759.007	5.417.050	4.501.868	3.810.903	3.193.344

In the light of Table 24, between 2007-2012, diclofenac had always the highest unit sales among the drugs. Diclofenac was followed by flurbiprofen, naproxen and etodolac respectively in 2012. Total unit sales started as 126.299.456 units in 2007 and finalized as 142.901.572 units in 2012. Examination of above Table 24, one sharp increase and decrease have been observed especially etodolac and meloxicam. Rate of increase of etodolac in unit sales was found approximately 98.95% and lapse rate of meloxicam in unit sales was found approximately %72.2 from 2007 to 2012. Unit sales of NSAIDs increased within all years except 2009. Rate of increase was calcutaled approximately 11.62% totally during the period.

Figure 6 shows the share of unit sales of top-10 active ingredients that are called as NSAIDs in 2012 as following:

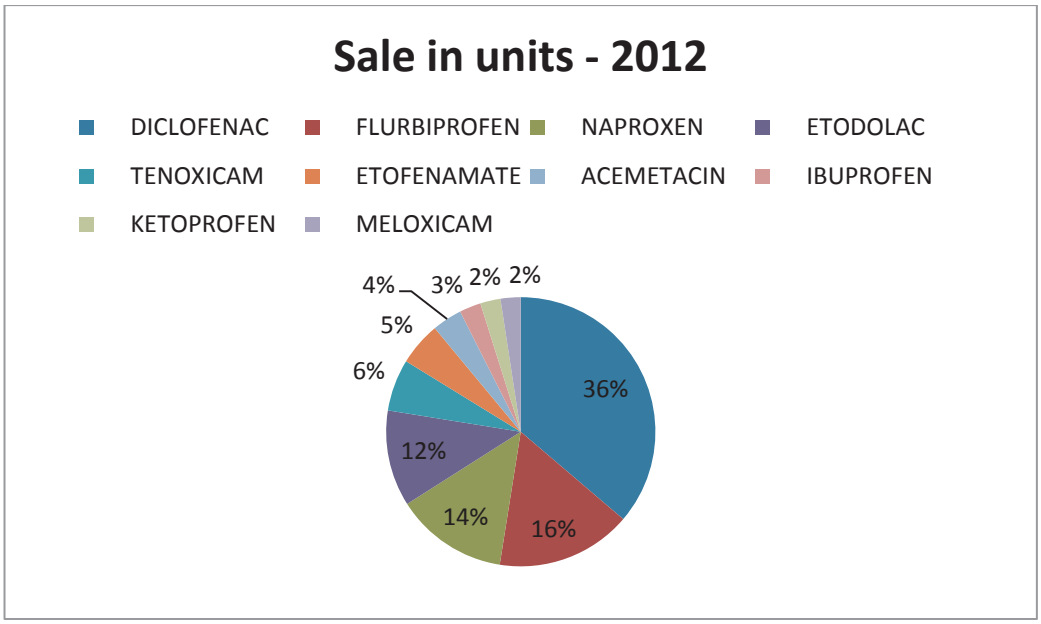

Figure 6: Top-10 active ingredients (related to NSAIDs) in unit sales in 2012

Moreover, Top-10 sales volume of active ingredients that are covered by NSAIDs between 2007-2012 in Turkey were shaped as followings;

Table 25: Top-10 sales volumes of active ingredients that are covered by NSAIDs between 2007-2012 in Turkey

Active Ingredient	Sales volume Year/07	Sales volume Year/08	Sales volume Year/09	Sales volume Year/10	Sales volume Year/11	Sales volume Year/12
ANTIRHEUMATICS NONSTEROIDAL PLAIN (M01A1)	434.062.673	419.504.751	459.082.931	486.275.593	501.980.928	502.585.043
DICLOFENAC	78.293.019	86.785.165	101.035.447	104.799.895	121.353.304	130.935.153
FLURBIPROFEN	94.604.867	85.082.772	85.760.322	105.132.067	105.232.818	97.427.049
ETODOLAC	52.999.657	56.845.513	84.343.618	101.280.682	89.479.303	77.669.917
NAPROXEN	53.380.207	47.079.056	52.305.764	53.429.296	56.578.234	69.587.375
ACEMETACIN	11.786.407	13.764.464	16.721.774	16.549.439	19.035.126	21.994.094
ETOFENAMATE	18.158.143	19.302.677	17.902.927	16.622.569	16.747.051	17.511.337
TENOXICAM	9.857.912	10.145.709	6.843.180	7.697.930	13.326.910	14.635.306
KETOPROFEN	12.338.248	13.129.489	16.340.416	15.676.372	14.615.985	14.526.913
MELOXICAM	43.846.041	24.822.652	17.893.639	13.874.880	11.836.941	10.035.349
NIMESULIDE	3.854.517	7.964.601	11.079.675	10.109.416	10.286.608	9.654.819

According to Table 25, diclofenac was the leader NSAID again as unit sales in Turkey market with 130.935.153 TL (2012) sales volume within last six years. Flurbiprofen was the second in the value base with 97.427.049 TL sales volume in the Turkish market for the year 2012. The two active ingredients are followed by etodolac, naproxen, acemetacin and the others respectively in 2012.

Total sales volume of NSAIDs between 2007-2012 was found as 434.062.673 TL, 419.504.751 TL 459.082.931 TL, 486.275.593 TL, 501.980.928 TL and 502.585.043 TL respectively. With the help of the data, 26.05% of sales volume of NSAIDs was constituted by diclofenac in 2012.

2.7. Pharmacovigilance and Dentistry

2.7.1. What is the meaning of pharmacovigilance?

Related to medications, safety and efficacy of medications are the two main issues. Efficacy can be evaluated with some methods but it may not be available for safety because drugs may have uncommon but serious adverse effects and patients can encounter serious and uncommon adverse effects. In addition, ADRs lead to significant mortality and morbidity. For example, ADRs are considered as the fourth cause of death in US according to recent estimates and the circumstance found out the branch of pharmacovigilance (94).

According to WHO, pharmacovigilance described as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other-drug related problems (95). As distinguish from WHO, Medicines and Healthcare Products Regulatory Agency (MHRA) defined pharmacovigilance as the process of following points (96):

- Monitoring the use of medicines in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of adverse effects
- Assessing the risk and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use
- Providing information to healthcare professionals and patients to optimize safe and effective use of medicines
- Monitoring the impact of any action taken.

2.7.2. Short History of Pharmacovigilance

FDA has started to record ADRs at the end of 1930s because of poisoning caused by an elixir of sulphanilamide and diethylene glycol in 1937 but many national authorities didn’t recognize the significance of monitoring ADRs in the beginning of 1960s even the cases of chloramphenicol have been observed related to aplastic anemia. On the other hand, the big thalidomide scandal required national authorities to approach ADRs seriously. Between 1960–1965, lots of European countries constituted their centers to monitor ADRs. In addition, WHO set up its international ADRs monitoring center in 1968 Although many measures has been taken to provide safety monitoring, there are some examples to show how the system has not been able to demonstrate serious ADRs. For example, rofecoxib (COX-2 inhibitor) caused lots of deaths because of serious cardiovascular problems despite many suspicions (97). Thus, all pharmacovigilance systems should be maintained rigorously to prevent such conditions and every clue should be taken into account.

Besides, experiences of pharmacovigilance in the world as well as Turkey are shown within following Table 26 and Table 27 (98).

Table 26: Manifestation of pharmacovigilance in the world

Date	Details
B.C. 4000	Euphoric effects of opium recognized by Sumerians
1600	Description of adverse effects of ergot alkaloids and ban of the products in some European countries
1937	Elixir of sulphanilamide contains diethylene glycol caused 139 deaths (n=353) in a week.
1938	First law regulation in US
1961	Reporting of many phocomelia cases with regards to Thalidomide
1962	A new regulation has been come out and authorized drugs have to provide their safety in addition to their efficacy by the regulation
1962	Publishing of England drug law
1967	20.51 numbered of motion of WHO
1968	Starting of pilot pharmacovigilance project in WHO
1971	Geneva meeting of WHO
1971	The Committee on the Safety of Medicines started their activities in England
1973	Pharmacovigilance system of France has been established
1975	Committee for Proprietary Medicinal Products has been constituted
1978	Adverse reaction monitoring system of WHO was moved into Uppsala
1988	European Rapid Alert System has been set up
1993	European Society of Pharmacovigilance has been established
1995	European Medicine Evaluation Agency has started to perform its activities
2000	International Society of Pharmacovigilance (ISoP) has been set up

Table 27: Legal developments with regards to pharmacovigilance in Turkey

Date	Details
1985	Center of Monitoring and Evaluation of Drug Adverse Effects has been founded
1987	Admitting to membership of WHO Drug Monitoring Center

24 November 2004	Establishment of branch office regarding drug safety monitoring and evaluation
14 January 2005	Setting up of monitoring, evaluation and advisory commission of safety of medicinal products
22 March 2005	Constitution of TUFAM
30 June 2005	The regulation came into force
6 July 2005	Pharmacovigilance guideline has been published
8 July 2005	Pharmacovigilance Training Programme in Istanbul and other educational activities performing with Pharmacovigilance Association (still-continuing)

Based on the chronological information, Turkey has started to perform activities related to pharmacovigilance very late in comparison with other countries. To close the gap, the term of pharmacovigilance and its importance for all stakeholders (healthcare professionals, patients, pharmaceutical companies etc.) have to be explained comprehensively. Moreover, healthcare professionals which can be considered as one of the main parts of pharmacovigilance should be encouraged to provide complete vigilance against ADRs by authorities.

2.7.3. Need for Pharmacovigilance Activities

Pharmacovigilance provides substantial information on the drugs that are available on the market (Phase IV studies). However, previous clinical studies, Phase I and Phase III are included limited number of participants (a few hundred) within suitable conditions like in the hospital, short-time period, low level of polypharmacy, limited number of high-risk patients. On the other hand, if any drug is marketed, it reaches broader range of patients and limitations of clinical studies are not applicable for any drug. Thus, the status may cause previously unidentified ADRs. For example, if the unrecognized ADR is rare (1/1000) and the drug that belongs to one of the most

commonly used pharmacological group in societies can be used up to 100,000 individuals thorough the first month so 100 (1000/100,000) patients may experience the ADR. Unlikely, there is no such a clinical design to show all serious ADRs before the marketing of a product. Thus, pharmacovigilance provides essential information to to describe and evaluate ADRs to prevent future occurrences (99).

Besides, British Medical Association demonstrated that post-marketing surveillance can be identified as a means to describe safety concerns not notified in pre-marketing studies and announce the new safety information or taken actions related to safety to users and prescribers. From the point of view, spontaneous reporting of suspected ADRs as a part of pharmacovigilance is very substantial to identify rare and delayed ADRs. In addition, pharmacovigilance plays an important role for the statuses such as drug development, epidemiological studies, medical understanding and rational drug use (95,100).

2.7.4. Spontaneous Reporting

Pharmacotherapeutics provide prevention, cure and control on many health problems. On the other hand, any treatment does not exist without risk of harm. Related risk has range from mild adverse reactions to serious and sometimes include fatal cases. Besides, spontaneous reporting that includes vigilant physicians and other healthcare professional is a cost-effective system to track safety of drugs throughout its lifecycle and serves as an important source to decide some regulatory actions such as withdrawal of drug from market or labelling changes regarding to safety information (101).

Moreover, lots of reasons are available to describe ADRs early and also prevent the reactions if circumstances are available. From the point, spontaneous reporting system is a useful tool to serve as early detection of ADRs that are resulted from the actions of drugs. Thus, spontaneous reporting system has been proved in terms of its value but under-reporting is still a problem. For instance, serious ADRs are not completely reported, low number of physicians report ADRs and reported ADRs don’t show the total number of ADRs. Behaviors and knowledge of spontaneous reporting system of clinicians are the main predictive factors about under-reporting (102). In parallel of the

information, Lopez-Gonzalez et al. (2009) demonstrated that personal as well as professional characteristics of healthcare providers and their knowledge and attitudes to reporting are among the factors of under-reporting (103). Besides, Sencan et al. (2010) provided that health care professionals do not report ADRs as much as expected because of inadequate knowledge, being unaware of pharmacovigilance system, excess work load, avoidance of making correct decision (104).

2.7.5. Pharmacovigilance and Dentistry

Patient safety is a very complex term and consists many factors in inside (105). Moreover, patient safety has become more important issue in recent years. With the publication of "To err is human" from the Committee on Quality of Health Care in America of the Institute of Medicine, seniority of healthcare authorities became safety in health care practices (106).

Based on the scope of dentistry, patient safety is also considered as an inherent concern but there are few organizations to developed patient safety in dentistry. Perez et al. (2011) demonstrated the reasons for the problem as following points (106):

- Severity of produced harm is generally low
- Ambulatory status of patients that makes it difficult to understand or recognize many adverse events
- It is hard to collect data because of great distribution of dental care
- Dental practices are generally conducted in private area and fear exists on the point of commercial side of clinics because of reporting adverse events
- Absence of general culture regarding patient safety

However, there are many reasons that make dental practices become more active in patients safety such as dangerous pharmaceuticals, aggressive techniques, potential transmission from blood or fluids and some harmful techniques (106).

In addition, Zarvas et al. (2013) provided that increased life time and some trends lead to population become older and dentists should be fully aware of medications that

their patients take. Thus, dentists have to participate the process of evaluation and reporting of adverse events to protect their patients well-being. Thus, dentists contribute to the pool of voluntary adverse event reporting and the source serves as a powerful data to find unsafe and failed products (107).

On the other hand, when considering the practices, it has been seen that adoption of pharmacovigilance to dentists or any other healthcare professional is not an easy way. Praveen et al. (2013) conducted a knowledge, attitude and practice study regarding ADRs reporting among medical and dental practitioners and the results demonstrated that there is an important gap in behavioral situation for ADR reporting (108). In addition, Yip et al. (2013) indicated that under-reporting of healthcare professional is a problem and general dental practitioners (GDPs) are not an exception in respective concern. They investigated many aspects of GDPs about United Kingdom yellow card reporting scheme and concluded that 88.5% of participants had never utilize yellow card scheme and 76.9% of participants stated the need for additional training (109).

As a result, deficiencies and problems of dentists must be find out and adopted into a better manner to provide complete protection of patients against pharmacotherapeutics as Kavitha (2010) says " Anything you can think of, anything you can see and something you don't even think of can be due to drug" (110).

Following section of the research includes the method that was used to achieve the aim of the study and related details.

3. METHOD

3.1. Pre-search Stage

National and international literature search has been done and publicly available data both in English and Turkish with regards to keywords including “drug safety, adverse reaction, dentistry, dental pain, analgesics”. In the matter of collecting information about analgesics, analgesics-dentistry relationship and any other information in line with the study, official websites consisting WHO, FDA, ISoP, MHRA, BPS, IMS, IASP, AIFD, Turkish Pharmacists’ Association, TDA and Republic of Turkey Ministry of Health were investigated.

To provide better understanding of related active ingredients’ properties especially relevant to their ADRs, the last version (2014) of RxMediaPharma was used to get useful information. When RxMediaPharma was not suitable or sufficient, TİK-6 was benefited to complete information gap. In addition IMS sales data of analgesics between 2007 – 2012 in Turkey was obtained. With the help of the data, sales volumes and sales in units of analgesics in Turkey was explained and showed by many figures and tables to clarify marketing status on analgesics.

3.2. Focus Group Interview

3.2.1. General Information of Focus Group Interview

Method that was needed to conduct the thesis is focus group interview. Focus group interviews are kinds of qualitative research method that include a carefully designed “discussion” which allows people to state their points of view in a group setting and ensure researchers with indicators of program impact. Focus group interviews generate different perceptions and points of view and are used to collect information for discovery, bench marking, evaluating, verifying perceptions, feelings, opinions and thoughts (111).

Participants in the focus group interview are kept together since they possess certain characteristics related to the subject under study. However, it is very important to select

participants who adequately represent the employee population and it has to be taken into account that random selection and voluntary participations are key element for the process (111,112).

A focus group optimal size can vary 6 to 12 but the group should be large enough to generate rich discussion but not so large to compensate some leavings from the interview (113). Moreover, conduction of successful and productive focus group interview is based on informative and appropriate questions to be asked of the participants. Generally, 5 –6 questions can be posed to participants. The questions should reflect the purpose of the study clearly and can be open-ended and flexible but target to main topic. However, sequences of the questions have to be descriptive, allow for opinions, feelings and be originated from participants knowledge and/or skill. In addition, the questions starting with "why" and questions which can be answered with "yes" or "no" should be limited and it must be noted that general questions generate general thoughts and specific questions generate specific thoughts that are necessary to define issues in an effective way (111).

Besides, focus group interviews are conducted by a moderator and assistant moderator. The moderator manages the discussion substantially; the assistant should be much more interested in recording than the moderator. If the moderator plays his or her role completely, an expressive result will be observed quite likely (112,114).

Recording and analyzing focus group interviews are also key elements. If it is possible, tape recorder should be used not to miss any information. If it is not possible, additional person should be admitted the sessions to take notes (113). When analyzing participants' comments and/or answers, all verbal data is collected and typed (111). Moreover, notes are organized and become into valuable material to consolidate with information from tape recorder (114).

3.2.2. Location and Date of the Study

Two focus group interviews have been done for this research. Before each interview, appointments were arranged as a result of long efforts made. These

interviews have been executed in October, 2014. However, the interview that could be called as preliminary interview has been conducted in July, 2014 with a dentist to prepare focus group interviews and control overall quality of questions and answers.

Preliminary Interview (0): One dentist, male, work in private sector and have no specialization.

Focus Group Interview (1): Assistant professor and assistants of a dentistry faculty, 6 dentists (4 male, 2 female).

Focus Group Interview (2): 7 members (2 male, 5 female) of a non-profit organization, all of them are dentists.

Focus group interviews lasted 15-30 minutes and interviews was conducted in an empty and quiet room. Unfortunately, there was no observer for the interviews. Participants sat around o-shaped table and Sony ICDUX 533B was used as recording device. Name/identity of participants were put into codes separately. However, all participants were dentists. The younger participant is 27 years old and the older one is 50 years old but some participants did not express their age. There was no anticipation regarding gender and age of them in the study. From the point of preliminary interview, this one has been evaluated as to check semi-structured questions and prepare the main interviews and that is why preliminary interview lasted more than focus group interviews (30 minutes). Preliminary interview contributed the formation of new semi-structured questions that were used in focus group interviews but provided information was not included into the study. Assessments of the study was based on number 1 and number 2 focus group interviews.

All opinions and thoughts are under individual's responsibility and must not be adopted as an organizational expression.

4. FINDINGS AND DISCUSSION

6 semi-structured questions were posed to each participants to assess ADRs experiences. Each finding has been compiled in line with the settlement of recordings. Transcription of recordings has been done approximately in two days. All documents (transcribed) were examined and analysis of content have been tried with the way of similar and different findings.

First of all, all participants were asked to introduce themselves. The high point from the introduction showed that focus group interview (2) did not include any dentists with a specialization. However, focus group interview (1) included many specialists and one teaching assistant.

Semi-structured question (1): In which conditions you write out a prescription and frequency of prescription

With regards to reasons for prescription, both group expressed similar phrases like acute conditions, abscess, pain and post-operative conditions. On the other hand, frequency of prescription was taken into consideration, dentists of focus group interview (1) stated that frequency level is generally low as dentists of focus group interview (2) but three dentists from focus group interview (2) did not tell same thing about frequency of prescription.

> *"I do not prescribe too much but I encounter many patients with pain or abscess in vigil. Thus, we may write more prescription" (F,2,A)**
> **: (gender, group number, interviewer code)*

> *"I have to prescribe frequently. A large number of patients with infection come to us" (F,2,G)*

> *"I prescribe generally. I prescribe dental floss or toothpaste in the worst case. Another reason is to prevent useless dentists' visit thoughts in patients' mind" (F,2,E)*

When view from first two sentences, this dissimilarity is mainly caused by dentists' work area. These two dentists are working in a public sector and their patient population includes more low-income people. In parallel, these people may face further oral health problems than high-income people. Thus, it can be said that dentists work in a public sector prescribe more than dentists work in a private sector.

In terms of last sentence, this kind of approach may provide people oral health positively but can cause dangerous ADRs. This situation might increase patients' expectation for dental treatment and they feel as untreated without a prescription. Moreover, misprescribing and/or overprescribing associated with ADR problems could come up.

Semi-structured question (2): What medications are commonly used by dentists?

According to answers from both groups analgesics and antibiotics were expressed as commonly used medications. In addition, dentists from focus group interview (1) also indicated antiseptic gargles. On the other hand, NSAIDs were the only suggested analgesic group specifically. This choice can be related that dental pain often appears with inflammation and NSAIDs are effective at pain relief with anti-inflammatory action.

"Antibiotics, analgesics and antiseptic gargles at most" (M,1,B)

"Generally, wide-spectrum antibiotics are preferred. NSAIDs are used for post-operative period. In addition, antiseptic gargles are favoured" (F,1,D)

"Antibiotics and analgesics. I prefer to use them in combination in general" (M,2,B)

"Antibiotics and analgesics are the most commonly used drug groups" (F,2,A)

Semi-structured question (3): Under what circumstances which analgesics should be suggested and shouldn't be suggested?

For this subject, related groups expressed different approaches. These differences are shown as followings:

"I do not offer any NSAIDs to patients suffer from gastrointestinal (GI) problems. At the same time, ASA and derivatives are not suggested to patient with bleeding problems. In addition, analgesics that increases ion level of blood like naproxen sodium should not be prescribed for hypertensive patients" (M,1,A)

"...if patient is pregnant we should communicate her doctor before the treatment. If we are not sure for patient risk status our treatment will be limited with paracetamol and its derivatives" (M,1,F)

"For post-operative situations, we generally prescribe NSAIDs but patients with GI problems should be treated with paracetamol. We do not prescribe medications that consist ASA for patient with bleeding problems" (F,1,D)

"..changing the group of medication or if patient complain about GI problems I will give him an additional gastroprotective drug" (M,2,F)

"If patient has pain you will suggest or there is no pain you will not. Gastroprotective drugs will be added if patient suffer from GI problems" (F,2,E)

"I tell them if you have pain, use analgesics" (F,2,C)

The approaches obtain from focus group interview (1) have been found effective because their cornerstone is based on patient. Act upon by a patient always be rational and by this way problems like misprescribing/overprescribing/ADRs that totally means irrational drug use will be disappeared. However, if dentists act with regards to patient reactions to the treatment they not only treat their pain problems but also cause another health concerns.

Semi-structured question (4): How often do you encounter an ADR?

Both groups indicated that ADRs are not a common thing that encountered by a dentist. In cases where ADRs appear, they are commonly due to analgesics/antibiotics related GI (complaints on stomach) problems. However, one dentist from each group stated different approaches when examined other dentists.

"Because of the comprehensive history taking, allergic problems or ADRs are not frequently observed" (M,1,F)

"I warn them about what they may encounter with their medication. In addition, I want them to make a quick feedback if they experience any ADR" (F,2,G)

Two sentences above are considered as important steps for pharmacovigilance or drug safety. Unfortunately, only two dentists made an expression like above. In this particular, a great gap has been observed.

Semi-structured question (5): Do you report any ADRs?

All dentists except one showed that they do not report any ADRs and they have no idea how and where they have to report them.

"I do not report anything but patient-follow up is done under my control" (F,2,A)

"Reporting about ADRs haven't been done. I don't think that dentists are aware of it" (M,2,B)

"I am learning it at the moment" (F,2,E)
"We do not report anything. Moreover, we don't know how and where to report them. However, patient-follow is always conducted" (F,1,C)

"If we encounter any ADRs that is not listed into patient information leaflet we report them to related Ministry of Health Department" (M,1,F)

When examined all answers dentists have no information about it and only one dentist is aware of it but it does not matter. In this respect, complete integrity should be ensured.

Semi-structured question (6): What are your suggestions to reduce the risk of ADRs in dentistry?

Considering the answers, two groups have used different (dentists-companies & patients) sources to answer it.

> *"Dentists should be informed about mechanisms of active ingredients, ADRs in detail. Moreover, these subjects may be integrated as a course of dentistry faculty" (M,1,A)*

> *"With devotion of companies, dentists should be instructed about active ingredients and their adverse reactions" (F,1,B)*

> *"Detail anamnesis and dentists' information level are important" (M,1,E)*

> *"...Systemic status of patient should be take into consideration and patients should be informed how to take medications in depth. If we do that we will minimize the risk of ADRs" (M,1,F)*

> *"Do not use medication if not really needed" (F,2,A)*

> *"I may suggest them not to use medication so much because some patients take medications like candies" (F,2,D)*

> *"Patients should be informed about report chain of ADRs" (F,2,G)*

Feedbacks from focus group interview (2) are not found sufficient. It could be possibly related to education level of dentists because education brings them new ideas and perceptions.

Primarily, all drugs produce adverse reactions that can be serious or not. When ADRs are taken into account a discipline spring to mind called as pharmacovigilance. Pharmacovigilance activities have been performed in US and European countries long before. However, Ministry of Health in Turkey has started pharmacovigilance activities that improve public health and safety in relation to the use of medicines since 2005. In this connection regulation and guideline related to pharmacovigilance have been published. 10 years later, a new and detailed regulation has been published based on EU good pharmacovigilance practices. Besides, many guidelines have been published so far and many of them are supposed to be publish in contrast to only one guideline in 2005.

One of the most important part of pharmacovigilance is reporting of ADRs. Medications are developed under controlled-circumstances and they are uncontrolled when they are marketed. When considering all of these, major safety information is collected in post-marketing session. Thus, if you want to provide these major safety information, you have to report ADRs to related department of Ministry of Health according to pre-determined requirements in regulation or guidelines.

In compliance with the new regulation of pharmacovigilance, doctors, pharmacists and dentists have a right to report ADRs primarily. In the light of this information the study is aimed to evaluate adverse reaction experiences of dentists with regards to one of the most commonly used drug group, analgesics.

Six questions have been directed to participants as two separate focus group to understand their behavior on the face of ADRs. According to question 1 and 2, *(In which conditions you write out a prescription and frequency of prescription & What medications are commonly used by dentists?),* frequency of prescription is found as generally low for both groups and analgesics and antibiotics are expressed as common drugs for dentists. It is not surprising that antibiotics and analgesics are common but these is an interesting point for prescription. Dentists work in public sector said that they frequently see patients that have to be prescribed. Thus, dentists work in public sector will face ADRs related to analgesics more than dentists work in private sector because of number of prescription and the possibility of ADR related to analgesics that was expressed as 2nd group after

antibiotics with regards to reporting of adverse reactions. The situation is probably related to patient profile because dentists work in public sector frequently meet low-income patients or families whose oral health problems could be more significant than patient with high-income. Furthermore, patients with low-income generally don't want to seek clinicians until the last minute so when dentists check their patients (low-income) prescription is necessary to relieve patients due to being late to go dentist.

According to answers from question 3, *(Under what circumstances which analgesics should be suggested and shouldn't be suggested?),* focus group whose participants are at least specialists remarked more detailed answers than the other focus group. Moreover, changing drug group and giving gastroprotective drugs put into words many times. It shouldn't be forgotten that dentists should check their patients' current medical status as well as their medical history and find suitable analgesic drug without the need for gastroprotectives or group changing. Besides, gastroprotectives may also cause serious ADRs.

For question 4, *(How often do you encounter an ADR?),* the frequency of ADRs was appeared as low (only GI-related problems expressed in interviews) in parallel as prescription behavior. The result is surprising because analgesics are commonly used in dentistry and their adverse reactions frequency ranked as 2nd. The situation could be related to knowledge about reporting of ADRs because if a dentist knows how to report, he/she will be more focused on patients' experience on ADRs. Moreover, another reason is unconsciousness of dentists towards patients' ADR experiences. Thus, education and/or knowledge is a very significant part for dentists behavior. In parallel with this, all dentists except one from focus group interviews do not know how and where to report ADRs and one dentist expressed that it was her first time to hear reporting process (question 5 - *Do you report any ADRs?*).

When it comes to question 6, many suggestions were raised. These suggestions included deficiencies of dentists and patients. Enlightening of dentists about active ingredients and their mechanism of actions and irrational drug use habits of patient were

emphasized. In short, lack of information related to both parts (dentists & patients) were found as important like in previous questions.

Table 28: Summary of answers from focus group interviews

Semi-structured question 1 : In which conditions you write out a prescription and frequency of prescription	
Focus group interview (1)	*Focus group interview (2)*
Post-operative processes, acute situations and prophylaxis needed problems. Overall rate is low.	Dentists (2 participants) work in public area stated high frequency. Other participants (except one) expressed that the rate is low and they prescripte medication when it is needed/infectious or painful situations. One dentist said that "I always write out a prescription even it includes dental floss"
Semi-structured question 2: What medications are commonly used by dentists?	
Focus group interview (1)	*Focus group interview (2)*
Antibiotics, analgesics and antiseptic gargles. NSAIDs are preferred by two dentists for post-operative conditions.	Antibiotics and analgesics. Some participants prefer combined use of antibiotics and analgesics. NSAIDs are preferred by two dentists.
Semi-structured question 3: Under what circumstances which analgesics should be suggested and shouldn't be suggested?	
Focus group interview (1)	*Focus group interview (2)*
NSAIDs are not recommended for patients suffer from GI problems and/or hypertension. ASA and derivatives are not suitable for patients with bleeding problems. Two dentists stated that paracetamol can be used under risky circumstances.	Generally, if pain exists, analgesics have to be given. Age, systemic conditions, patient medical history and anamnesis were provided as important points by dentists separately. In the event of stomach problem or any other conditions, gastroprotective medications or changing drug group were declared as useful methods.
Semi-structured question (4): How often do you encounter an ADR?	
Focus group interview (1)	*Focus group interview (2)*

Frequency level is low. Generally, GI problems is observed associated with antibiotics and analgesics. One dentist showed that detailed history taking is an important thing to reduce the risk of adverse drug reactions.	Frequency level is low. GI problems were stated by a dentists associated with analgesics. One dentist said that I warn them about what they may encounter with their medication. In addition, I want them to make a quick feedback if they experience any ADR.
Semi-structured question (5): Do you report any ADRs?	
Focus group interview (1)	*Focus group interview (2)*
Dentists do not report any ADRs except one. Two dentists clearly stated that they do not know how and where to report ADRs.	Dentists do not report any ADRs. Three dentists clearly stated that they do not know how and where to report ADRs. In addition, one dentist said that I heard it for the first time.
Semi-structured question (6): What are your suggestions to reduce the risk of ADRs in dentistry?	
Focus group interview (1)	*Focus group interview (2)*
Education with related subjects (drug mechanism, ADRs etc.), taking detailed anamnesis from patients, communication should be improved between dentists and patients.	Unnecessary drug use should be prevented. Taking detailed anamnesis, controlled use of drug and patients should be informed with regards to the reporting chain of ADRs.

Apart from previous information, interviews lasted shorter than expected. The situation showed that dentists from interviews are not really interested in drug safety. In addition, the adoption of pharmacovigilance seems hard for them. However, dentists should be more active and their role & contribution to pharmacovigilance have to be improved.

As a result, dentists as one of the most significant stakeholders of pharmacovigilance do not have much experience against ADRs of analgesics but when

they encounter any ADRs they do not know about reporting of ADRs which is one of the most significant part of pharmacovigilance.

4.1. Limitations of the Study

During the research, some challenges have been encountered. Especially working hours & standards for dentists made heavy weather of the study. Moreover, it was hard to meet minimum 6 dentists at the same time, same place to perform interviews because of the beginning of summer season but in consequence much efforts for 3 months it was achieved. Despite all, number of participants were lower than thought. Thus, duration of interviews were short. Besides, many groups (4 or 5) have been decided to incorporate into interviews but the situation was not available and only two groups have been included for interviews.

Unfortunately, there was no observer in the interviews due to lack of time and imagery data recording was not compatible. In addition, informed consents of participants have not been taken throughout the interviews.

On the other hand, the study was the first in the field of pharmacovigilance and dentistry so there was no previous study about it. Because of this, some disadvantages for being first were experienced. Besides, public pharmacovigilance database was not reached in Turkey so real-time information could not be included into the study.

5. CONCLUSION

The study demonstrated that dentists have no much ADR experiences about analgesics and knowledge about reporting of ADRs as well. On the other hand, it was clear that dentists were not sufficiently informed about pharmacovigilance activities because nearly all of them said that we have no idea related to reporting of ADRs although they have a right to do it. Following objects include suggestions to enhance current situation of dentists regarding ADRs and their behaviors against them:

- It is clear that Ministry of Health was not good enough to communicate with dentists with regards to pharmacovigilance. Thus, activities devoted to dentists associated with pharmacovigilance should be performed periodically at various locations of country.

- One of the most important stakeholders of healthcare is pharmaceutical companies. Due to this reason, they also play crucial role to maintain healthcare safely. For that matter, pharmaceutical companies have to inform dentists about their own products including mechanism of action, ADRs and new safety information but this work should be performed devotedly and without considering prescription potential of dentists.

- Congress performed by dentists yearly should contain a pharmacovigilance session at least to keep their knowledge updated. If some few are not available to join congress, online learning should be designed for them. Moreover, online learning should be available for all dentists.

- It must be noted that clinicians like dentists have to improve themselves day to day for drugs because safety information of drugs have been changed many times in a year. Thus, refresher training and exam (with minimum point criteria) should be set up by Ministry of Health or related Chambers of Dentists.

- Considering lack of personal development, pharmacovigilance can be entegrated into pharmacology course of dentistry to ease dentists' adaptation and to increase awareness of dentists.

- On the side of patients, they should be informed by dentists or their assistants (e.g. time of payment or after treatment immediately) associated with ADRs of analgesics and any other drugs and how to behave when they encounter with one of them.

- When patients go to a doctor, detailed anamnesis should be taken by dentist to understand patient profile and reduce the risk of possible allergic reaction or ADRs caused by given drugs. In addition, patient follow-up should be performed if necessary.

- Informative brochures should be shared with patients and posters that includes warnings and information about drugs should be hanged in waiting room of dentist to increase awareness of reporting of ADRs.

- Further studies are needed to evaluate ADR experiences and behaviors of dentists with regards to analgesics because this study is the first for related field.

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