A Survey on knowledge and attitude about analgesic use, its indication and side effects

A Dissertation submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy

Submitted by

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Declaration by the Research Candidate

I, **Mst.Sharmin Sultana ID:2013-3-70-078** , hereby declare that the dissertation entitled— A Survey on Knowledge and attitude about analgesic us, its indication and side effects ‖ submitted by me to the Department of Pharmacy, East West University in partial fulfillment of the requirement for the award of the degree of Bachelor of Pharmacy is a record of research work under the supervision and guidance of **Ms.Farah Shahjin,** Senior Lecturer, Department of Pharmacy, East West University,Dhaka.

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Certificate by the Supervisor

This is to certify that the thesis entitled- A Survey on Knowledge and attitude about analgesic use, indication and side effects " submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a bonafide record of original and genuine research work carried out by **Mst.Sharmin Sultana ID:2013-3-70-078** in 2017 of her research in the Department of Pharmacy, East West University, under the supervision and guidance of me.

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Dedication

This research work is dedicated to my beloved parents, honorable faculties and loving friends.

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List of Abbreviation

1.	AGS	The American Geriatrics Society
2.	GI	Gastrointestinal
3.	NSAIDs	Non-steroidal anti inflammatory drugs
4.	OTC	Over-The-Counter
6.	CNS	Central Nervous System
7.	H3G	Hydromorphone-3-glucronide
8.	NMDA	N-metyl-D-asparate
9.	PME	Parenteral Morphine Equivalents
10.	CTZ	Chemoreceptor Trigger Zone
11.	VC	Vomiting Center
12.	PIL	Patient Information Leaflet

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Abstract

A study was conducted in hospitals of Bangladesh which is entitled by “A Survey on Knowledge and attitude about analgesic use and its indication and possible side effects ”.The aims and objectives of the study were to find out that is the patients aware about the uses of analgesics and its possible side effects. Through the study informing that the proper instruction need when taking analgesic and find out self medication take by patients without prescription. The survey was based on questionnaire had a sample size 122 where 67 were women and 55 were male. Anyone unwilling to participate or unable to comply with protocol requirements were excluded. Only 27.04 % participant have health science background in education. They responds that maximum (72.95%) taking medication for pathophysiological condition, only 5.73% and 4.92% take medication for injury and dental pain respectively. Medication used by patients are group belong to Acetic acid, Ibuprofen and less amount of Cox-2 and Oxicam derivatives which take by about 73% under prescription and 27% self medicated. From the study also get a infor- mation that only 55% patients get information from doctor about side effects. Doctor also prescribe other drug along with analgesic. It is important to read leaflet information by patients when they take medication and also aware about food-drug and drug-drug interaction.

Key word:- NSAIDs, Geriatric , Side effects, Analgesic, ADR.

Chapter 1
Introduction

1.1 Overview

The treatment of pain—especially chronic pain—with medications can be a demanding task in patients of any age. Clinicians are often faced with the difficulty of measuring possible benefits against potential serious, even life-threatening, adverse events. Because geriatric patients frequently have multiple health problems and use other medications that can interact with analgesics, pain management is particularly challenging. It would be wonderful to report that recent research has provided clearer pathways for managing geriatric pain and has eased clinicians' concerns. However, the truth is that research has continued to highlight the complexity in choosing the safest and most efficacious analgesic agents for older patients.

The American Geriatrics Society (AGS) issued its first practice guideline on chronic pain in 1998 and has updated it twice. The first 2 guidelines reviewed both pharmacologic and nonpharmacologic treatments. The most recent guideline addresses only the former1; it does, however, provide a useful overview of analgesic medications with particular focus on the adverse effects that may be especially problematic for geriatric patients. The AGS panel recommends starting treatment with acetaminophen because of its relatively benign adverse-effect profile, as long as the recommended daily dose is not exceeded. NSAIDs are traditionally the next step. However, the guideline notes that while multiple adverse effects, including GI toxicity, effects on renal function, and cardiovascular problems (ie, myocardial infarctions and strokes), are associated with these drugs in any age-group, there is a heightened risk of these sequelae in the geriatric population. It therefore concludes that for many geriatric patients, other drugs—including opioids—may be a safer choice. The guideline identifies the potential promise of topical NSAIDs to achieve the benefits of oral NSAIDs with a markedly reduced risk of adverse effects. However, even these medications are far from risk-free. A literature review on use of topical NSAIDs by

geriatric patients with osteoarthritis published after the most recent AGS guideline found that although patients using these formulations were less likely to suffer severe GI effects, up to about 17.5% did report systemic adverse effects. Up to another 39% of patients had problems at the application site of the topical drug, and there were 5 cases of warfarin potentiation. Perhaps most surprising was the finding that discontinuation rates for topical NSAIDs secondary to adverse events was similar to that for oral NSAIDs (Steven A. King, 2017).

1.2 Analgesic drugs

Analgesics are drugs designed specifically to relieve pain. There are several types of analgesics: acetaminophen (Tylenol), which is available without a prescription, and a variety of opioid analgesics, which are available only with a prescription. Some products combine acetaminophen with an opioid analgesic for added relief. Analgesics are for anyone with pain, and that includes almost everyone with arthritis or a related condition. Doctors once reserved opioids (also called narcotics) for treating severe acute pain, such as that from surgery or a broken bone but in more recent years, opioids have been increasingly prescribed for chronic pain, such as pain from arthritis. Unlike NSAIDS, opioids don't cause gastrointestinal bleeding; they may be a better alternative for people who cannot take NSAIDs due to allergies or kidney or liver issues.

But opioid use for chronic (non-cancer) pain is controversial because they're associated with a high risk of abuse, addiction and accidental overdose. Certain factors predict the suitability of long-term opioid use for individuals with chronic pain. A tool called DIRE (Diagnosis, Intractability, Risk and Efficacy) helps doctors to assess those factors – including the patient's cause of pain, psychological health, chemical health and social support. A high composite score suggests the person is

likely to gain the greatest benefits from opioid analgesics with the least risk of adverse effects. Opioid analgesics are not appropriate for people at risk of addiction (Arthritis.org, 2017).

1.3 Tolerance and dependency

Most people can take the simple analgesics and NSAIDS without developing a dependency on these drugs.With opioids, in the longer term, however, people may develop a tolerance to the medications resulting in a reduction of efficacy. With tolerance comes breakthrough withdrawal, which can be worse than the pain which occasioned the use of analgesics initially. A typical example of this is analgesic rebound headaches which can result in the patient taking more pills to reduce the ever increasing pain – resulting in a chronic headache which becomes difficult to treat.Chronic pain of any type is difficult to treat because of the effect of tolerance. It is considered that all long term users of opioids will develop physical dependence and it is, therefore essential that the amount of medication is not increased beyond certain limits. (Reconnexion.org.au,2017).Although opioids provide effective analgesia, largely unsubstantiated concerns about opioid-induced tolerance, physical dependence and addiction have limited their appropriate use. As a consequence, many patients receive inadequate treatment for both malignant and non-malignant pain. However, it has been shown that analgesic tolerance develops less frequently during chronic opioid administration in a clinical context than in animal experiments, and that instituting an appropriate dosing regimen can minimise withdrawal symptoms. Early studies had suggested that addiction might result from chronic opioid therapy, though more recent data indicate a low risk in patients with no history of drug abuse. New treatment regimens may also reduce the risk of tolerance, physical dependence and addiction. Long-acting preparations, such as transdermal fentanyl and possibly some forms of other slow release opioids, which maintain constant opioid concentrations in the plasma, minimise the occurrence of the

'between-dose' symptoms such as withdrawal and opioid-induced euphoria. This review discusses the development of tolerance, physical dependence and addiction during opioid therapy, and the influence of these factors on the choice of treatment (researchgate, 2017).

1.4 Analgesics in geriatric patients

Pain is a widespread symptom in clinical practice. Older adults and chronically ill patients are particularly affected. In multimorbid geriatric patients, pharmacological pain treatment is an extension of a previously existing multimedication. Besides the efficacy of pain treatment, drug side effects and drug-drug interactions have to be taken into account to minimize the health risk for these patients. Apart from the number of prescriptions, the age-related pharmacokinetic and pharmacodynamic changes significantly increase the risk among older adults. The use of non-steroidal anti-inflammatory drugs (NSAID) is widespread but NSAIDs have the highest risk of adverse drug reactions and drug interactions. In particular, the gastrointestinal, cardiovascular, renal and coagulation systems are affected. Apart from the known toxic effect on the liver (in high doses), paracetamol (acetaminophen) has similar risks although to a lesser degree. According to current data, metamizol is actually better than its reputation suggests. The risk of potential drug interactions seems to be low. Apart from the risk of sedation in combination with other drugs, tramadol and other opioids can induce the serotonin syndrome (Goach, 2017).

1.5 Pain Management in the Elderly Population

The elderly population comprises the fastest growing segment of the world's population. As patients age, the incidence and prevalence of certain pain syndromes increase. Pain may be underreported as some elderly patients incorrectly believe that

pain is a normal process of aging. A comprehensive pain assessment includes a thorough medical history and physical examination, review of systems and pertinent laboratory results, imaging studies, and diagnostic tests. Pain physicians should have a broad range of understanding of the pharmacologic and physiological changes that occur in the geriatric population. The present review on pain management in the elderly focuses on relevant information for the pain clinician. Included are appropriate pain assessment, physical examination, pathophysiologic changes in the elderly, pharmacokinetic and pharmacodynamic changes, and present pain management modalities. Elderly patients present with increased fat mass, decreased muscle mass, and decreased body water, all of which have important ramifications on drug distribution. Hepatic phase I reactions involving oxidation, hydrolysis, and reduction appear to be more altered by age than phase II conjugation such as acetylation, glucuronidation, sulfation, and glycine conjugation. There is a predictable age-related decline in cytochrome P-450 function and, combined with the polypharmacy that much of the elderly population experiences, this may lead to a toxic reaction of medications (Alan D. Kaye, 2017).

1.6 Analgesic for medical conditions

Virtually any disease as well as most injuries and surgical procedures involve some degree of pain. It's not surprising, then, that pain medications, also known as analgesics, are among the most commonly used drugs in the U.S. Different medications are used depending on the type of pain. For minor complaints, such as muscle sprains or headaches, an over-the-counter (OTC) pain reliever will usually do. Prescription pain relievers, especially opiate analgesics -- are normally reserved for moderate-to-severe pain – such as that seen after surgery, trauma, or from certain diseases like cancer or rheumatoid arthritis. Other common "painful"

situations in which analgesics find use include labor, back pain, fibromyalgia, and urinary tract infections and also use for the followings Heart Attack, Myocardial Reinfarction Prevention, Treatment to Prevent a Heart Attack, Acute Syndrome of the Heart, Unpredictable Severe Constricting Chest Pain, Prevention for a Blood Clot going to the Brain, Acute Thromboembolic Stroke, Transient Ischemic Attack, Prevention of Transient Ischemic Attacks, Blood Clot Prevention Following Percutaneous Coronary Intervention, Rheumatoid Arthritis, Joint Inflammatory Disease in Children and Young Adults, Joint Damage causing Pain and Loss of Function (WebMD, 2017).

1.7 Clinical pharmacology of analgesics in frail older people

Rational prescribing of analgesics in frail older people is complex due to heterogeneity in drug disposition, comorbid medical conditions, age-related changes in body composition, polypharmacy and variability in analgesic response in this population. In general terms, the pharmacologically-guided approach to optimizing pain management requires a systematic understanding of the pharmacokinetics and pharmacodynamics of analgesics in the target population to inform drug and dose regimen selection. The implementation of the dose regimen then requires careful monitoring of efficacy and safety with dose titration. In the absence of rigorously controlled trials in frail older people, an understanding of the changes in these parameters enables greater confidence in prescribing. The following sections review the evidence of the effects of age and frailty on the pharmacokinetics and pharmacodynamics of paracetamol and selected opioids. While a number of analgesic medicines may be commonly used in older people, some analgesics pose an unacceptable risk to frail older people who may also be cognitively impaired due to the risk of potential medicine related harms. Non-steroidal anti-inflammatory drugs (both selective and non-selective NSAIDs) are generally accepted as posing a risk of

life-threatening gastrointestinal bleeding and significant adverse effects on renal function in the frail older patient . Due to the risk of drug–drug and disease–drug interactions in frail older people NSAIDs are not reviewed here but have been considered by others . Pethidine has an active metabolite that has the potential to accumulate in older people with renal impairment . Dextropropoxyphene has a long half-life in older people and has been associated with a significant risk of side effects in older people . Despite their wide use the weak opioid agents codeine and tramadol have a limited role in frail older people, especially those with cognitive impairment, due to the risk of significant drug–drug and drug–disease interactions as well as considerable variability in response and adverse effects . Both codeine and tramadol are metabolized by CYP2D6 to active metabolites such that pharmacogentic determinants or drug interactions have the potential to shift significantly the harm to benefit ratio for these medicines in this patient population. A number of these analgesics carry an unacceptable risk of falls and fracture in older people which highlights the need to limit their use (Thomson, 2005).

1.8 Physiologic changes with aging

Opiates are highly varied, however except for fentanyl and methadone, it is generally thought that they possess similar pharmacokinetic activity. In general young adults, opiates are rapidly absorbed in the gut, have high rate of first pass in the liver, are conjugated in the liver, have metabolites, and vary in distribution based on their differing protein affinity, and then are excreted via bile to feces or via kidneys. It is important to understand normal age-associated changes in the pharmacokinetic and pharmacodynamic action of drugs. Pharmacodynamic affects are complex and depend upon poorly measured variables such as receptor function and intracellular response which can alter drug action. Pharmacokinetic actions of drug absorption,

distribution, and elimination are more measurable. In general, the rate at which certain drugs are absorbed can be altered in the elderly because of decreased gastrointestinal transit time and increased gastric pH secondary to use of proton pump inhibitors, H_2 receptor antagonist, or antacids. With aging, there are changes in body composition: increase in adipose tissue, decrease in lean body mass and decrease in total body water. These changes can affect drug distribution.

Therefore, lipophilic drugs tend to have greater volume of distribution, and it can take more time to be eliminated from the body. Aging can also bring reduction in hepatic blood flow and volume which can decrease metabolism of drugs. Additional impairments in drug metabolism can occur with impaired Phase I reactions which include oxidation, hydroxylation, and dealkylation. This can specifically reduce the first pass affect of opiates in elderly .Elimination of drugs can be altered with age related reductions in renal blood flow and glomerular filtration rate. For opiates that have primary renal clearance, such as morphine and hydromorphone, decreases in GFR lead to more side effects .The above changes generally cause drugs used in elderly to be more potent and have a longer duration of action than predicted (Diane L Chau, 2017).

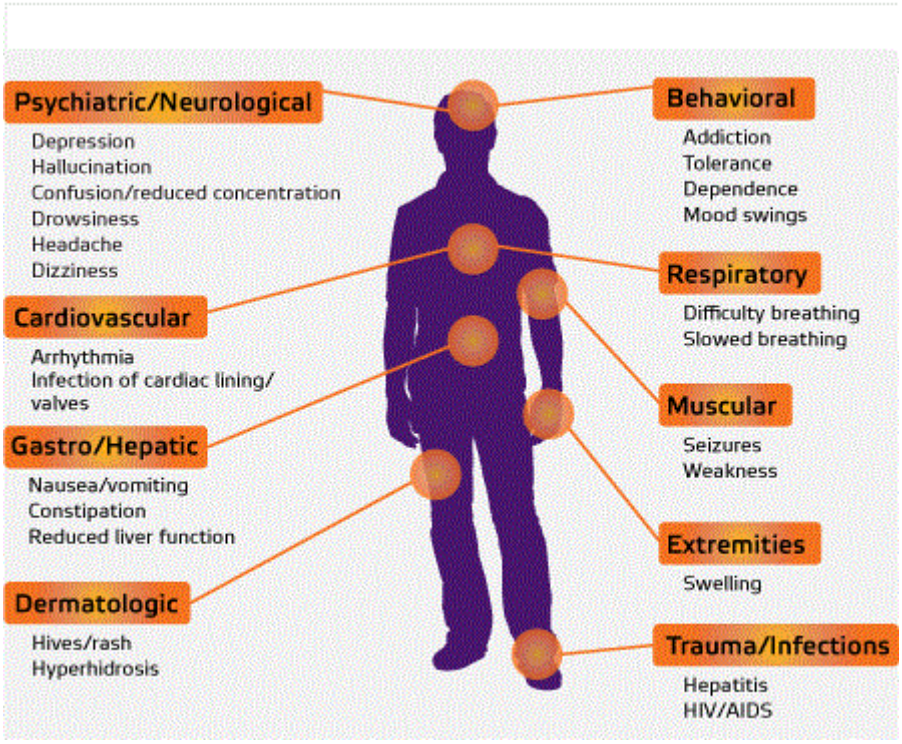

Figure:- ADR of Opioid

1.9 Adverse Drug events due to Opioids

1.9.1 Urinary retention

Urinary retention is the anticholinergic side effect of opioids and can be secondary to opioid-induced constipation (Diane L Chau, 2017). .

1.9.2 Central nervous system adverse effects

Sedation and mild cognitive impairment are the other common side effects of opioids in elderly Combinations of opioids and other central nervous system (CNS) depressant drugs such as barbiturates, benzodiazepines, antidepressants, and antipsychotics may have additive effects on sedation. Since most of the elderly are on polypharmacy, a careful review of medications is crucial while they are on opioid therapy . Myoclonus is the other CNS adverse effect and occurs in patients with

chronic opioid therapy. It appears to be dose related and more common with oral morphine than parenteral which suggests it may be due to a production of morphine metabolites by the liver (Diane L Chau, 2017).

1.9.3 Pruritis

Pruritis develops in about 2%–10% of patients with opioid use. This generally resolves within one week.

1.9.4 Respiratory depression

The agonist activity of opioids at the μ-opiate receptors is very important clinically in the alleviation of pain. However; it is also the cause of an unwanted side effect which is the marked depression of breathing that can complicate their clinical administration and be potentially life threatening when opiates are abused. The degree of respiratory depression depends upon the serum level of opioids. First, patients become somnolent, and then they become less arousable and finally obtunded. The pattern of respiration becomes shallower and slower. Naloxone is the opioid receptor antagonist and is not recommend for use until the patient's respiratory rate is less than 8 breaths per minute or the oxygen saturation is less than 90%. This is done to avoid pain crisis and acute withdrawal symptoms (Cavalcante et al., 2016).

1.9.5 Hyperalgesia

Patients who are receiving increasing doses of opioids may have opioid-induced hyperlagesia. This is the phenomenon of increasing sensitivity to both pain (hyperlagesia) and nonpainful stimuli (allodynia). The mechanism of action is due to toxic metabolites of opioid (morphine-3-glucuronide (M3G) or hydromorphone-3-glucronide (H3G), activation of N-metyl-D-asparate (NMDA) receptors in the CNS.

Since it is due to the effect of toxic metabolites, the other opioid hyper excitability effects such as myoclonus, delirium or seizures can also be present (Lorenzetti and Ferreira, 1985).

1.9.6 Cardiovascular system

QT prolongation and torsades de pointes were found to take place in individuals infected with HIV and treated with methadone. Methadone dose correlated positively with the QTc interval prolongation. This finding supports the possibility that methadone contributed to the development of arrhythmias (Gooding And Corssen, 1977).

1.9.7 Delirium adverse drug events

A systematic review of medications (including opioids) that may increase the risk of delirium in older adults. Opioids had more than a two-fold increased risk of delirium. Opioid use was converted to parenteral morphine equivalents (PME) per day. Of all the individual opioids used, meperidine had the highest increased risk of delirium. In a study, those who had severe pain measured by a 5-point Likert scale had a 9-fold increased risk of delirium. This latter point suggests that while opioids do have an increased risk of delirium, under treating severe pain may be riskier. This issue of controlling for confounding by indication/severity is an important consideration that will be revisited below. Further studies examining the risk of opioids on cognitive function in older adults in other care settings are needed (Giacoia, 2001).

1.9.8 Renal Failure

Opioid Use It is important to note that opioids are commonly used safely in anesthesia and pain control in the perioperative period in those with kidney disease.

The renal toxicity appears in the context of inappropriate use: either inadvertently higher than needed doses, in the presence of other toxins, with pre-existing dehydration, or prostate enlargement. Chronic use of opioids, results in greater incidence of toxicity due to accumulation of metabolites, which could cause unwanted side effects. One reason is that with chronic use, a steady state of the drug is reached with distribution and accumulation in the various body compartments. With a pro-drug that is metabolized to morphine, both the drug and the intermediary metabolite levels may also build up in the various compartments, resulting in unwanted side effects. Opioid overdose can result in acute kidney injury (AKI) due to dehydration, hypotension, rhabdomyolysis, and urinary retention. CKD may result due to the mode of administration of the drug: skin-popping resulting in amyloidosis. Heroin-associated nephropathy (HAN) is now considered to be related to a toxin introduced into the heroin during the processing of the drug. Administration methods like intravenous drug abuse may also result in the spread of hepatitis B and C and human immunodeficiency virus (HIV). There have been three case reports of renal lipoidosis on kidney biopsy in patients on methodone, however, confounding factors, including hepatitis B and C, were noted in these cases (Elseviers and De Broe, 1993).

1.9.8.1 Mechanisms of Kidney Damage

with Opioid Use There are complex interactions within the body's neuroendocrine systems in response to opioids that are described below, including alterations in the autonomic nervous system (sympathetic and parasympathetic nervous system), the renin–angiotensin–aldosterone system and anti-diuretic hormone. In addition, there are also other mechanisms involved including dehydration, rhabdomyolysis and urinary retention. These changes may be measured by levels of neurotransmitters, hormones, cytokines and various peptides. The levels of the factors being measured

are specific to the site where they are measured (cardiac, plasma) and their role and as either initiating or as a compensatory response. Further local versus systemic levels of the substance and additive pathologic states due to co-morbidities also need to be considered in the pathophysiology of opioid related kidney damage (Elseviers and De Broe, 1993).

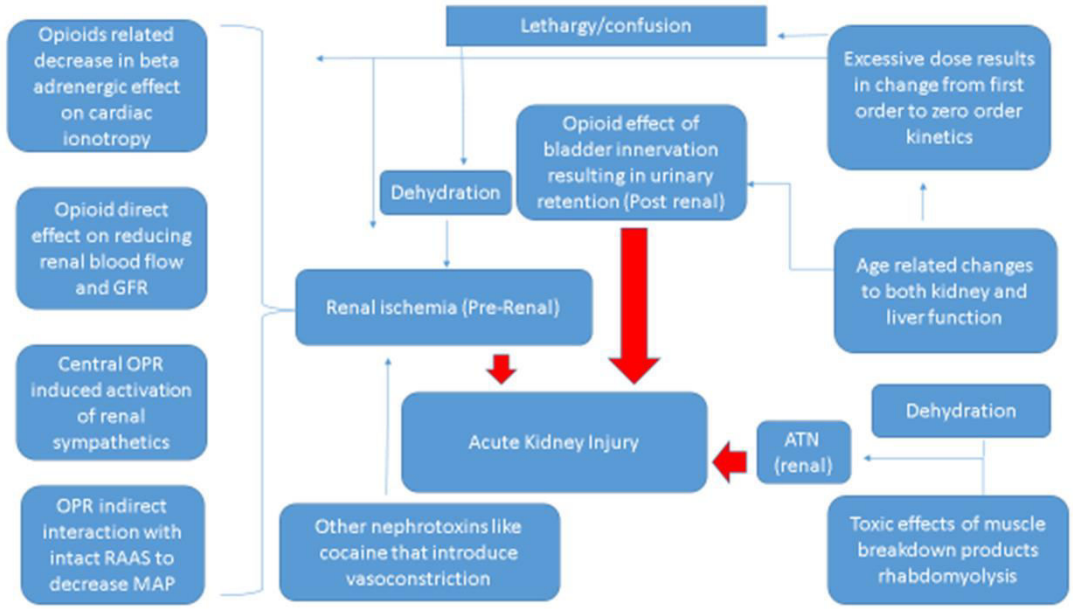

Figure:- Mechanism of opioid-related kidney failure

1.9.9 Endocrine system effects

Opioids have effects on two levels in the endocrine system: hypothalamic-pituitary-adrenal axis and also on the hypothalamic-pituitary-gonadal axis resulting in reduced serum luteinizing hormone, cortisol levels and increased prolactin levels. Diminished bone density, decreased libido and impaired sexual performance are reported with chronic opiate use. Heroin use results in acute suppression of luteinizing hormone (LH) release from the pituitary followed by a secondary drop in plasma testosterone levels.

1.9.10 Constipation

Opioid peptides and opioid receptors are distributed along the gastrointestinal (GI) tract, indicating endogenous opiates released peripherally may modulate GI motor and secretory functions. Most opiates that have a selective or predominant mu agonist activity inhibit gastric motility and delay gastric emptying by acting centrally; delta and kappa agonist are inactive when injected systemically. This increase in colonic motility and the delay in colonic transit are associated with a reinforcement of tonic contractions and reduced propulsive waves. This in turn leads to opiate induced constipation (O'Neil, Hanlon and Marcum, 2017).

1.9.11 Nausea

The mechanism of action of opioid-induced nausea is through the direct stimulation on chemoreceptor trigger zone (CTZ), which detects noxious chemicals in the blood and sends signals to the vomiting center (VC) in the medulla and initiates the vomiting reflex. The other mechanisms are through the direct stimulation of the vestibular apparatus and anticholinergic effects on the gastrointestinal system (O'Neil, Hanlon and Marcum, 2017).

1.10 Age-related changes in NSAID pharmacokinetics

There have been several publications that have been reviewed the pharmacokinetics of NSAIDs. In general, most of these agents are extensively hepatically metabolized by Phase I cytochrome P450 isoenzymes. Most NSAIDs are well-absorbed and highly plasma protein bound. Therefore, frail elders with hypoalbuminemia are likely to have higher free drug concentrations. Some agents have longer half-lives in older adults when compared to those determined in younger adults (i.e., celecoxib, diflunisal, naproxen, oxaprozin, piroxicam, sulindac). It is unknown whether these

changes in pharmacokinetics are responsible for increases in NSAID ADEs (O'Neil, Hanlon and Marcum, 2017).

1.11 Adverse drug events due to NSAIDS

NSAIDs have been shown to increase the risk of several outcomes in older adults. These include GI, cardiovascular/cerebrovascular and renal adverse drug events as well as cognitive effects.The risks of NSAIDs need to be balanced by their analgesic effectiveness for pain not controlled by APAP, and diligent monitoring and patient education is essential to preventing adverse drug events. In general, if an NSAID is required one should consider the use of nonacetylated salicylates as they rarely cause GI bleeding, and they do not interfere with platelet function, even in patients taking aspirin (Rahme et al., 2004).

1.11.1 Gastrointestinal adverse drug events

Recently, an evidence-based table was published as part of the updated 2012 Beers criteria for the risk of GI toxicity associated with NSAID use. However, there are some additional studies worth discussing, which are summarized in. The incidence of serious GI side effects associated with the use of oral NSAIDS (and acetaminophen). The adjusted hazard ratio (HR) for GI-related hospitalization (perforation, ulcer, bleeding) was higher in patients receiving oral non-selective NSAIDs than in patients being treated with low dose (≤3g/day) acetaminophen. It was also shown that patients receiving high dose (>3g/day) had a higher risk of GI hospitalization compared to those receiving low dose APAP (1.20, 95% CI 1.03–1.40). However, the HR was highest among those patients treated with NSAIDs plus high dose APAP (2.55, 95% CI 1.98–3.28). Multiple studies support this finding of an increased risk of GI-related adverse drug events due to non-selective NSAIDs. However, the

compounded deleterious effect of APAP on NSAID-related GI side effects is less well-established, and future research is needed (Publications, 2017).

1.11.2 Cardiovascular adverse drug events

Ibuprofen, aspirin, and COX-2s all belong to the class of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). Most of them boost blood pressure and can counteract the effect of some blood-pressure drugs. They can also impair blood vessels' ability to relax and may stimulate the growth of smooth muscle cells inside arteries. All these changes can contribute to the artery-clogging process known as atherosclerosis.

Researchers have determined that use of a COX-2 inhibitor increases the chances of having a heart attack. Vioxx, which was taken off the market because of possible heart complications, may lead to or worsen heart failure-but so can traditional NSAIDs. In general, cardiovascular side effects are most likely to happen in people with existing heart disease or those at high risk for it (Publications, 2017).

1.11.3 Renal adverse drug events

NSAIDs depress prostaglandins synthesis through inhibition of COX-1 that is involved in maintaining cell integrity and COX-2 that, although presents particularly in the kidneys, is overexpressed in response to inflammation. Both the beneficial and side effects of NSAIDs are, therefore, through their inhibition of COX enzymes. Introduction of COX-2-selective inhibitors has improved the safety profile of the drugs with regard to their most common side effect which occurs at the gastrointestinal level but has not rendered them less cardio-nephrotoxic. Renal side effects of NSAIDs are rare, sometimes transient and often reversible upon drug withdrawal. The incident rate and the severity of the renal side effect, however, increase in

patients with risk factors such as those with diabetes, heart failure, renal dysfunction and in the elderly. The side effects range from electrolyte retention and reduce glomerular filtration to nephritic syndrome and chronic renal failure. These effects are shared among NSAIDs with evidence of dose and exposure dependency. There is no known predictor for the nephrotoxicity. However, a relationship has been found between high plasma concentration and the renal adverse effect of NSAIDs. The usefulness of therapeutic drug monitoring in patients with risk factors needs to be explored (O'Neil, Hanlon and Marcum, 2017).

1.12 Paracetamol

Paracetamol is an effective agent for pain relief and is generally regarded as a safe medication at therapeutic doses. It is widely used in elderly patients with recommendations that are common to those for adults. Recent reports have however questioned the safety of recommended doses and suggest that the elderly patient might be at an increased risk of developing adverse events when on paracetamol treatment. Glutathione depletion, polymedication including CYP450 inducing drugs and anticoagulant therapy, increased incidence of organ insufficiency with age, malnutrition, dehydration, fragility are factors that may favour the development of serious adverse events. While the benefit/risk ratio of paracetamol is evident in clinical practise, clinicians should be aware of the potential and preventable adverse side-effects of this centenarian pain treatment favourite analgesic. When metabolized in the liver, small amounts of an intensely active metabolite, which is normally immediately inactivated by glutathione, are produced. An overdose causes a glutathione deficiency; the reactive metabolite may then cause hepatocellular damage and necrosis leading to acute liver failure. Toxic effects have been observed in adults treated with doses of more than 10 g (20 tablets). However, if there is a pre-

existing liver insufficiency, paracetamol can be hepatotoxic even in small amounts (Infomed.ch, 2017).

1.12.1 Major Side Effects of Paracetamol

- Bloody or black, tarry stools
- Bloody or cloudy urine
- Fever with or without chills (not present before treatment and not caused by the condition being treated)
- Pain in the lower back and/or side (severe and/or sharp)
- Pinpoint red spots on the skin
- Skin rash, hives, or itching
- Sore throat (not present before treatment and not caused by the condition being treated)
- Sores, ulcers, or white spots on the lips or in the mouth
- Sudden decrease in the amount of urine
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Yellow eyes or skin.

1.13 Potential drug interactions with OTC analgesics

The risk of drug interactions with concurrent use of multiple medications is a clinically relevant issue. Many patients are unaware that over-the-counter (OTC) analgesics can cause potentially serious adverse effects when used in combination with other common medications such as anticoagulants, corticosteroids, or antihypertensive agents. Of particular significance is the increased risk of upper abdominal gastrointestinal adverse events in patients who take traditional nonsteroidal anti-

inflammatory drugs (NSAIDs). This risk is dose dependent and further increased in patients who take more than one NSAID or use NSAIDs in combination with certain other medications. Some NSAIDs may also mitigate the antiplatelet benefits of aspirin and may increase blood pressure in patients with hypertension. Clinicians should be aware of potential drug interactions with OTC analgesics when prescribing new medications. Additionally, patients should be properly counseled on the appropriate and safe use of OTC analgesics (Moore and Derry, 2012).

1.13.1 Increased GI bleeding risk

Inhibition of COX by aspirin and other NSAIDs interferes with the production of protective mucosal PGs . This mechanism likely explains the increased incidence of gastric ulcers and upper GI bleeding with use of NSAIDs. Listed below are several risk factors that increase the likelihood of developing GI toxicity with NSAIDs use .

• Advanced age

• History of GI events

• Increased NSAID dose or multiple NSAID use

• Concomitant aspirin use.

Elderly patients are at greater risk of developing GI complications and often have comorbidities that require analgesic treatment. Thus, careful monitoring of the amount of OTC and prescription NSAID consumption is imperative in the management of elderly patients. To minimize GI adverse events, proton-pump inhibitors (PPIs) or other gastroprotective agents may be useful for patients who require NSAIDs for anti-inflammatory therapy and are at risk for increased GI events (Smalley, 2002).

1.13.2 Interference with the antiplatelet effects of aspirin

Many patients use low-dose aspirin for primary or secondary prevention of myocardial infarction and stroke. Aspirin induces irreversible COX-1 inhibition in the platelet, a process that in turn inhibits the formation of thromboxane A_2 and prevents platelet aggregation . Because aspirin completely inactivates platelet COX-1, antiplatelet benefits last for the lifetime of the platelet and are only attenuated by the regeneration of new platelets. As a result, even low doses of aspirin may provide beneficial CV effects. Nevertheless, recent studies have shown that traditional NSAIDs may interfere with the antiplatelet effects of aspirin by providing competition for the platelet COX-1 binding site . This may limit the utility of aspirin as a cardioprotective agent in patients who require certain NSAIDs to manage pain effectively.

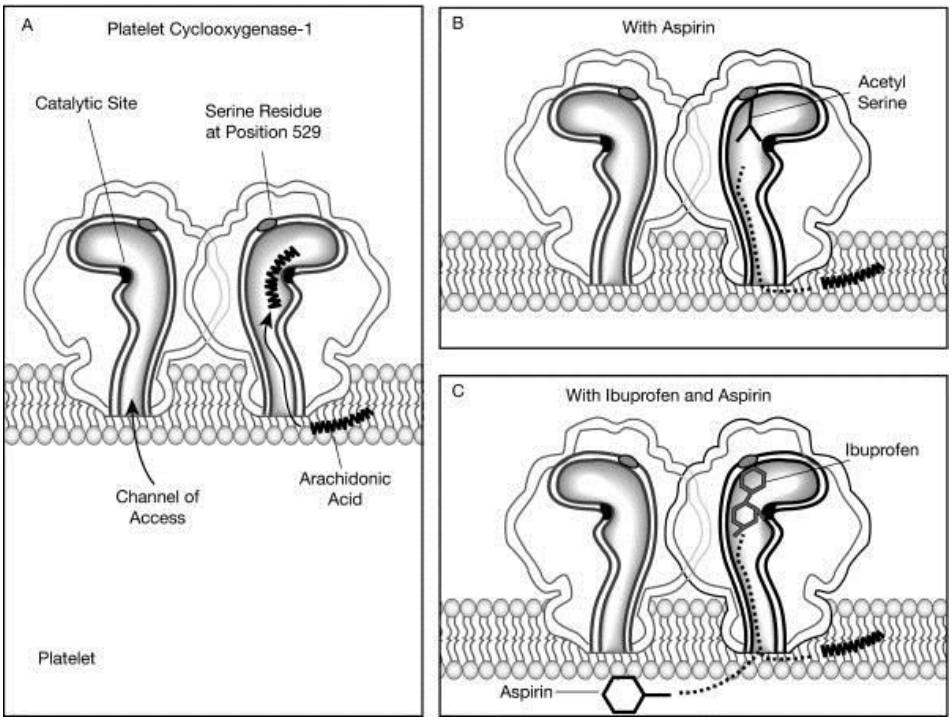

Figure:- antiplatelet effects of aspirin

1.13.3 Other potential interactions and issues

By inhibiting prostaglandin synthesis, NSAIDs can induce sodium retention and vasoconstriction . Clinical studies have linked the use of NSAIDs to elevated blood pressure, particularly in patients with a history of hypertension who are already on antihypertensive medications . In a meta-analysis of randomized trials studying the effect of NSAIDs on blood pressure, NSAIDs raised mean blood pressure by 5.0 mm Hg . Patients who were concomitantly using β-blockers experienced greater elevations in mean blood pressure (6.2 mm Hg) compared with those using either vasodilators or diuretics. Careful monitoring of blood pressure and cardiac function is therefore recommended for hypertensive patients when initiating NSAID therapy. The potential risk of CV events with use of NSAIDs has been studied extensively in recent years. In 2005, the US Food and Drug Administration issued a request that manufacturers of all nonaspirin NSAIDs, including COX-2 inhibitors, revise package inserts to include a black box warning highlighting the increased risk for CV events and GI bleeding with use of these drugs (Fendrick, Pan and Johnson, 2017).

Chapter 2
Literature Review

2. Literature review

2.1 Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: a cross-sectional prevalence study

The treatment of pain caused by multiple myeloma first starts with therapy directed at disease control, using cytotoxics, biological targeted drugs, radiotherapy and corticosteroids. Bone disease is also managed systemically using bisphosphonates, which are used principally to reduce future skeletal-related morbidity and may also reduce pain. In addition, local pain control may be achieved using vertebroplasty or balloon kyphoplasty for vertebral fractures and surgical fixation for unstable long bones or spine. Alongside these tumour-directed and supportive care measures, most patients with MM also receive pharmacological analgesic therapy, including opioid drugs.The recognition of specific side effects of prescribed analgesics is of great importance in the effective management of pain and optimisation of health-related quality of life (HRQoL) .In a large US survey of 501 patients with terminal cancer, of whom 52 % reported having 'moderate to severe pain', additional pain therapy was only sought by 29 % of them. The reasons for not seeking additional therapy in terminal cancer patients who had been seen by their primary physician within the previous 4 weeks included: fear of addiction (37 %), fear of physical side effects (33 %), fear of mental side effects (34 %) and fear of pills and injections (29 %). Whilst some of these concerns represent real hazards of cancer pain treatment, it has been suggested that the adoption of a more multimodal pain strategy, with greater emphasis on the newer opioids, the use of non-opioids acting on the NMDA receptor and earlier use of non-pharmacological approaches, could reduce the emergence of adverse effects and thus improve patient experience (Sloot et al., 2014).

2.2 Perceptions of Analgesic Use and Side Effects: Public Values in Pain Management, texas, USA

In this population-based telephone survey, we evaluated the attitudes of 302 adults toward analgesic use and related side effects. Over half (68%) reported prior experience with 2 or more side effects. Vomiting (34%), confusion (32%), and nausea (17%) were ranked as the worst side effects. Exploratory cluster analysis grouped responses to 6 questions about willingness to use analgesics into two categories. Participants in Cluster I (n _ 106), “Conservatives,” were less willing to take analgesics for pain as compared to those in Cluster II (n _ 153), “Liberals.” Univariate analysis found Hispanics, women, those less affluent or educated, and those with prior side-effect experience were more likely to be Conservative. Experience with side effects (OR _ 1.3) and being female (OR _ 2.1) were the strongest predictors of conservative cluster membership. To achieve better pain outcomes, clinicians and patients must identify factors that contribute to conservative decisionmaking about analgesic use and side effect management (Palos et al., 2004).

2.3 A questionnaire based survey study for the evaluation of knowledge of pakistani university teachers regarding their awareness about ibuprofen as an over the counter analgesic

In recent time, due to convenient availability of number of over the counter (OTC) drugs, patients are able to treat minor ailments by themselves. The self-medicated regimen has lead to certain health problems in all age groups irrespective of their professions. People are usually unaware about the safe use of NSAIDs (non-steroidal anti-inflammatory drugs) and currently there is no study carried out in COMSATS Institute of Information Technology (CIIT), Abbottabad, regarding the

choice of faculty members for NSAIDs to relieve pain and their knowledge about its safety and use. A questionnaire based survey was carried out to collect data about the choice of CIIT faculty for a specific NSAID and their cognition related to ibuprofen. Two hundred fifty faculty members (comprising of 53 pharmacy faculty members and 197 faculty members who belonged to other departments) of which 87 were females, took part in this study. Average age of participants was 34.86 ± 9.02 years. Ibuprofen was the drug of choice NSAID among the participants. Four percent participants experienced pain almost every day. Analgesia was the well known indication for ibuprofen (31%) by both the groups and in general more educated and younger participants showed better apprehension related to indications. Sixty one percent participants comprising of non-pharmacy faculty were unaware of any undesirable effects and 79% (comprising of 72% pharmacists and 5% non-pharmacists) were affirmative that ibuprofen had no adverse effects. Fifteen percent participants of department other than pharmacy were not aware of any interactions of ibuprofen. 34% of participants (comprising of 32% non-pharmacists and 2% pharmacists) entrusted their physician

for an analgesic. Regardless that many participants suffered from pain almost every day and their drug of choice would be ibuprofen, they had inadequate information related to the safety and use of ibuprofen (Vilches, 2004).

2.4 Use of anti-inflammatory and analgesic drugs in an elderly population registered with a Family Health Program

The aim of this study was to analyze the prevalence of the use of anti-inflammatory and analgesic drugs among elderly persons from the Family Health Program in Porto Alegre, Rio Grande do Sul, and investigate associated factors such as sociodemographic and health data; continuous or as needed use of drug, drug used subject to medical prescription or self-medicated. Data collection occurred between

March 2011 and December 2012. Community health workers applied a questionnaire relating to sociodemographic and health data and medication use. Non-steroidal anti-inflammatory drugs, glucocorticoids, non-opioid analgesics and opioids were evaluated. A total of 758 elderly persons were included and anti-inflammatory and analgesic drugs were used by 28.8% of the population. Acetaminophen and ibuprofen were the most frequently used drugs. Regarding self-perception of health, the worse the perception of

health, the greater was the use of therapy ($p<0.001$). Liver disease and osteoarthritis/ arthritis/rheumatism were found to be associated with anti-inflammatory and analgesic use ($p<0.001$). The prevalence of anti-inflammatory and analgesic use was considered moderate when compared to previous studies (28.8%). In addition, most of the elderly persons used the drugs when only needed, most probably due to feeling minor to moderate pain or because they had suffered the adverse effects of these medications in the past and so chose to use them sporadically (Nuki, 1990).

2.5 Side Effects From Oral Opioids in Older Adults During the First Week of Treatment for Acute Musculoskeletal Pain

This was a cross-sectional study of individuals age 65 years or older initiating analgesic treatment following emergency department (ED) visits for acute musculoskeletal pain. Patients were called by phone 4 to 7 days after their ED visits to assess the intensity of six common opioid-related side effects using a 0 to 10 scale and to assess medication discontinuation due to side effects. Propensity score matching was used to compare side effects among patients initiating treatment with any opioidcontaining analgesics to side effects among those initiating treatment with only nonopioids. Of 104 older patients initiating analgesic treatment following ED visits for musculoskeletal pain, 71 patients took opioid-containing analgesics, 15 took

acetaminophen, and 18 took ibuprofen. Among the patients who took opioids, at least one side effect of moderate or severe intensity (score ≥ 4) was reported by 62%. Among patients with matching propensity scores, those taking opioids were more likely to have had moderate or severe side effects than those taking only nonopioids (62%, 95% confidence interval [CI] = 48% to 74% vs. 4%, 95% CI = 1% to 20%) and were also more likely to have discontinued treatment due to side effects (16%, 95% CI = 8% to 29% vs. 0%, 95% CI = 0% to 13%). The most common side effects due to opioids were tiredness, nausea, and constipation. discontinued treatment due to side effects (16%, 95% CI = 8% to 29% vs. 0%, 95% CI = 0% to 13%). Themost common side effects due to opioids were tiredness, nausea, and constipation (Hunold et al., 2013).

2.6 Persistent nonmalignant pain management using nonsteroidal anti-inflammatory drugs in older patients and use of inappropriate adjuvant medications.

Due to the high risk of life-threatening side effects, nonsteroidal anti-inflammatory drugs (NSAIDs) are not favored for treating persistent nonmalignant pain in the elderly. We report national prescription trends with determinants of NSAIDs prescription for persistent nonmalignant pain among older patients (age 65 and over) in the US outpatient setting. A cross-sectional analysis was performed using National Ambulatory Medical Care Survey data. Prescriptions for NSAIDs, opioids, and adjuvant agents were identified using five-digit National Ambulatory Medical Care Survey drug codes.About 89% of the 206,879,848 weighted visits in the US from 2000 to 2007 recorded NSAIDs prescriptions in patients (mean age =75.4 years). Most NSAIDs users had Medicare (75%), and about 25% were prescribed with adjuvant medications considered inappropriate for their age. Compared to men, women were 1.79 times more likely to be prescribed NSAIDs. The high percentage of

NSAIDs prescription in older patients is alarming. We recommend investigating the appropriateness of the high prevalence of NSAIDs use among older patients reported in our study (Rasu et al., 2015).

Chapter 3
Methodology

3. Methodology

3.1 Type of study

The study was a questionnaire based study.

3.2 Study Area

The study was conducted in many hospitals in Dhaka and Sylhet in Bangladesh.

3.3 Study Population

The study was performed on 67 women and 55 male , from January, 2017 to April, 2017.

3.4 Inclusion Criteria

In this survey both male and female were included.

3.5 Exclusion Criteria

In this survey,

- Children's under age of 18 are exclusion from the study

3.6 Study Tool

To facilitate the study of knowledge and attitude about analgesics use and there side effects in Bangladesh, a questionnaire was established in November 2016. Through this questionnaire, demographic information was collected along with some medical information and knowledge and awareness information.

3.7 Questionnaire Development

The questionnaire was developed based on some common criteria that influence knowledge and awareness of analgesics use and side effects in other country.

Questionnaire (Intentionally kept incomplete)

Demographic Information

1. Age: _____

2. Gender: □ Male □ Female

Medical Information

5. Medical condition that requires an analgesic(s):_____

6. Name of the analgesic (s): Brand name_____

Knowledge and Awareness information:

9. When prescribed an analgesic, did the doctor discuss the possible side effects?

□ Yes □ No

13. Were you given any special instructions while taking the medication?

□ medications that you must avoid when taking your analgesics:

_____

3.8 Data Analysis

After data collection, these data were set on the Microsoft Office Excel and filtered out according to the age range, educational qualification, Medical condition that requires analgesic medication, Patients knowledge about Indication, Side effects and instruction during taking medication.

3.9 Ethics

This study was done without conflicting the ethical issues. Ethical consideration was checked by the research supervisor with the research policy of the East West University. Oral consent was taken prior to study from the participants.

Chapter 4
Result

4.1 Demographic information

4.1.1 Age of respondents

Table 4.1.1 : Age of respondents

Age	Total Number	Percentage (%)
20-39	62	50.81
40-59	44	36.07
60 and above	16	13.11

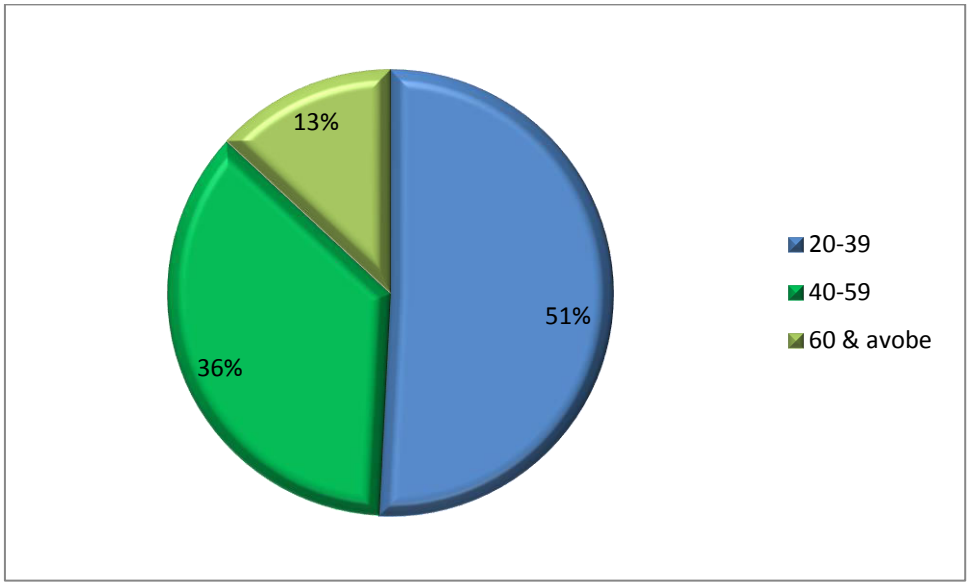

Figure: Age of respondents

The study showed that among 122 peoples, 51% of the population belonged to the age group 20-39, 36% of the population belonged to the age group 40-59, 13.11% of the population belonged to the age group above 60.

4.1.2 Gender

Table 4.1.2 : Gender

Gender	Total Number	Percentage (%)
Male	52	45.08
Female	67	54.92

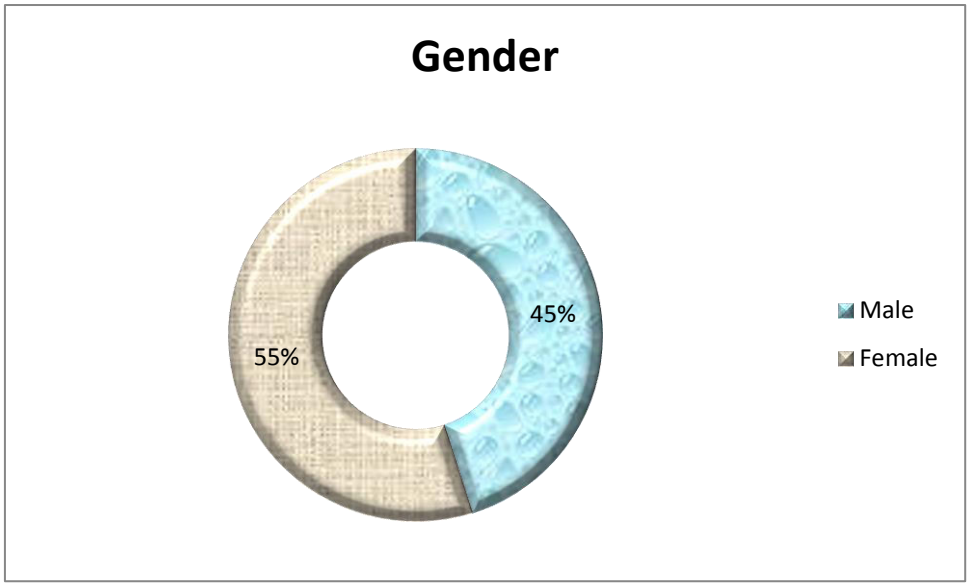

Figure: Gender

Majority of the respondents about 55% was female and 45% male

4.1.3 Education level

Table 4.1.3 : Education level

Education level	Total Number	Percentage (%)
Illiterate	23	18.85
Primary school certification	11	9.01
High school certification/college	46	37.70
Graduate/Post Graduate	42	34.42

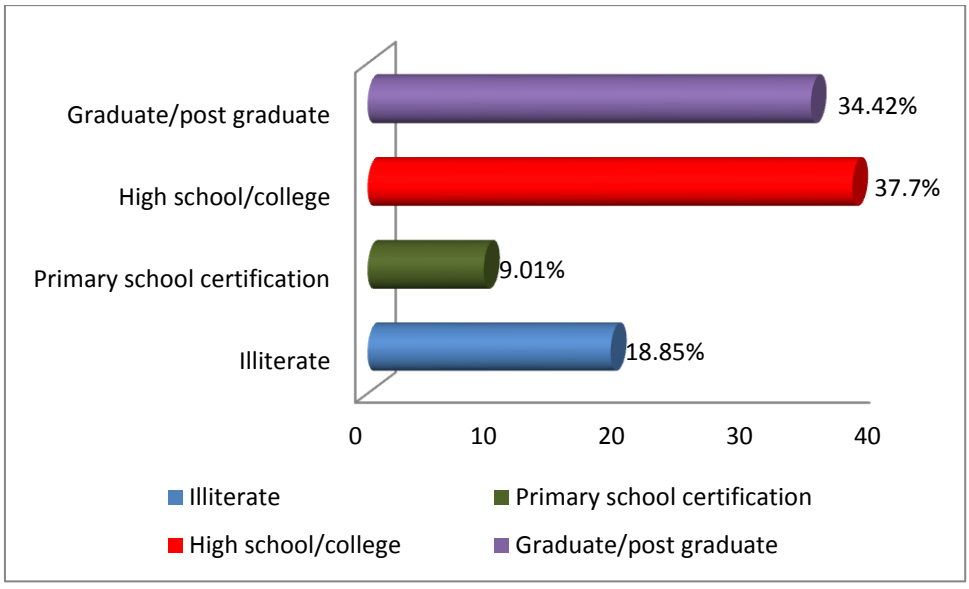

Figure 4.1.3: Education level

From the graph we see that maximum respondents have education level High school certificate (37.7%) and graduate/post graduate (34.42%),primary school certification are about 9% and remaining respondents are illiterate (18.85%).

4.1.4 Medical/Health science background in education

Table 4.1.4: Medical/Health science background in education

Medical/Health science background in education	Total Number	Percentage (%)
Yes	32	27.04
No	90	72.96

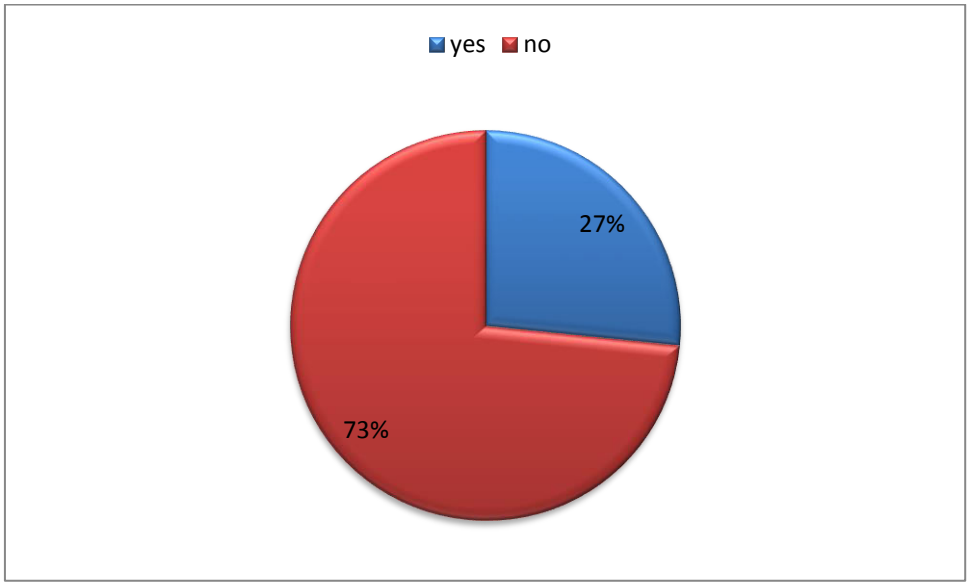

Figure 4.1.4 : Medical/Health science background in education

From the chat we see maximum (72.96%) have no medical/health science background in education, only 27.04% have this knowledge.

4.2 Medical Information

4.2.1 Medical condition that requires an analgesic

Table 4.2.1 : Medical condition that requires an analgesic

Medical condition	Total Number	Percentage (%)
Pathophysiological condition	89	72.95
Dental pain	6	4.92
Injury	7	5.73
Autoimmune disorder	17	13.93
Post operation	3	2.46

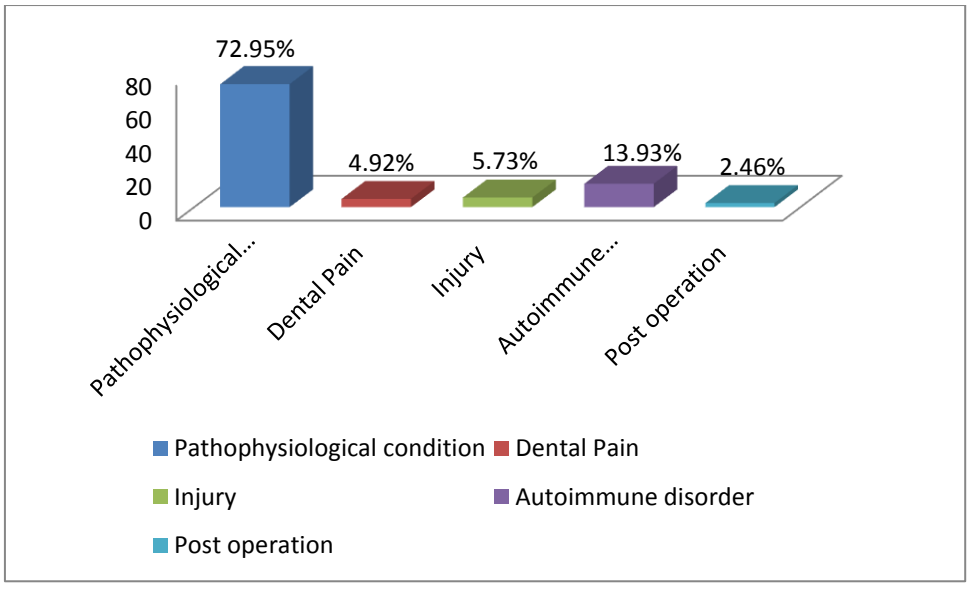

Figure 4.2.1: Medical condition that requires an analgesic

From the column chart we see maximum respondents requires analgesics for pathophysiological condition (72.95%), 13.93% for autoimmune system, 5.73% for injury. 4.92% responds for Dental pain and remaining 2.46% for post operation.

4.2.2 Drug Used for treatment

Table 4.2.2: Drug Used for treatment

Drug	Total Number	Percentage (%)
Acetic acid	69	56.56
Cox-2	5	4.09
Oxicam derivatives	3	2.45
Propinoic acids	45	36.89

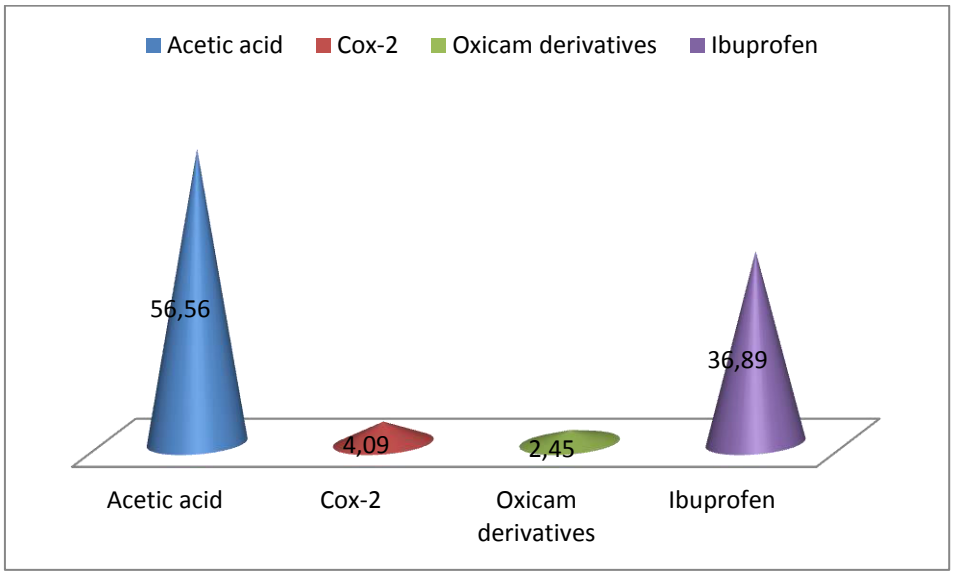

Figure 4.2.2 : Drug Used for treatment

From the graph we see maximum medication provide was Acetic acid (56.56%), Propinonic acids (45%) and prescribed less amount are Cox-2 (4.09%) and Oxicam derivatives (2.45%).

4.2.3 Time period for analgesic Usage

Table 4.2.3 : Time period for analgesic Usage

Time period	Total Number	Percentage (%)
Acute	60	49.18
Chronic	62	50.82

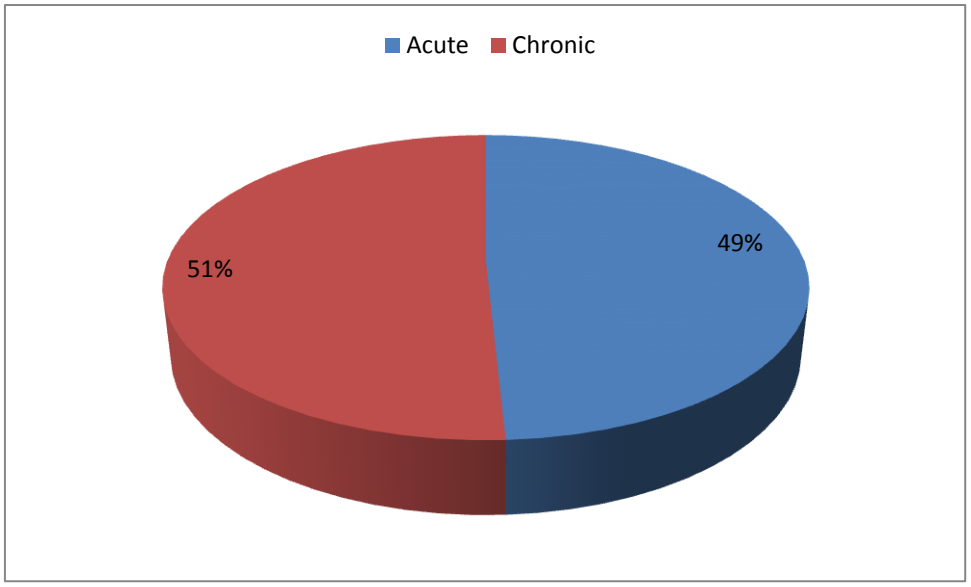

Figure 4.2.3: Time period for analgesic Usage

Graph showed that chronic duration for analgesic usages is slightly more about 51% then acute (49.18%)

4.3 Knowledge and Awareness information

4.3.1 Patient-Doctor interactions regarding side effects

Table 4.3.1: Patient-Doctor interactions regarding side effects

Discussion	Total Number	Percentage (%)
Yes	55	45.08
No	67	54.92

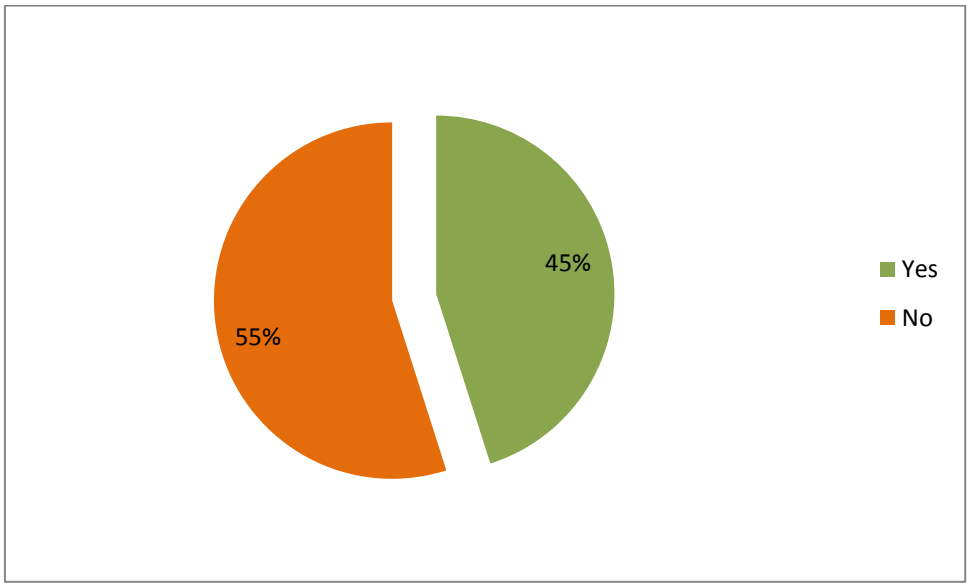

Figure 4.3.1: Patient-Doctor interactions regarding side effects

From the chart we see that about 45% doctor discussed about side effects and about 55% was not .

4.3.2 Patient read the patient information leaflet (PIL) during the taking medication

Table 4.3.2: Patient read the patient information leaflet (PIL) during the taking medication

Patient read about PIL	Total Number	Percentage (%)
Yes	42	34.42
No	79	65.58

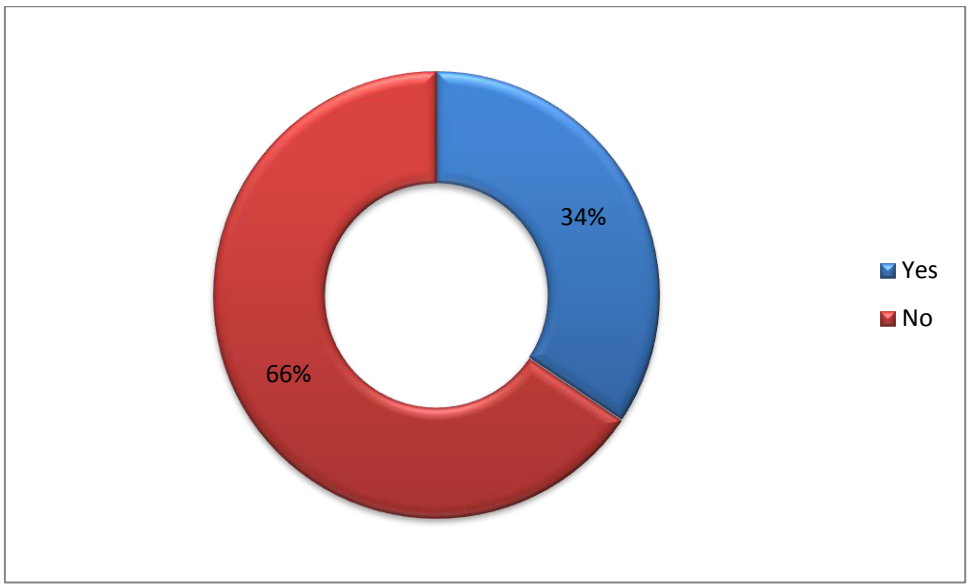

Figure 4.3.2: Patient read the patient information leaflet (PIL) during the taking medication

The above graph showed that about 66% respondents didn't read leaflet information and remaining (34.42%) was .

4.3.3 Patients self medicating

Table 4.3.3: Patients self medicating

Self medicate	Total Number	Percentage (%)
Yes	32	27.04
No	90	72.96

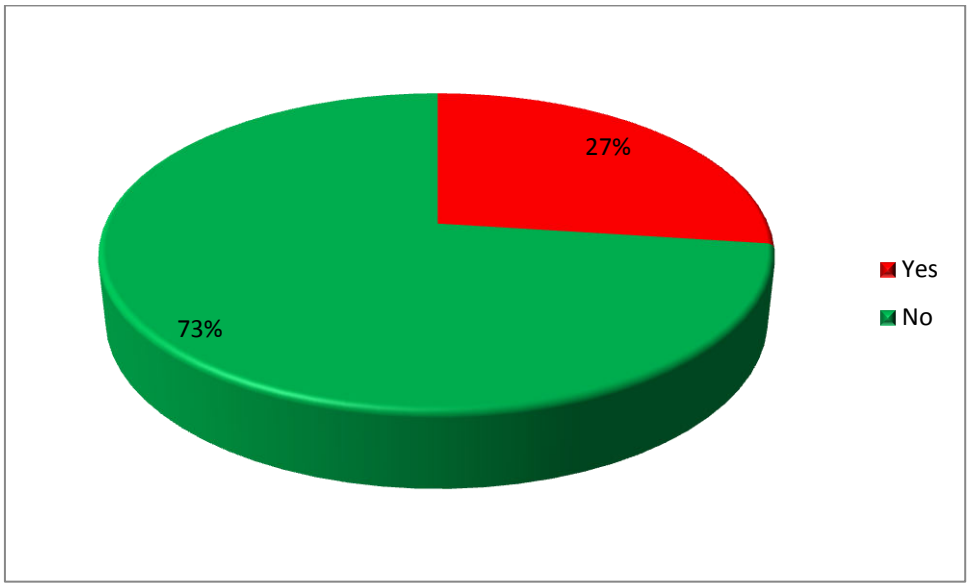

Figure 4.3.3: Patients self medicating

There are only few respondents about 27% did self medicating and 73.04% was not.

4.3.4 Patient takes other medication along with the analgesic

Table 4.3.4: Patient takes other medication along with the analgesic

Take other medication	Total Number	Percentage (%)
Yes	122	100

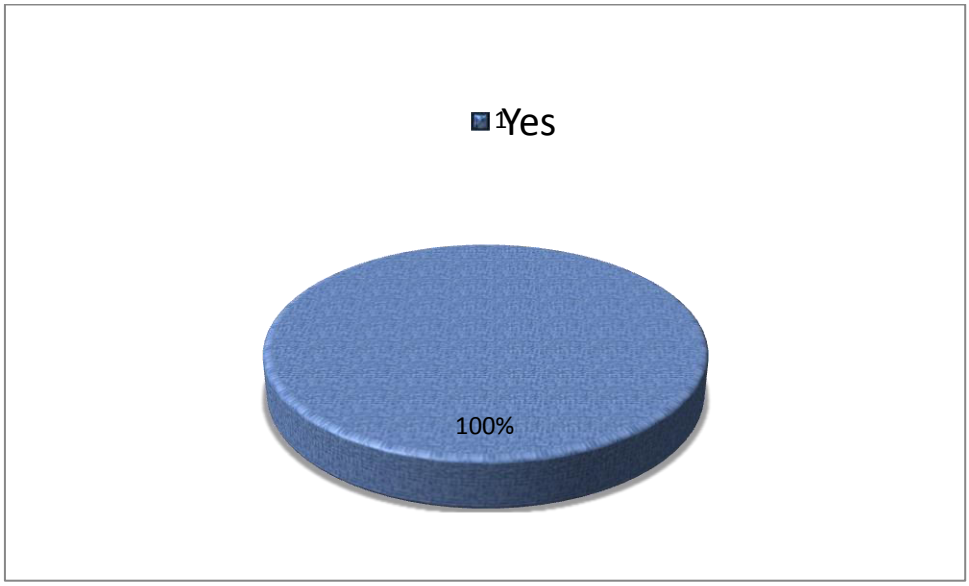

Figure 4.3.4: Patient takes other medication along with the analgesic

All respondents take other medication along with the analgesic

4.3.5 Special instructions given to the patients when they taking medication

Table 4.3.5: Special instructions given to the patients when they taking medication

Special instructions given	Total Number	Percentage (%)
Answer correctly	42	34.43
Answer wrong	11	9.02
Didn't answer	69	56.56

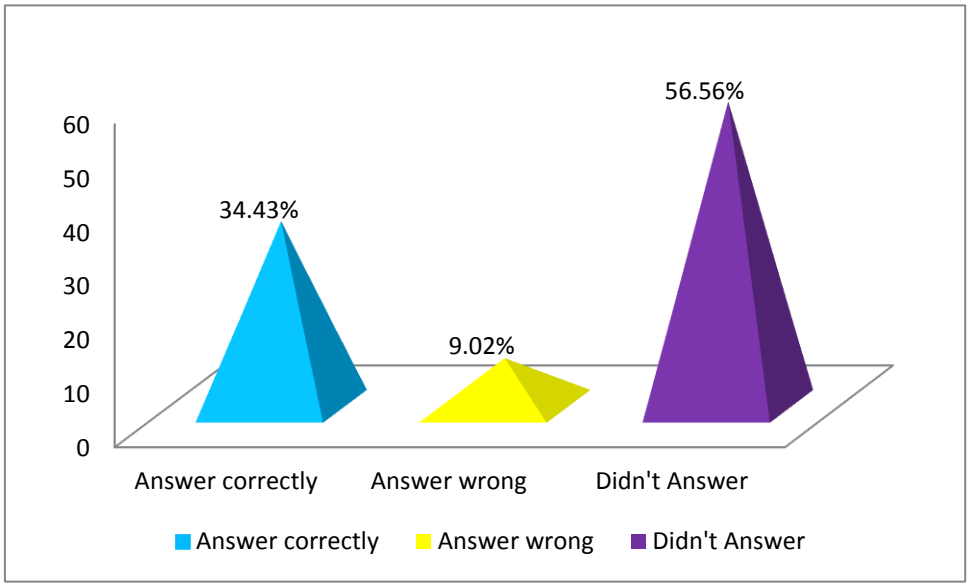

Figure 4.3.5: Special instructions given to the patients when they taking medication

From the graph we see the respondents answer correctly (34.43%) about any special instruction given and majority (56.56%) did not answer. About 9% answer wrong.

Chapter 5

Discussion and Conclusion

5.1 Discussion

In the population-based survey in texas, USA Perceptions of Analgesic Use and Side Effects: Public Values in Pain Management**,** they evaluated the attitudes of 302 adults toward analgesic use and related side effects. Over half (68%) reported prior experience with 2 or more side effects. Vomiting (34%), confusion (32%), and nausea (17%) were ranked as the worst side effects. Exploratory cluster analysis grouped responses to 6 questions about willingness to use analgesics into two categories. Participants in Cluster I (n _ 106), “Conservatives,” were less willing to take analgesics for pain as compared to those in Cluster II (n _ 153), “Liberals.” Univariate analysis found Hispanics, women, those less affluent or educated, and those with prior side-effect experience were more likely to be Conservative. Experience with side effects (OR _ 1.3) and being female (OR _ 2.1) were the strongest predictors of conservative cluster membership. To achieve better pain outcomes, clinicians and patients must identify factors that contribute to conservative decisionmaking about analgesic use and side effect management.

In another study Uses of anti-inflammatory and analgesic drugs in an elderly population The aim of this study was to analyze the prevalence of the use of anti-inflammatory and analgesic drugs among elderly persons from the Family Health Program in Porto Alegre, Rio Grande do Sul, and investigate associated factors such as socio-demographic and health data. drug used subject to medical prescription or self-medicated. In the study Community health workers applied a questionnaire relating to sociodemographic and health data and medication use. Non-steroidal anti-inflammatory drugs, glucocorticoids, non-opioid analgesics and opioids were evaluated. A total of 758 elderly persons were included and anti-inflammatory and analgesic drugs were used by 28.8% of the population. Acetaminophen and ibuprofen were the most frequently used drugs. Regarding self-perception of health,

the worse the perception of health, the greater was the use of therapy (p<0.001). Liver disease and osteoarthritis/ arthritis/rheumatism were found to be associated with anti-inflammatory and analgesic use (p<0.001). The prevalence of anti-inflammatory and analgesic use was considered moderate when compared to previous studies (28.8%). In addition, most of the elderly persons used the drugs when only needed, most probably due to feeling minor to moderate pain or because they had suffered the adverse effects of these medications in the past and so chose to use them sporadically.

In our survey based study conducted on Bangladesh among 122 peoples, In the study Where 55 male and 67 Female participated. From the respondents 51% of the population belonged to the age group 20-39, 36% of the population belonged to the age group 40-59, 13.11% of the population belonged to the age group above 60. Here maximum respondents have education level High school certificate (37.7%) and Graduate/post Graduate (34.42%),Only 18.85% was illiterate and in there education only 27.04% have medical science background so few people have the knowledge about our study. When we trying to get medical information about analgesic use from those respondents and asked in which condition they required this maximum respondents replied for for pathophysiological condition (72.95%), 13.93% for autoimmune system, 5.73% for injury and remaining 2.46 % responds for Post operation and they informed that maximum medication provide was belong to the group Acetic acid (56.56%), Propinoic acids (45%) and prescribed less amount are Cox-2 (4.09%) and Oxicam derivatives (2.45%). 63 patients from the participant take those medication for long duration and 60 for short duration. We also conducted study about patient's knowledge about their safety and if they are aware about the information needed during taking medication. Then through our questionnaire based study we knew that about 45% doctor discussed about side effects and 55% was

not and they also informed that From them 66% people didn't read leaflet information and remaining (34.42%) was . We found 32 people who were take those medication without prescription. Finally when we search about and knowing from them about possible side effects and interactions only 34.43% answer correctly.

5.2 Conclusion

Since most ADRs in the elderly are predictable and therefore potentially avoidable, good communication is pivotal in developing an effective therapeutic partnership with the patient and with fellow health professionals. Whenever possible, the careful prescriber, faced with a choice, should choose the drug with the highest therapeutic ratio, provided efficacy is comparable. He/she should avoid combinations that exhibit additional or synergistic toxic effects. Knowledge of pharmacological principles and how ageing affects drug kinetics and response is essential if we are to promote safe prescribing.

Chapter 6
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