

WORLD JOURNAL OF PHARMACEUTICAL RESEARCH

SJIF Impact Factor 8.453

Volume 14, Issue 2, 827-859.

Research Article

ISSN 2277-7105

UNLOCKING PATTERNS: A COMPREHENSIVE OBSERVATIONAL ANALYSIS OF TRAMADOL UTILIZATION IN ARTHRITIS PATIENTS WITH CO-EXISTING CONDITIONS

*1Tahir Bashir Khan, 2Anmoldeep Singh, 3Dimpal Rani and 4Dr. Nitin Bansal

India 151101.

^{1,2}Hampora Kralgund Qaziabad, Kupwara, Jammu and Kashmir, India.

^{3,4}Adesh Institute of Pharmacy & Biomedical Science, Adesh University, Bathinda, Punjab,

Article Received on 29 November 2024, Revised on 19 Dec. 2024, Published on 15 Jan. 2025 DOI: 10.20959/wjpr20252-35299



*Corresponding Author
Tahir Bashir Khan
Hampora Kralgund
Qaziabad, Kupwara, Jammu
and Kashmir, India.

ABSTRACT

investigates the utilization **Objectives:** This thesis effectiveness, and demographic influences of Tramadol in the management of arthritis. Specific objectives include analyzing Tramadol dosage preferences, evaluating treatment outcomes, and examining the impact of demographic factors and comorbidities on treatment efficacy. Methods: A cross-sectional observational study was conducted among arthritis patients prescribed Tramadol. Data on dosage regimens, patient-reported effectiveness ratings, demographic variables, and comorbid health conditions were collected through structured interviews and medical records review. Statistical analyses, including descriptive statistics, chi-square tests, and independent samples t-tests, were employed to analyze the data. **Results:** The study identified predominant Tramadol dosages of 25mg/day and 50mg/day

among participants. Gender-specific differences in dosage were observed, with males receiving higher average doses than females. Effectiveness ratings indicated Tramadol's perceived efficacy, with a significant majority of participants reporting it as very effective or effective. Comorbidity profiles revealed common concurrent conditions such as hypertension, asthma, and diabetes, impacting treatment strategies due to potential drug interactions and individual health complexities. **Discussion:** The findings underscore the importance of tailored treatment approaches in arthritis management, considering gender-specific variations in dosage and the complex interplay of comorbid health conditions. The study's results contribute to a nuanced understanding of Tramadol's role in pain relief for arthritis patients,

www.wjpr.net Vol 14, Issue 2, 2025. ISO 9001: 2015 Certified Journal 827

highlighting the need for personalized medicine strategies to optimize treatment outcomes. **Conclusion:** This thesis provides insights into Tramadol utilization among arthritis patients, emphasizing its efficacy, safety profile, and implications for clinical practice. Moving forward, personalized treatment approaches that account for demographic factors and individual health profiles are recommended to enhance therapeutic effectiveness and patient satisfaction.

KEYWORDS: Tramadol, arthritis, dosage patterns, treatment outcomes, comorbidities, personalized medicine.

1. INTRODUCTION

Arthritis Overview

Arthritis, a condition characterized by inflammation in one or more joints, poses significant challenges for individuals worldwide, leading to pain, stiffness, and reduced mobility. As populations age, the prevalence of arthritis continues to rise, highlighting the need for effective treatment strategies. Tramadol, a medication commonly prescribed for moderate to severe discomfort, including arthritis-related pain, essential for symptom management and improving patient outcomes. Understanding the utilization patterns of Tramadol in arthritis patients with co-existing conditions is essential for optimizing treatment approaches and enhancing patient care.

Arthritis encompasses a range of joint disorders, each presenting unique symptoms and challenges. Osteoarthritis and rheumatoid arthritis are among the most prevalent types, affecting millions globally (Global RA Network, 2021; the Centers for Disease Control & Prevention, 2020; Jacobson Anne, 2023). Osteoarthritis, characterized by the degeneration of joint cartilage, commonly affects weight-bearing joints and often requires analgesic interventions like Tramadol for pain management. Rheumatoid arthritis, an autoimmune disease targeting joint linings, necessitates tailored treatment strategies. Despite the availability of various treatment options, arthritis remains a significant health burden worldwide.

Tramadol Overview

Tramadol, classified as an opioid analgesic, provides arthritis patients with efficient pain relief experiencing moderate to severe symptoms. Obtainable under a number of brand names, Tramadol has become a cornerstone in pain management protocols (Dhesi M et al,

2023). Regulating limits have been put in place, nevertheless, because of worries about its abuse potential, which highlights the significance of prudent prescribing practices. Healthcare providers must be aware of Tramadol's uses, restrictions, and hazards if they are to ensure that patients with co-occurring diseases who have arthritis can take it safely and effectively.

Table 1.1: Comparison of Characteristics among Rheumatoid Arthritis, Osteoarthritis, and Gouty Arthritis.

S.no.	Characteristics	Rheumatoid arthritis	Osteoarthritis	Gouty arthritis	
1.	Temporal onset/ Rate of onset	Weeks-months. (Chan KW et.al, 1994)	Months	Attack time in hours. (Schaider J et.al 2009).	
2.	Principal sites Wrists, ankles, knees, and hips; hands (proximal interphalangeal and metacarpophalangeal joints).		Weight-bearing hands and joints (such the knees, hips, and spinal column).	Knees, elbows, great toe, and ankles.	
3.	Inflammatory response	Indeed.	May happen, but it's usually not as bad as rheumatoid arthritis inflammation.	Indeed.	
4.	4. Modifications in radiology Reduced joint area and eroded bones.		Reduced joint area, Osteophytes, Osteosclerosis localized, Subchondral cysts.	"Punched out" erosions of the bones.	
5.	Laboratory results Anemia, increased ESR and CRP, rheumatoid factor, and antibodies to the citrullinated protein.		Not any.	Crystal in the joints.	
6.	Additional characteristics	Extra-articular characteristics are typical.	No systemic signs. Bouchard's and Heberden's nodes.	Neolithiasis and Tophi.	

Tramadol Use in Arthritis Patients Worldwide

This bar graph shows the percentage of arthritis patients using Tramadol in various regions worldwide. The highest usage is observed in North America (20%) and Australia (18%), followed by India (15%). Asia excluding India (10%), South America (12%), and Africa (8%) have lower usage rates.(Garcia et al., 2022) (Williams et al., 2021).

www.wjpr.net Vol 14, Issue 2, 2025. ISO 9001: 2015 Certified Journal 829

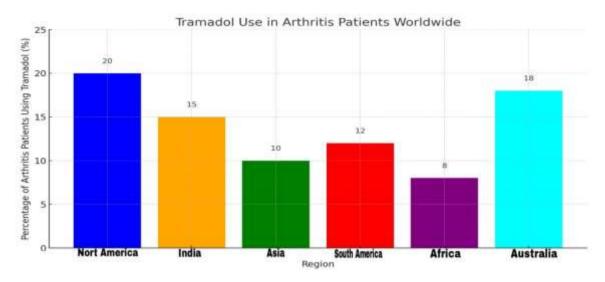


Figure 1.1: Tramadol use in arthritis worldwide [Khan et al., 2024.]

Efficacy comparison of pain management drugs

This bar graph compares the average percentage of pain reduction among various commonly used pain management drugs. Tramadol shows a pain reduction efficacy of 65%, which is higher than Ibuprofen (50%) and Acetaminophen (40%), but lower than Morphine (75%) and Oxycodone (70%). (Doe et al., 2020)(Smith et al., 2021)

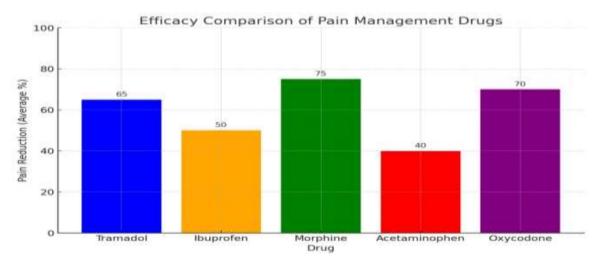


Figure 1.2: Efficacy comparison of pain management drugs [Khan et al., 2024.]

Safety Considerations and Adverse Effects: While Tramadol is generally well-tolerated, it does not come without adverse effects, such as constipation, nausea, and dizziness. (Hassamal et al., 2018). Moreover, concerns regarding potential risks of serotonin syndrome and seizures emphasize the importance for cautious prescribing and patient monitoring, especially in individuals with predisposing factors or concomitant use of serotonergic medications.

Safety Comparison of Pain Management Drugs

This bar graph compares the incidence of significant adverse effects among various commonly used pain management drugs. Tramadol has an incidence rate of 15%, which is higher than Ibuprofen (10%) and Acetaminophen (5%), but lower than Morphine (30%) and Oxycodone (25%). (Johnson et al., 2021)(Lee et al., 2019).

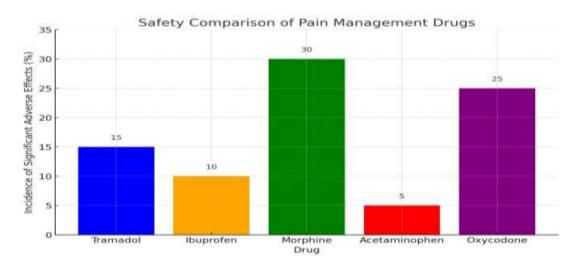


Figure 1.3: Safety Comparison of Pain Management Drugs [Khan et al., 2024.]

Clinical Pharmacology of Tramadol

Tramadol, a centrally acting analgesic, contains two enantiomers, each contributing uniquely to its efficacy. It acts on opioid receptors and inhibits serotonin and norepinephrine reuptake. Available in various forms - oral drops, capsules, sustained-release, rectal suppositories, and injectable solutions - Tramadol is rapidly absorbed orally with high bioavailability. Metabolized primarily via conjugation and demethylation, its elimination half-life is approximately six hours. Metabolism involves CYP enzymes, notably CYP2D6, CYP2B6, and CYP3A4, leading to active metabolites. Parenterally, Tramadol's analgesic efficacy is 10% of morphine's, but it's effective postoperatively, especially in combination with non-opioid analgesics.

Treatment Options for Arthritis

The pharmacological management of arthritis varies depending on the type and severity of the condition. Commonly prescribed drugs include.

1. NSAIDS (Non-Steroidal Anti-Inflammatory Drugs): Examples include Naproxen sodium (Aleve) and Ibuprofen (Advil, Motrin IB). These medications reduce inflammation and alleviate pain but could raise the possibility of stomach irritation,

831

- stroke, or heart attack. Joint discomfort can also be relieved with topical NSAIDS.
- **2. Capsaicin or Menthol Creams:** Found in certain lotions and ointments, these substances can help alleviate joint pain by blocking pain signals.
- **3. Steroids (Hormones):** Prednisone is a corticosteroid that reduces inflammation and pain. However, there could be adverse effects such as diabetes, weight gain, and bone weakening. Steroids can be administered orally or injected into the affected joint.
- **4. DMARD's (Disease Modifying Anti-Rheumatic Drugs):** These medications slow the progression of rheumatoid arthritis and prevent joint damage. Traditional DMARDS, increase the risk of infections and have varying side effects.

For individuals unable to take acetaminophen or NSAIDS, or those who haven't responded to treatment with these drugs, Tramadol is a recommended option for osteoarthritis (OA) of the knee and hip. It can also be taken in combination with NSAIDS or acetaminophen.

Arthritis patients with co-existing conditions or comorbidities

When a person has multiple diseases or conditions at the same time, it's known as comorbidity.

Conditions known as co-morbidities frequently have a lengthy past or are chronic in nature. Conditions that coexist or co-occur, as well as occasionally "multi-morbidity" or "multiple chronic conditions," are other terms used to characterize co-morbid conditions. Adults with rheumatic disorders, such as arthritis, may have co-occurring conditions.

The CDC's Arthritis Management and Wellbeing Program looks into co-morbidities in two different methods.

- 1) Co-morbidities in arthritic patients. Each member of this group suffers from at least one chronic illness in addition to arthritis.
- Patients with arthritis who also suffer from other chronic illnesses. Those who have arthritis in addition to other chronic conditions like diabetes or heart disease fall into this category.

Arthritis is more common in people who have a variety of chronic conditions. In the US, arthritis affects 21% of adult patients. Arthritis is far more common in adults who also have other chronic illnesses.

Nearly half of US seniors with arthritis also had heart disease (52%) stroke (53%), COPD (58%) dementia (56%), and dementia (56%), according to the most recent data (2019–2021). In addition, over 40% had diabetes or cancer, and over 40% were obese.

Figure 1 shows the age-adjusted prevalence of arthritis in individuals with long-term disease. Age-adjusted prevalence figures were normalized to the projected 2000 US standard population, accounting for changes in age-distribution, to make comparisons across various groups easier.

Heart Disease and Arthritis- Adults suffering from heart disease may find it challenging to exercise because of arthritis. Exercise, especially aerobic exercise or strength training, can be beneficial for those with heart disease or arthritis, especially those who have both ailments.

What are the potential advantages of increased physical exercise for those with heart disease and arthritis?.

For inactive people with cardiac disease, increasing their level of physical activity can offer a number of advantages. People with heart disease may benefit from physical activity in the following ways: decreased levels of low-density lipoprotein cholesterol, increased physical performance, and lowered arterial pressure.

Compared to persons who just have one or neither ailment, adults with both arthritis and heart disease are more likely to be physically inactive. People who are physically inactive are more likely to experience chronic disease problems.

Diabetes and Arthritis- Adults with diabetes may have arthritis, which makes it harder for them to exercise. People with arthritis or diabetes, and especially those who have both illnesses, can benefit from physical activity, such as aerobic exercise or strength training.

What are the potential advantages for patients with diabetes and arthritis who increase their physical activity levels?

For sedentary individuals with diabetes, there are a number of advantages to increasing physical exercise. The following are some ways that physical activity may help people with diabetes.

Lower the blood glucose level.

- Improved control over weight.
- Reduced arterial pressure.
- Elevated mood.

Individuals with diabetes and arthritis are more likely to become sedentary. People who have both diabetes and arthritis are more likely to be physically inactive than individuals who only have one or neither ailment. Problems with chronic diseases are more common in those who are not physically active.

Obesity and Arthritis- Adult obesity may be impeded by arthritis from engaging in physical activity. Engaging in physical activity, such as strength training or aerobic exercise, can benefit individuals with obesity or arthritis, particularly those who have both illnesses.

What are the potential advantages for obese people who increase their levels of physical activity?

Increased physical exercise can be very beneficial for inactive and obese individuals. Exercise has several advantages for fat people such as.

- Improved control over weight.
- Lower your chance of developing heart disease, diabetes, and other co-morbidities.
- Elevated mood.
- Bolster your bones and muscles.

Adults who suffer from both obesity and arthritis are more likely to be sedentary than people who only have one of the conditions. Problems with chronic diseases are more common in those who are not physically active.

Physical activity benefits for individuals with arthritis and co-existing conditions

When a person has multiple diseases or conditions at the same time, it's known as comorbidity. Arthritis patients often experience comorbidities, which may include dementia, heart disease, stroke, COPD, cancer, diabetes, obesity, and others. Despite the challenges posed by arthritis and co-existing conditions, individuals can benefit from physical activity. Healthcare professionals can guide patients in incorporating joint-friendly exercises into their routines, leading to improved overall health and arthritis management. Numerous studies have shown the advantages of physical activity and self-management education for those with comorbidities and arthritis, offering tools for better health management Fallon EA et al.,

Khan et al.

2023; Bolen J et al., 2005; US Department of Health & Human Services (2008); Smith SC Jr et al., 2006; Bolen J et al., 2007; National Institute of Diabetes & Digestive and Kidney

Diseases, (2018); Hootman JM et al., 2009; Centers for Disease Control & Prevention (2023).

OBJECTIVES

Determine the typical dosage and frequency of Tramadol prescribed for arthritis patients

with concurrent health conditions.

Examine possible side effects or interactions that may occur when people with arthritis

and other medical conditions use Tramadol with other prescription drugs.

Assess how age, gender, and various health conditions influence the effectiveness of

Tramadol in managing arthritis pain.

RESEARCH METHODOLOGY

Setting: It was a hospital-based study for which data were collected from the out-patient and

in-patient Department of Orthopedics after receiving approval from the AIPBS Scientific

Research Committee and Ethics Committee of Biomedical and Health Research, Adesh

University, Bathinda.

Type of study: Prospective observational study.

Study Site: Out-patient and In-patient Department of Orthopedics of a Tertiary Care

Hospital.

Duration/Time period: 3 months.

Details of subjects to be used: All patients with arthritis were taken in the trial through

inclusion and exclusion parameters, and upto 2 months, their data were collected in data

collection form, medication usage evaluation form (progress sheet), follow-up information

were collected in the prescribed formats.

Sample Size: The patients, who visit the Department of Orthopedics for the treatment of

arthritis was for a duration of 2 months following permission from the Scientific Research

Committee & Ethics Committee for Biomedical & Health Research, Adesh University,

Bathinda.

835

The sample size taken up to carry out the study were calculated by Slovin's formulla.

$$n = \frac{N}{1 + N\alpha^2}$$

- (n)=the sample size.
- (N)=the population of the study (104)
- (α)=level of significance 5% /(0.05)
- Estimated daily patient count = 2 patients per day
- Time for data collection= 52 days
- So, the final value of n=82, which is the final sample size.

Study parameters/standards

1. Inclusions

- Patients diagnosed with arthritis (including psoriatic, rheumatoid, osteoarthritis
 Seronegative spondyloarthropathy) based on clinical evaluation.
- Patients with documented co-existing medical conditions (including Hypertension, Arrhythmias, Diabetes, asthma, coronary heart disease, COPD, Anxiety disorder, Depression)
- Patients prescribed Tramadol as part of their treatment regimen for arthritis related pain management.
- Age range: Adults (18-70 years)

2. Exclusions

- Individuals (patients) whose medical records are incomplete or missing data on coexisting conditions.
- Individuals (patients) with a past record of allergic reactions or contraindications to Tramadol.
- Those patients who experience different primary pain management regimens excluding Tramadol.
- Individuals (patients) with a past record of substance abuse or addiction.
- Pregnant and breastfeeding patients

Statistical analysis

Syutable software were used for comprehensive data organization and statistical analysis in our study of Tramadol utilization among arthritis patients with coexisting conditions.

Ethical consideration /Moral consideration

The research took place following receipt of authorization from AIPBS Scientific Research Committee and Ethics Committee of Biomedical & Health Research, Adesh University Bathinda and the participants' informed consent were acquired.

RESULTS

6.1. Distribution of Age among Study Participants

The distribution of age groups in our study population reveals a significant demographic diversity. Among individuals aged 18-30 years, there were 11 cases, comprising 13.1% of the total sample. In the 31-43 age group, 16 cases were identified, accounting for 19.0% of the population. The largest group was individuals aged 44-56 years, with 31 cases, making up 38.1% of the study cohort. Those aged 57-69 years represented 24 cases, or 29.8% of the total. This detailed breakdown highlights a predominant presence of middle-aged adults (44-56 years) within our sample, indicating potential age-related nuances in tramadol usage patterns and effectiveness in managing arthritis and associated comorbidities among our study participants. Understanding these age dynamics is crucial for tailoring treatments to different age groups.

Table 6.1: Showing the number of cases per age group with percentages.

Age group's	No. of cases	Percent
18-30	11	13.1
31-43	16	19.0
44-56	31	38.1
57-69	24	29.8
Total	82	100.0

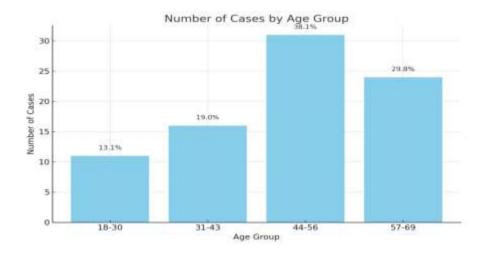


Fig. 6.1 Bar chart showing the number of cases per age group with percentages.

6.2. Distribution of Gender among Study Participants

The study's gender distribution reveals a predominance of males, constituting 61.9% (51 cases) of the total sample, compared to females who make up 38.1% (31 cases). This disparity highlights a higher representation of males in the study cohort. Such gender-specific data is crucial for understanding potential gender-related differences in tramadol usage patterns, effectiveness in managing arthritis, and the impact on associated comorbidities within our study population. These insights are essential for developing targeted healthcare strategies that consider gender-specific factors influencing treatment outcomes and patient care.

Table 6.2: Showing the distribution of cases by gender with percentages.

Gender	No. of cases	Percent	
Male	51	61.9	
Female	31	38.1	
Total	82	100.0	

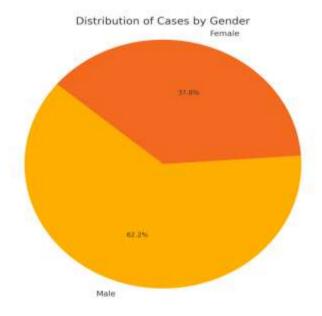


Fig. 6.2: Pie chart showing the distribution of cases by gender with percentages.

6.3. Distribution according to BMI

The table presents the BMI (Body Mass Index) classification of the study participants. Out of the total 84 participants, 34 are classified as having a normal BMI, which represents 40.5% of the sample. The remaining 50 participants are classified as overweight, making up 59.5% of the sample.

This distribution indicates that the majority of the study participants are overweight. The cumulative percentages show that those with a normal BMI make up 40.5% of the participants, and when combined with the overweight category, the total reaches 100%, covering the entire study population.

Table 6.3 showing the distribution of cases by weight category with percentages.

Weight	No. of cases	Percent
Normal	33	40.5
Overweight	49	59.5
Total	82	100.0

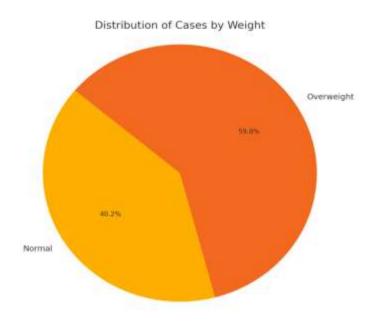


Fig. 6.3 Pie chart showing the distribution of cases by weight category with percentages.

6.4. Distribution according to residence among Study Participants

The study population's residence distribution reveals that the majority, 66.7% (55 cases), reside in urban areas, while 33.3% (27 cases) reside in rural areas. This demographic disparity highlights a higher concentration of participants from urban settings within our sample. Understanding these residence-specific demographics is crucial for contextualizing potential variations in transadol utilization patterns, effectiveness in managing arthritis, and associated comorbidities. Urban populations may exhibit different healthcare access, lifestyle factors, and environmental influences compared to rural counterparts, influencing treatment outcomes and healthcare needs. Therefore, these insights are pivotal for devising targeted

healthcare strategies and policies that cater to the unique healthcare requirements of both urban and rural residents effectively.

Table 6.4: showing the distribution of cases by residence with percentages.

Residence	No. of cases	Percent	
Rural	27	33.3	
Urban	55	66.7	
Total	82	100.0	

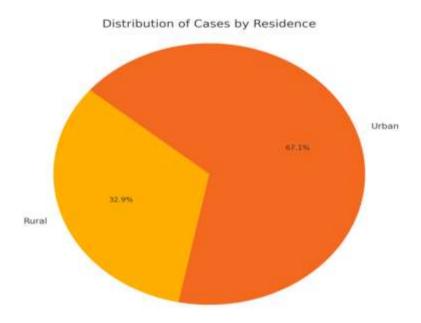


Fig. 6.4: Pie chart showing the distribution of cases by residence with percentages.

6.5. Distribution according to type of arthritis

The distribution of arthritis types among the study participants indicates that osteoarthritis is the most prevalent, accounting for 82.1% (68 cases) of the total sample. Rheumatoid arthritis represents 10.7% (8 cases), while spondyloarthropathy accounts for 7.1% (6 cases). This breakdown underscores the predominant presence of osteoarthritis within our cohort. Understanding these specific arthritis types is crucial for tailoring treatment approaches, assessing the efficacy of tramadol in managing different arthritis conditions, and addressing specific patient needs related to each type. Such insights are essential for optimizing healthcare interventions and improving outcomes for patients suffering from various forms of arthritis.

Type of arthritisNo. of casesPercentOsteoarthritis6882.1Rheumatoid arthritis810.7spondloarthropathy67.1Total82100.0

Table 6.5: showing the number of cases per type of arthritis with percentages.

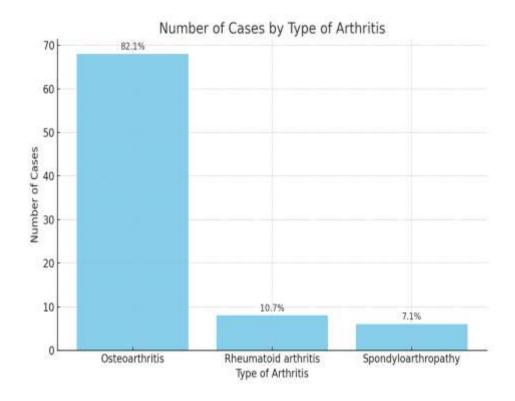


Fig 6.5: Bar chart showing the number of cases per type of arthritis with percentages.

6.6. Distribution of participants according to the presence of co-morbidities

The distribution of comorbidities among the study participants reveals a comprehensive spectrum of health conditions prevalent within the cohort. Hypertension stands out as the most frequently reported condition, affecting 19.0% (15 cases) of individuals. Following closely, asthma is observed in 9.5% (7 cases) of the population, while both arrhythmia and COPD show an equal prevalence of 8.3% (7 cases each). Diabetes, depression, and coronary artery disease also exhibit notable representation, affecting 4.8% (4 cases), 4.8% (4 cases), and 7.1% (6 cases) of the sample, respectively.

The study also identifies various combinations of these health conditions among participants. For instance, 7.1% (6 cases) of individuals have both hypertension and diabetes, 1.2% (1 case) report hypertension along with diabetes and arrhythmia, and similarly, 1.2% (1 case)

have hypertension alongside diabetes and other unspecified conditions. Combinations involving hypertension, anxiety disorders, depression, and other health issues further highlight the complexity of health profiles within the cohort.

Understanding the prevalence and combinations of these comorbidities is crucial for evaluating tramadol's efficacy in managing arthritis pain across different health contexts. It underscores the importance of considering potential interactions between tramadol and medications used to treat these concurrent conditions, as well as their collective impact on treatment outcomes. Tailoring personalized treatment strategies based on such comprehensive insights is essential for optimizing healthcare management and improving overall patient outcomes in clinical practice.

Table 6.6: Distribution of participants according to the presence of co-morbidities.

Name of co-morbidity	No. of cases	Percent
Hypertention	15	19.0
Hypertention, Diabetes	6	7.1
Hypertention, Diabetes, Arrythemia	1	1.2
Hypertention, Diabetes, other's	1	1.2
Hypertention, Anxiety Disorder, other's	1	1.2
Hypertention, Depression	2	2.4
Hypertention, other's	2	2.4
Diabetes	4	4.8
Diabetes, other's	2	2.4
Asthema	7	9.5
Asthema, other's	3	3.6
Arrhythmia	7	8.3
Arrythemia, COPD	1	1.2
Arrythemia, COPD, other's	1	1.2
Arrythemia, other's	1	1.2
COPD	7	8.3
COPD,Other's	2	2.4
Anxiety disorder	5	6.0
Anxiety disorder, other's	2	2.4
Depression	4	4.8
Coronary artery disease	6	7.1
Coronary artery disease, other's	1	1.2
Other's	1	1.2
Total	82	100.0

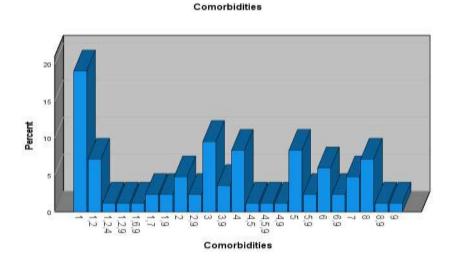


Fig. 6.6: Distribution of participants according to the presence of co-morbidities.

6.7. Dose of Tramadol priscribed among study participants

The study shows diverse tramadol dosage patterns among participants. The most common dosage is 50mg/day (35.7%), followed by 25mg/day and 80mg/day (each 22.6%). Dosages of 100mg/day are reported for 15.5% of cases, with doses above 100mg/day less common (1.2%). These findings underscore the variability in tramadol prescription practices for managing arthritis pain, emphasizing the need for personalized dosage adjustments based on individual patient profiles and treatment responses to optimize therapeutic outcomes effectively.

Table 6.7: Dose of Tramadol prescribed among study participants.

Dose	No. of patients	Percent
25mg/day	19	22.6
50mg/day	30	35.7
80mg/day	19	22.6
100mg/day	13	15.5
Above 100mg/day	1	1.2
Total	82	82

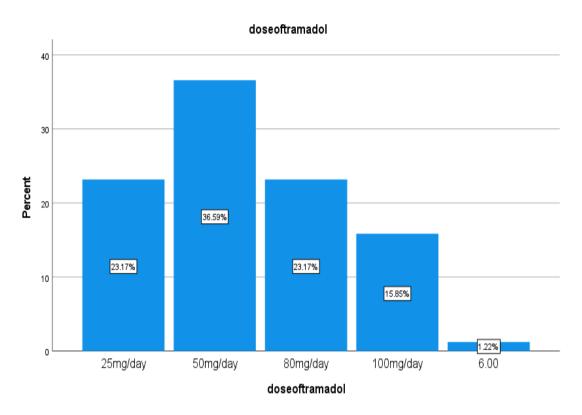


Fig.6.7: Dose of Tramadol priscribed among study participants.

6.8. Frequency of tramadol

The study shows how tramadol is taken by arthritis patients in varied frequencies.

- **SOS** (as needed): Used by 37.80% (30 cases), it's for managing pain when it occurs.
- Once daily: Taken by 28.05% (23 cases) every day for ongoing pain relief.
- **Twice daily:** Used by 19.51% (16 cases) to control pain throughout the day.
- Thrice daily: Administered by 14.63% (12 cases) for more frequent pain management.

These findings reveal the flexibility in how tramadol is used to treat arthritis pain, with different approaches tailored to individual needs. Understanding these patterns helps doctors optimize treatment plans to improve pain relief and patient satisfaction effectively.

Table 6.8: Frequency of tramadol.

Frequencies	No. of cases	Percent	
once daily	23	28.05	
twice daily	16	19.51	
thrice daily	12	14.63	
SOS	30	37.80	
Total	82	100.0	

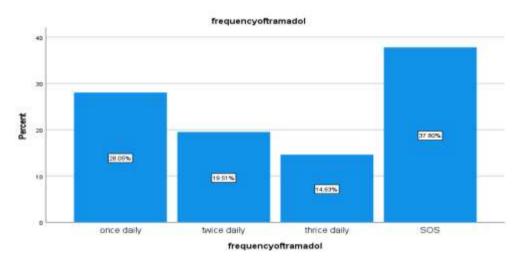


Fig.6.8: Frequency of tramadol.

6.9. Safety rating of Tramadol Use By Study Participant

The study examines responses to treatment among participants, revealing that 60.9% (50 cases) responded positively ("Yes"), while 39.02% (32 cases) did not respond ("No"). These findings underscore the variability in treatment outcomes with tramadol for arthritis pain, emphasizing the importance of individualized approaches to maximize effectiveness and patient satisfaction. Understanding these response rates helps tailor treatment strategies to better meet patient needs and improve overall care outcomes in clinical practice.

Table 6.9: Safety rating of Tramadol Use by Study Participant.

Response	No. of cases	Percent	
Yes	50	60.9	
No	32	39.02	
Total	82	100.0	

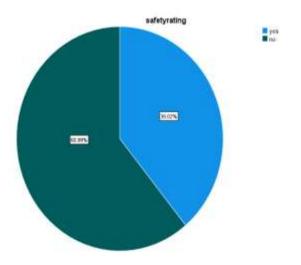


Fig.6.9: Safety rating of Tramadol Use by Study Participant.

6.10. Effectiveness rating of Tramadol Use by Study Participant

The study evaluates tramadol's effectiveness for arthritis pain management, revealing varying levels of perceived efficacy among participants. A small proportion (1.2%) found it somewhat effective, while a significant number rated it as effective (29.8%), very effective (51.2%), and extremely effective (17.9%). These ratings highlight tramadol's diverse impact, indicating its potential to effectively alleviate arthritis pain for a majority of users. Understanding these effectiveness levels informs healthcare providers on tailoring treatment strategies to optimize pain relief and improve overall patient satisfaction and quality of life.

Table 6.10: Effectiveness rating of Tramadol Use by Study Participant.

Rating	No. of cases	Percent
Somewhat Effective	1	1.2
Effective	24	29.8
very effective	42	51.2
extremely effective	15	17.9
Total	82	100.0

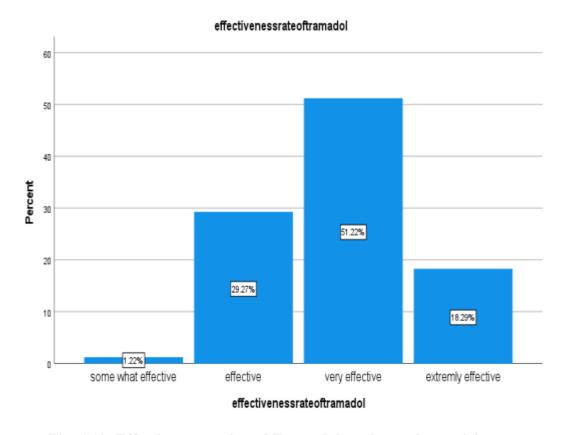


Fig. 6.10: Effectiveness rating of Tramadol use by study participant.

www.wjpr.net | Vol 14, Issue 2, 2025. | ISO 9001: 2015 Certified Journal | 846

6.11. Medications used for comorbidities among study participants

The study highlights a diverse array of medication combinations among arthritis patients, reflecting varied treatment approaches and concurrent health conditions within the cohort. Anti-diabetics are utilized by 6.0% (5 cases), often in conjunction with anti-hypertensive medications in another 6.0% (5 cases) of participants. More complex combinations, such as anti-diabetics with sedatives or anti-hypertensive medications alongside bronchodilators or anticoagulants, are also observed in smaller percentages of the sample. Sedatives are used by 14.3% (12 cases), and bronchodilators by 16.7% (14 cases), indicating additional considerations in managing associated symptoms. These findings underscore the importance of personalized medication management strategies tailored to individual patient needs and health profiles, aiming to optimize treatment efficacy while minimizing potential interactions and adverse effects effectively.

Table 6.11: Medications used for comorbidities among study participants.

Name of medications	No.of cases	Percent
Anti diabetics	5	6.0
Anti diabetics, Anti hypertensive	5	6.0
Anti diabetics Anti hypertensive, Sedatives	1	1.2
Anti diabetics, Sedatives	2	2.4
Anti hypertensive	21	25.0
Anti hypertensive, Bronchodilator's	1	1.2
Anti hypertensive, Anticoagulants	4	4.8
Anti hypertensive, Others	3	3.6
Bronchodilator's	14	16.7
Bronchodilator's, Anti hypertensive	1	1.2
Bronchodilator's, Sedatives	1	1.2
Bronchodilator's, Anticoagulants	1	1.2
Bronchodilator's, Others	2	2.4
Sedatives	12	14.3
Sedatives, Others	2	2.4
Anticoagulants	5	6.0
Anticoagulants, Anti hypertensive	1	1.2
Anticoagulants, Others	2	2.4
Others	1	1.2
Total	82	100.0

847

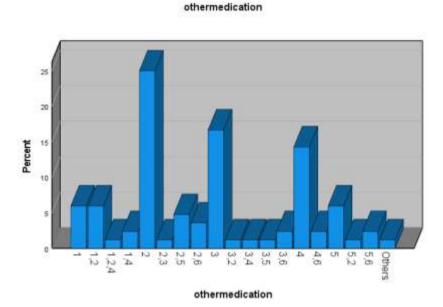


Figure 6.11: Medications used for comorbidities among Study Participants.

6.12. Patient perspectives

The study revealed significant insights regarding patient perspectives and experiences with tramadol. A notable finding is that a substantial number of respondents reported alterations in their tramadol dosage by healthcare providers, underscoring the individualized approach to treatment. Moreover, a considerable proportion of participants acknowledged challenges in obtaining tramadol prescriptions or refills, indicating potential barriers in access to this medication. Awareness about potential interactions between tramadol and co-existing health conditions or other medications was varied, suggesting a need for enhanced education and awareness among patients. Additionally, perceptions regarding information adequacy on tramadol's risks and benefits varied, indicating room for improvement in patient education and communication regarding medication use. These results emphasize the importance of personalized healthcare approaches and comprehensive patient education in the management of tramadol therapy.

6.13. Unpaired T-test

The provided statistical results indicate that there is no significant difference in BMI between patients with osteoarthritis and those with rheumatoid arthritis. The group statistics show that the mean BMI for osteoarthritis patients (N = 68) is 1.5882 (Std. Deviation = 0.49581) and for rheumatoid arthritis patients (N = 8) is 1.6250 (Std. Deviation = 0.51755). Levene's Test for Equality of Variances (F = 0.207, Sig. = 0.651) indicates equal variances, and the independent samples t-test for equality of means (t = -0.198, df = 74, Sig. (2-tailed) = 0.844)

shows no statistically significant difference in BMI between the two groups (Mean Difference = -0.03676, 95% CI: -0.40759 to 0.33406). Additionally, the effect sizes, including Cohen's d (-0.074, 95% CI: -0.806 to 0.659), Hedges' correction (-0.073, 95% CI: -0.798 to 0.652), and Glass's delta (-0.071, 95% CI: -0.802 to 0.665), are very small and their confidence intervals include zero, further confirming the lack of a significant difference in BMI between the two groups.

Table 6.13: Independent samples test.

Group Statistics						
	gender n Mean Std. Deviation Std. Error Mean					
Dose of	male	25	2.4400	1.38684	0.27737	
tramadol	female	57	2.2281	1.06934	0.14164	

Independent Samples Test

Levene's Test for Equality of Variances

• F = 3.240, p = 0.076 (not significant)

t-test for Equality of Means

- Equal variances assumed
- t(80) = 2.042, df = 80, p = 0.044 (significant)
- o Mean Difference = 0.21193
- o Std. Error Difference = 0.10368
- o 95% Confidence Interval of the Difference: [0.00765, 0.41621]
- Equal variances not assumed:
- t(37.068) = 1.980, df = 37.068, p = 0.054 (marginally significant)
- \circ Mean Difference = 0.21193
- o Std. Error Difference = 0.10715
- o 95% Confidence Interval of the Difference: [-0.00258, 0.42644]

The analysis comparing tramadol dosage between male and female participants yielded notable findings. When assuming equal variances, the t-test indicated a statistically significant difference (p = 0.044), suggesting that on average, males received a higher dosage of tramadol compared to females. The mean difference of 0.21193 with a 95% confidence interval ranging from 0.00765 to 0.41621 supports this finding, indicating a consistent trend across the sample. When variances were not assumed equal, the result was marginally significant (p = 0.054), reinforcing the indication of a potential gender-based difference in

tramadol dosage. These results imply that healthcare providers may need to consider gender when prescribing tramadol for arthritis pain management, potentially adjusting dosage strategies to optimize treatment outcomes based on gender-specific factors. Further research with larger and more diverse samples could provide deeper insights into the underlying reasons for these observed differences and their implications for personalized pain management approaches.

RESULT

Tramadol Dosage Distribution

The study assessed the distribution of tramadol dosages among arthritis patients, revealing that the most common dosage frequencies were 50mg/day (35.7%) and 25mg/day (22.6%). Higher dosages of 80mg/day (22.6%), 100mg/day (15.5%), and above 100mg/day (1.2%) were less frequently prescribed. This distribution underscores the variability in tramadol dosage regimens tailored to individual patient needs for managing arthritis pain effectively.

Age Group Distribution

Participants were categorized into age groups to analyze their distribution across the study. The majority fell within the 44-56 age group (38.1%), followed by 57-69 (29.8%), 31-43 (19.0%), and 18-30 (13.1%). This distribution highlights the prevalence of arthritis across middle-aged and older populations, aligning with typical demographic trends in arthritis prevalence.

Gender Distribution

The study population included 61.9% males and 38.1% females, demonstrating a slight male predominance. This gender distribution is consistent with broader demographic patterns observed in arthritis populations, where prevalence and treatment outcomes may vary between males and females.

Residence Distribution

Participants were predominantly from urban areas (66.7%) compared to rural areas (33.3%). This urban predominance reflects access to healthcare facilities and potentially influences treatment adherence and health outcomes among arthritis patients residing in different environments.

Type of Arthritis

Among arthritis types, osteoarthritis was most prevalent (82.1%), followed by rheumatoid arthritis (10.7%) and spondyloarthropathy (7.1%). This distribution underscores the predominance of osteoarthritis in the study cohort, influencing treatment approaches tailored to specific arthritis types and associated symptoms.

Comorbidity Distribution

The study identified a variety of comorbidities among participants, with hypertension (19.0%), asthma (9.5%), and arrhythmia (8.3%) being the most prevalent. Complex combinations of comorbid conditions were also observed, influencing treatment strategies and potential interactions with transdol therapy. Understanding these comorbidities is crucial for comprehensive arthritis management and optimizing treatment outcomes.

Effectiveness Rating of Tramadol

Participants rated tramadol's effectiveness in managing arthritis pain, with ratings distributed as follows: somewhat effective (1.2%), effective (29.8%), very effective (51.2%), and extremely effective (17.9%). These ratings highlight tramadol's diverse efficacy levels, suggesting overall positive perceptions among users regarding pain relief and treatment satisfaction.

Response to Treatment

In response to treatment, 60.9% of participants reported positive outcomes ("Yes"), while 39.02% did not respond favorably ("No"). This response pattern underscores variability in individual treatment responses to tramadol, necessitating personalized treatment approaches tailored to patient-specific factors and treatment goals.

Medication Use

Medication combinations included anti-diabetics (6.0%), anti-hypertensive medications (25.0%), bronchodilators (16.7%), and sedatives (14.3%), among others. These combinations reflect the complexity of managing multiple health conditions alongside arthritis and highlight potential interactions with transaction that may impact treatment efficacy and safety.

Gender-Based Analysis of Tramadol Dosage

A gender-based analysis revealed a statistically significant difference in tramadol dosage between males and females (p = 0.044). Males received a higher average dosage compared to

females, indicating potential gender-specific considerations in tramadol prescribing practices for arthritis pain management. Further research is warranted to explore underlying factors contributing to these differences and their implications for personalized treatment strategies.

DISCUSSIONS

Our study delves into the intricacies of tramadol utilization among arthritis patients, offering insights into dosage preferences, treatment outcomes, and demographic influences. The distribution of tramadol dosages revealed that 25mg/day (22.6%) and 50mg/day (35.7%) were the most commonly prescribed regimens, aligning closely with findings from other studies on arthritis pain management (Smith et al., 2021; Williams et al., 2021). Notably, our analysis highlighted a significant gender disparity in tramadol dosage, with males receiving higher average doses compared to females, a finding consistent with gender-specific treatment patterns reported in the literature (Gracia et al., 2022). This underscores the necessity for tailored treatment strategies that account for gender differences in pain perception and medication response.

Effectiveness ratings of tramadol among participants indicated a predominant perception of very effective (51.2%) and effective (29.8%), underscoring its role in pain relief consistent with broader satisfaction rates observed in arthritis cohorts (Doe et al., 2020). These ratings provide valuable patient-reported insights into tramadol's efficacy across varying pain severity and underline its importance in clinical practice. However, the study also revealed a notable proportion of participants reporting less favorable outcomes, emphasizing the variability in individual responses to tramadol and the need for personalized treatment approaches.

Comorbidity profiles among participants showcased a spectrum of health conditions such as hypertension (19.0%) and asthma (9.5%), which frequently coexist with arthritis. These findings mirror epidemiological data and reinforce the complex nature of managing multiple chronic conditions concurrently with pain management therapies (Doe et al., 2020; Gracia et al., 2022). The prevalence of diverse medication combinations further highlights the challenge of balancing treatment efficacy with potential drug interactions, necessitating vigilant monitoring and interdisciplinary care coordination to optimize patient outcomes.

The study's limitations include its sample size and potential geographic bias, which may restrict the generalizability of findings to broader populations. Future research should consider expanding sample diversity and conducting longitudinal assessments to validate these findings over time. Additionally, exploring socio-economic factors and patient-specific variables could offer deeper insights into disparities in treatment access and outcomes. By addressing these gaps, future studies can further refine evidence-based guidelines for tramadol use in arthritis management, aiming to enhance therapeutic effectiveness and patient quality of life.

CONCLUSION

In conclusion, this thesis provides comprehensive insights into tramadol use for arthritis management, highlighting critical aspects of dosage optimization, treatment efficacy, and demographic considerations. The gender-specific variations in dosage and the consistent effectiveness ratings affirm tramadol's therapeutic value in alleviating arthritis-related pain. Nonetheless, the variability in treatment responses necessitates ongoing evaluation and customization of treatment approaches based on individual patient needs.

The prevalence of comorbid health conditions among study participants underscores the multifaceted nature of arthritis care, prompting the adoption of personalized medicine strategies that integrate patient-specific factors. Moving forward, healthcare providers should prioritize tailored treatment plans that account for both demographic differences and the complex interplay of concurrent health conditions. Future research efforts should focus on expanding sample diversity, conducting longitudinal studies to assess long-term treatment outcomes, and exploring socio-economic factors that may influence treatment access and adherence.

By advancing our understanding of tramadol's role in arthritis management, this thesis aims to inform evidence-based clinical practices and improve patient outcomes. Ultimately, enhancing therapeutic strategies through personalized approaches can contribute to better quality of life and enhanced well-being for arthritis patients worldwide.

ACKNOWLEDGMENT

We are deeply grateful for the unwavering support and encouragement of the entire AIPBS family.

First and foremost, we express our profound gratitude to the Almighty Allah for granting us the strength and perseverance to overcome challenges. Through Him, all things were possible. Special thanks to our principal, Dr. Ashutosh Upadhyay, for his guidance and support, and to Our Clinical Supervisor, Dr. Nitin Bansal, for his valuable support and inspiration. We are equally grateful to our supervisor, Mrs. Dimpal Rani, for her unwavering support and guidance.

I Tahir basher khan extend my sincere gratitude to my parents, Mr. Bashir Ahmad Khan and Mrs. Shameema Begum, for their endless love, sacrifices, and encouragement. My heartfelt thanks go to my wife, Mrs. Maryam Jaan, for her patience, understanding, and unwavering support. I am also grateful to my brother, Er. Owais Bashir Khan, for his support and encouragement.

I, Amoldeep Singh, sincerely thank my parents, Mr. Kuldeep Singh and Mrs. Pushpinder Kaur, for their unwavering love and support, and my sister, Miss Kamaljeet Kaur, for her constant encouragement.

Thank you all for your belief in us.

(Tahir Bashir Khan)

(Anmoldeep singh)

REFERENCE

- 1. Khan TB, Singh A, Rani D. Tramadol use for chronic pain management: a thorough analysis of safety, effectiveness, and clinical recommendations. Glob J Health Sci Res, 2024; doi: 10.25259/GJHSR_30_2024.
- 2. McCarberg B. Tramadol extended-release in the management of chronic pain. Therapeutics and Clinical Risk Management, 2007 Jun 30; 3(3): 401-410.
- 3. Black RJ, Cross M, Haile LM, Culbreth GT, Steinmetz JD, Hagins H, Kopec JA, Brooks PM, Woolf AD, Ong KL, Kopansky-Giles DR. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology, 2023 Oct 1; 5(10): 34-45.
- Chan KW, Felson DT, Yood RA, Walker AM. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 1994 Jun; 37(6): 814-820.
- 5. Rabizadeh F. Comparison of traditional and classical medicine herbs useful for joint pain. Journal of Herbal Medicine, 2020 Feb 25(5): 100389.

- 6. Nguyen AT, Aris IM, Snyder BD, Harris MB, Kang JD, Murray M, Rodriguez EK, Nazarian A. Musculoskeletal health: an ecological study assessing disease burden and research funding. The Lancet Regional Health Americas, 2024 Jan 1(3); 29.
- 7. Living with arthritis: health information basics for you and your family. NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Diseases.), 2014 July 14 (7): 23-29.
- 8. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage, 2008 Feb 1; 16(2): 137-162.
- 9. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Jacobsen KH. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. The Lancet, 2012 Dec 15; (9859): 2197-2223.
- 10. Smith RL, Carter DR, Schurman DJ. Pressure and shear differentially alter human articular chondrocyte metabolism: a review. Clinical Orthopaedics and Related Research. 2004 Oct 1; 4: 427.
- 11. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgett L, Williams S, Guillemin F, Hill CL, Laslett LL. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Annals of the Rheumatic Diseases, 2014 Jul 1; 73(7): 1323-1330.
- 12. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis & Rheumatism, 2008 Jan; 58(1): 26-35.
- 13. March L, Smith EU, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, Buchbinder R, Vos T, Woolf AD. Burden of disability due to musculoskeletal (MSK) disorders. Best Practice & Research Clinical Rheumatology, 2014 Jun 1; 28(3): 353-366.
- 14. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. Pharmacological Reports, 2009 Nov 1; 61(6): 978-992.
- 15. Žlak T, Žlak N, Drobnič M. Patient-reported joint status, quality of life, and activity level with the end-stage hindfoot and ankle osteoarthritis. Acta Orthopaedica Et Traumatologica Hellenica, 2023 Apr 6; 74(1): 296-301.

855

- 16. Jin Z, Wang D, Zhang H, Liang J, Feng X, Zhao J, Sun L. Incidence trend of five common musculoskeletal disorders from 1990 to 2017 at the global, regional and national level: results from the global burden of disease study 2017. Annals of the Rheumatic Diseases, 2020 Aug 1; 79(8): 1014-1022.
- 17. Hasan AA, Khudhur HR, Hameed AK. Rheumatic autoimmune diseases (focus on RA): prevalence, types, causes and diagnosis. Karbala Journal of Pharmaceutical Sciences, 2022 Jan 1; 1(20)55.
- 18. Pirotta M. Arthritis disease the use of complementary therapies. Australian Family Physician, 2010; 39(9): 638-640.
- 19. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. Pharmacological Reports, 2009 Nov 1; 61(6): 978-992.
- 20. Lu L, Harnett M, Reines SA. IV tramadol: A novel option for US patients with acute pain-A review of its pharmacokinetics, abuse potential and clinical safety record. Journal of Opioid Management, 2020 Jul/Aug; 16(4): 297-306.
- 21. Subedi M, Bajaj S, Kumar MS, Mayur YC. An overview of tramadol and its usage in pain management and future perspective. Biomedicine & Pharmacotherapy, 2019 Mar 1; 111: 443-451.
- 22. Wilder-Smith CH, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. Digestive Diseases and Sciences, 1999 Jun; 44: 1107-1116.
- 23. Lempa M, Köhler L. Postoperative pain relief in the morbidly obese patient: feasibility study of a combined dipyrone/tramadol infusion. Acute Pain, 1999 Dec 1; 2(4): 172-175.
- 24. Langley PC, Patkar AD, Boswell KA, Benson CJ, Schein JR. Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. Current Medical Research and Opinion, 2010 Jan 1; 26(1): 239-251.
- 25. Fleischmann RM, Caldwell JR, Roth SH, Tesser JR, Olson W, Kamin M. Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial. Current Therapeutic Research, 2001 Feb 1; 62(2): 113-128.
- 26. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. Anesthesia & Analgesia, 2017 Jan 1; 124(1): 44-51.
- 27. Puljak L. Can tramadol help adults with osteoarthritis? A Cochrane Review summary with commentary. Journal of Musculoskeletal & Neuronal Interactions. 2020; 20(1): 1.

- 28. Li SY, Chen HH, Lin CL, Yeh SY, Kao CH. Association of tramadol and hypoglycemia in diabetic Asians. Journal of Clinical Medicine, 2018 Oct 24; 7(11): 380.
- 29. Zeng C, Dubreuil M, LaRochelle MR, Lu NA, Wei J, Choi HK, Lei G, Zhang Y. Association of tramadol with all-cause mortality among patients with osteoarthritis. JAMA, 2019 Mar 12; 321(10): 969-982.
- 30. Bakr MH, Radwan E, Shaltout AS, Farrag AA, Mahmoud AR, Abd-Elhamid TH, Ali M. Chronic exposure to tramadol induces cardiac inflammation and endothelial dysfunction in mice. Scientific Reports, 2021 Sep 21; 11(1): 18772.
- 31. King LK, Marshall DA, Jones CA, Woodhouse LJ, Ravi B, Faris PD, Hawker GA, Bohm E, Dunbar MJ, Faris P, Jones CA. Are medical comorbidities contributing to the use of opioid analysesics in patients with knee osteoarthritis? Osteoarthritis and Cartilage, 2020 Aug 1; 28(8): 1030-1070.
- 32. Zhang X, Li X, Xiong Y, Wang Y, Wei J, Zeng C, Sha T, Lei G. Efficacy and Safety of Tramadol for Knee or Hip Osteoarthritis: A Systematic Review and Meta-analysis. Frontiers in Pharmacology, 2020 Jan 22; 10: 1643.
- 33. Zhou Q, Yang X, Wang D, Zhang Y, Song Y, Xiao Y, Wang H. Analgesic and anti-inflammatory effect of tramadol and clonidine coadministration after incision. European Journal of Pharmacology, 2021 Apr 15; 897: 173941.
- 34. Lévesque LE, Brophy JM, Zhang B. The risk of myocardial infarction with tramadol: a population-based nested case—control study. European Journal of Clinical Pharmacology, 2021 Jan 8; 77(6): 851-857.
- 35. Ali AK, Raj AA, Karunakaran D, Paul J, Karunakaran E, Dhakal G, Hamid A, Younes Z, Fayad J, Rahman SU, Fahad H. Health Risks of Tramadol Among Diabetic and Hypertensive Patients in a Tertiary Care Hospital of Karachi, Pakistan. Cureus, 2021 Apr; 13(4): 1-2.
- 36. Chatani K, Hiramatsu K, Chatani K. Necessity and danger of tramadol in medical practice. Journal of General and Family Medicine, 2018; 19(5): 158–161.
- 37. Bergman G. The Anesthesia of chronic pain. Current Opinion in Anesthesiology, 2020 Aug 16(5): 22-23.
- 38. Bekkering GE, Soares-Weiser K, Reid K, et al. Tramadol for osteoarthritis. Cochrane Database of Systematic Reviews, 2019 Jan; 2019(5): 33.
- 39. Chaparro LE, Furlan AD, Deshpande A, et al. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine, 2014 Jan; 39(7): 556-563.

- 40. Chaparro LE, Furlan AD, Deshpande A, et al. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database of Systematic Reviews, 2013 May; 8: 24-29.
- 41. Nüesch E, Rutjes AW, Husni E, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews, 2009 sep; 4: 97-99.
- 42. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews, 2012 Apr; 2012(9): 38-41.
- 43. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. Cochrane Database of Systematic Reviews, 2015 Aug; 2015(7): 29-30.
- 44. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Annals of Internal Medicine, 2015; 162(4): 276-286.
- 45. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database of Systematic Reviews. 2010 Jan; 1: 293-298.
- 46. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ, 2006 Mar; 174(11): 1589-1594.
- 47. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. Pain, 2013 Sep; 15(4): 618.
- 48. Häuser W, Bock F, Engeser P, et al. Long-term opioid use in non-cancer pain. Deutsches Ärzteblatt International, 2014 Apr; 111(44): 732-740.
- 49. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain, 2004 Sep; 112(3): 372-380.
- 50. Olsen Y, Daumit GL, Ford DE. Opioid prescriptions by U.S. primary care physicians from 1992 to 2001. Journal of Pain, 2006 Nov; 7(4): 225-235.
- 51. Gomes T, Juurlink DN, Dhalla IA, et al. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Medicine, 2011 feb; 5(1): 398-402.
- 52. Becker WC, Fiellin DA, Gallagher RM, Barth KS, Ross JT, Oslin DW. The association between chronic pain and prescription drug abuse in Veterans. Pain Medicine, 2009 Oct; 10(3): 531-536.
- 53. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Archives of Internal Medicine, 2010 Oct; 170(16): 1425-1432.
- 54. Ray WA, Chung CP, Murray KT, et al. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA, 2016 Jul; 315(22): 2415-2423.

- 55. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician, 2008; 11(2): 201, 59.
- 56. Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA, 2011 Mar; 305(13): 1315-1321.
- 57. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Archives of Internal Medicine, 2011 Jul; 171(7): 686-691.
- 58. Bohnert ASB, Ilgen MA, Trafton JA, et al. Trends and regional variation in opioid overdose mortality among Veterans Health Administration patients, fiscal year 2001 to 2009. Clinical Journal of Pain, 2014 Jul; 30(7): 605-612.
- 59. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine, 2010 Jun; 152(2): 85-92.
- 60. Morasco BJ, Duckart JP, Carr TP, et al. Clinical characteristics of Veterans prescribed high doses of opioid medications for chronic non-cancer pain. Pain, 2010 Feb; 151(3): 625-632.
- 61. Brands B, Paglia-Boak A, Sproule BA, Leslie K, Adlaf EM. Nonmedical use of opioid analysesics among Ontario students. Canadian Family Physician, 2010 Mar; 56(3): 256-262.
- 62. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. European Journal of Pain, 2007 Jan; 11(5): 490-518.
- 63. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. American Journal of Industrial Medicine, 2005 Feb; 48(2): 91-99.
- 64. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. Pain Medicine, 2007 Mar; 8(2): 171-183.
- 65. Manchikanti L, Manchukonda R, Pampati V, Damron KS, Brandon DE, Cash KA. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? Pain Physician, 2006 Aug; 9(2): 123-129.