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Opioidų sunaudojimas. Lyginamasis Lietuvos, Norvegijos ir Švedijos tyrimas analizuojant 2014 - 2021 metus

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MASTER'S THESIS

Utilization of Opioids. Comparison Study Between Lithuania, Norway, and Sweden during 2014 and 2021

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List of Abbreviation

ASA - American Society of Anesthesiologists

ATC - Anatomical Therapeutic Chemical

CNCP - Chronic non-cancer pain

CNS - Central nervous system

CDC - Centres for Disease Control and Prevention

DDD - Defined daily dose

DOR - Delta-opioid receptor

INCB - International Narcotics Control Board

IDU - Injection drug use

IASP - International Association for the Study of Pain

JCAHO - Joint Commission on Accreditation of Healthcare Organizations

KOR - Kappa-opioid receptor

LTOT - Long-Term Opioid Therapy

MAT - Medication-Assisted Treatment

MTD - Maximum tolerated dose

MIC - Minimum effective dosage

MOR - Mu opioid receptor agonist

MOH - Medication Overuse Headache

NMDAR - N-Methyl-D-aspartate receptor

NPS - New Psychoactive Substances

NRI - Norepinephrine reuptake inhibitor

OUD - Opioid use disorder

PAG - Periaqueductal grey

PCA - Patient-controlled analgesia

RVM - Rostral ventromedial medulla

SRSOs - Slow-release strong opioids

ABSTRACT:

Background: Opioids have become one of the most prevalent treatment of pain and a commonly used medicine across the globe. The recent opioid crisis in the US and other parts of the world has strained the controlling and regulating authorities worldwide to evaluate the related on the use of opioids among the population and the adverse effects for the individual users. This reflects the critical nature of the issue and the need for a better treatment and care for people with pain.

Aim: This research is aimed at the following objectives analyse opioid utilization rates in Lithuania, Sweden, and Norway between 2014 and 2021.

Objectives:

1. Assess if there are any differences in total use of opioids through comparing wholesale data in Lithuania, Sweden, and Norway between 2014 and 2021.
2. Examine the distribution of different substances (opioids) in Lithuania, Sweden, and Norway between 2014 and 2021.
3. Assess sex- and age differences prescribing of opiods in Lithuania through comparison using two months for reference (2017-04 and 2017-06)

Methodology: The study uses wholesale data records to compare the trends in opioid use across the three countries from 2014 to 2021. The comparative analysis provides key insights regarding the use trends and growth of opioid use in healthcare and medication. Moreover, Lithuanian prescription data has been used to get deeper insight into opioid utilization patterns between different sex and age groups.

Results and conclusions: The research reveals that Norway and Sweden have reduced opioid use. At the same time, Lithuania has increased it due to a lack of regulation, opioid availability, and awareness of the consequences. Even though, it is still far lower than Norway and Sweden. Codeine, paracetamol, and tramadol were the most often used opioids in Norway, Sweden, and Lithuania, respectively. The key findings of this study are as follows:

In Lithuania, Opioid usage increased progressively from 2014 (1.71 DDD/TID) to 2021 (3.26 DDD/TID). The use of fixed combination of codeine and paracetamol use slightly increased from 2014 (0.16 DDD/TID) to 2021 (0.38 DDD/TID), while tramadol remained constant at around 0.93 DDD/TID. Fentanyl use slightly increased from 2014 to 2021 (0.36-0.44 DDD/TID), while morphine use slightly decreased (0.23-0.19 DDD/TID). In April and June

2017, prescription amounts for females were higher than for males, and prescription amounts increased significantly from April to June for both sexes. The prescription amount across all the relevant matrices almost doubled between April and June 2017.

In Norway, Opioid usage was highest in 2014 (19.93 DDD/TID) and lowest in 2021 (18.22 DDD/TID). Tramadol usage slightly reduced from 2014-2021 (4.09-3.94 DDD/TID). The utilization of codeine and paracetamol in fixed combinations was highest in 2014 (9.90 DDD/TID) and slightly reduced in 2021 (7.72 DDD/TID). Oxycodone usage was lowest in 2014 (1.94 DDD/TID) and increased substantially in 2021 (2.45 DDD/TID). Fentanyl usage reduced slightly from 2014 to 2021 (1.36-1.29 DDD/TID). Morphine usage showed a similar reduction pattern from 2014 to 2021 (1.17-1.06 DDD/TID).

In Sweden, Opioid usage was highest to 2021 (17.67 DDD/TID) and lowest in 2021 (10.65 DDD/TID). Fixed combination of codeine and paracetamol usage were highest in 2014 (6.37 DDD/TID) and lowest in 2021 (3.86 DDD/TID). Tramadol usage was highest in 2014 (4.66 DDD/TID) and lowest in 2021 (1.70 DDD/TID). Oxycodone usage was lowest in 2014 (1.82 DDD/TID) and increased substantially in 2021 (2.24 DDD/TID).

The research study identified large differences in trends of opioid utilization between three neighbouring countries. It promotes the significance of addressing the root causes of opioid usage in each country and there may be opportunies for learning between countries to utilise opioids more efficiently. Finally, it advocates safe opioid use, according to international healthcare organisation guidelines.

SANTRAUKA:

Pagrindiniai faktai: Opioidai tapo vienu iš labiausiai paplitusių skausmui gydyti naudojamų vaistų ir vieni dažniausiai naudojamų vaistų visame pasaulyje. Pastaroji opioidų krizė JAV ir kitose pasaulio dalyse privertė visame pasaulyje kontroliuojančias ir reguliuojančias sveikatos institucijas įvertinti opioidų vartojimą tarp gyventojų ir šalutinį poveikį pacientams. Tai atspindi kritinį problemos pobūdį ir reikalingumą geresnėms gydymo strategijoms ir priežiūrai pacientų grupei kenčiančiai skausmą.

Tikslas: Šio tyrimo tikslas – išanalizuoti opioidų vartojimo rodiklius Lietuvoje, Švedijoje ir Norvegijoje 2014–2021 metais.

Darbo uždaviniai:

1. Įvertinti ar yra skirtumų bendrame opioidų suvartojime Lietuvoje, Švedijoje ir Norvegijoje 2014-2021 metais, naudojantis didmeninės prekybos duomenimis.

2. Išnagrinėti įvairių vaistų (opioidų) suvartojimo pasiskirstymą lyginant Lietuvą, Švediją ir Norvegiją 2014-2021 metais.

3. Įvertinti ar yra skirtumas tarp lyties, amžiaus ir suvartojamo opioidų kiekio Lietuvoje, palyginimui, naudojant du mėnesius (2017-04 ir 2017-06).

Metodologija: magistro darbe buvo naudojami didmeninės prekybos duomenų įrašai, siekiant palyginti opioidų suvartojimo kiekį trijose šalyse 2014–2021 m. Lyginamoji analizė suteikia pagrindines įžvalgas apie opioidų suvartojimo kiekį ir jų suvartojimo augimą medicinos srityje. Be to, Lietuvos receptų duomenys buvo naudojami siekiant giliau suprasti opioidų vartojimo tendencijas skirtingose lyties ir amžiaus grupėse.

Rezultatai ir išvados: Tyrimas atskleidžia, kad Norvegijoje ir Švedijoje sumažėjo opioidų suvartojamas kiekis. Lietuvoje jis galimai padidėjo dėl laisvesnių taisyklių paskiriant gydymą opioidų turinčiais vaistais, didesnio opioidų prieinamumo ir mažesnio supratimo apie opioidų priklausomybę. Nepaisant to, jis vis dar yra daug mažesnis nei Norvegijoje ir Švedijoje. Norvegijoje, Švedijoje ir Lietuvoje dažniausiai vartojami opioidai buvo kodeinas kombinacijoje su paracetamoliu ir tramadolis.

Pagrindinės šio tyrimo išvados yra šios: Lietuvoje opioidų vartojimas palaipsniui didėjo nuo 2014 m. (1,71 DDD/TID) iki 2021 m. (3,26 DDD/TID). Fiksuoto kodeino ir paracetamolio derinio vartojimas šiek tiek padidėjo nuo 2014 m. (0,16 DDD/TID) iki 2021 m. (0,38

DDD/TID), o tramadolio išliko pastovus – maždaug 0,93 DDD/TID. Fentanilio vartojimas šiek tiek padidėjo nuo 2014 m. iki 2021 m. (0,36–0,44 DDD/TID), o morfino suvartojimas šiek tiek sumažėjo (0,23–0,19 DDD/TID). 2017 m. balandžio ir birželio mėnesiais receptų kiekis moterims buvo didesnis nei vyrams, o nuo balandžio iki birželio mėnesio abiem lytims išrašytų receptų kiekis labai padidėjo. Receptų kiekis visose atitinkamose grupėse nuo 2017 m. balandžio mėn. iki birželio išaugo beveik dvigubai.

Norvegijoje opioidų suvartojimas buvo didžiausias 2014 m. (19,93 DDD/TID), o mažiausias – 2021 m. (18,22 DDD/TID). Tramadolio vartojimas šiek tiek sumažėjo nuo 2014–2021 m. (4,09–3,94 DDD/TID). Kodeino fiksuotoje kombinacijoje su paracetamoliu suvartojimas fiksuotuose deriniuose buvo didžiausias 2014 m. (9,90 DDD/TID), o 2021 m. šiek tiek sumažėjo (7,72 DDD/TID). Oksikodono vartojimas buvo mažiausias 2014 m. (1,94 DDD/TID), o 2021 m. labai išaugo (2,45 DDD/TID). Fentanilio vartojimas šiek tiek sumažėjo nuo 2014 m. iki 2021 m. (1,36–1,29 DDD / TID). 2014–2021 m. morfino suvartojimas sumažėjo panašiai (1,17–1,06 DDD/TID).

Švedijoje opioidų suvartojimas buvo didžiausias iki 2021 m. (17,67 DDD / TID) ir mažiausias 2021 m. (10,65 DDD / TID). Kodeino fiksuotoje kombinacijoje su paracetamoliu vartojimas buvo didžiausias 2014 m. (6,37 DDD/TID) ir mažiausias 2021 m. (3,86 DDD/TID). Tramadolio vartojimas buvo didžiausias 2014 m. (4,66 DDD / TID), o mažiausias 2021 m. (1,70 DDD / TID). Oksikodono suvartojimas buvo mažiausias 2014 m. (1,82 DDD/TID), o 2021 m. labai išaugo (2,24 DDD/TID). Magistro darbe atliktas tyrimas nustatė didelius opioidų suvartojimo tendencijų skirtumus trijose tirtose šalyse. Jis skatina suprasti pagrindines opioidų sunaudojimo priežastis kiekvienoje tirtoje šalyje ir pabrėžia, jog tarp šalių yra galimybė mokytis ir tobulėti. Galiausiai, šiame magistro darbe atliktame tyrime yra skatina saugus opioidų naudojimas, laikantis tarptautinių sveikatos priežiūros organizacijų rekomendacijų ir normų.

CHAPTER # 1. INTRODUCTION

Pain has a substantial social and economic toll, making it a major public health concern (1). Biological, psychological, and social elements are all recognized to interact dynamically, making chronic non-cancer pain a complicated biopsychosocial phenomenon (2). Varied chronic pain classifications, different evaluation methodologies, and population differences contribute to a broad range of estimates for the prevalence of Chronic non-cancer pain (CNCP) in epidemiological research (3). One-fifth of Europe's projected adult population of 250 million people reported having had moderate or severe pain in the previous month, according to a large-scale internet-based study conducted across Europe (United Kingdom, France, Spain, Italy, and Germany) (4). A systematic review indicated a frequency of 19% among adults, with 65% reporting moderate pain and 35% reporting severe pain (5). Sixty per cent said their pain lasted between two and fifteen years, while 21 per cent said it lasted twenty years or more. One-third of people with pain do not obtain therapy, 40% receive insufficient pain management, and only 2% are handled by pain management professionals. Chronic back pain and arthritis, especially osteoarthritis, are the most frequent chronic pain problems by two of the largest pan-European studies (6). Unfortunately, despite pain's widespread prevalence, there is a lack of solid and trustworthy epidemiological data.

Opioids have been used to treat both acute and chronic pain for hundreds of years. Sumerians began growing opium poppies in southern Mesopotamia around 3400 BC, referring to them as "joy plants" because of their euphoric effects (7). In ancient Egyptian papyri, opium was documented as a pain reliever, and in 1170, the earliest book on Western surgery detailed its usage during operations. Modern opioids include both naturally occurring opiates like morphine and codeine, as well as synthetic opioids like tramadol and oxycodone (e.g., methadone, buprenorphine, and fentanyl) (8). Opioids can be classified as either mild (like codeine and tramadol) or powerful (like heroin) (e.g., morphine, oxycodone). As opioids are more effective when administered in high dosages, the usefulness of such a categorization is also doubtful (9). Both immediate-release and extended-release forms of certain opioids have been produced.

In Lithuania, the rate of legal opioid usage increased from 0.34 per 1000 people to 1.45 from 2015 to 2018 (10). In 2020, opioid dependence represented 80.3% of all drug dependence in Lithuania. Drug effectiveness is a concept that should be applied to research on drug dependency in order to measure outcomes including social functioning, physical and mental health, quality of the surrounding environment, and overall happiness (11). The goal of measuring quality of life is to ascertain how effective a therapy is in improving a patient's ability

to live a normal, healthy life. It is now widely accepted that the drug effectiveness is a useful metric for gauging the efficacy of drug treatment initiatives (12). Over the past two decades, there has been an improvement in our understanding of opioid usage due to the advancement of national and international studies. The majority of research in Lithuania so far, employ standardized self-report or parent-report questionnaires to measure the prevalence of legal opioid usage rather than depending on physician diagnosis (10). But recently, a growing number of studies have concentrated on documenting opioid use globally. Studies on drug use, particularly ones that contrast national consumption, are relatively uncommon in Lithuania. A cross-national comparison is a helpful tool for learning since it gives a general idea of the patterns in opioid consumption across various contexts. In this master's thesis, I have conducted an independent review of the literature, developed the project's goals and objectives under the supervision of the project coordinators, conducted a descriptive statistical analysis, presented the findings, compared them to those of earlier similar studies, and coma to conclusions.

A poll indicates that roughly 3.2% of Lithuania's population overall has Medication Overuse Headache (MOH) (10). Also, according to statistics from the Official Statistical Portal on the population of Lithuania between the ages of 18 and 65 in 2015, there may be as many as 59,000 individuals in Lithuania who have MOH (13). Another research found that compared to Netherlands, Germany, Cyprus, and Greece, Lithuania had one of the lowest rates of problem drug usage. In 2005 and 2007, the majority of Lithuania's problem drug users were young males of working age (14). Another study checked the reliability and validity of the questionnaires used in Lithuania and formulated patient-centred recommendations for better cancer pain management (15). However, there is a lack of study regarding opioid utilization rates, opioid substances in market, and the distribution of different opioids in Lithuania, Sweden, and Norway. Sweden and Norway are interesting countries to study in this case as it is worth noting that while the rates of opioid use and overdose deaths in Sweden and Norway are lower than in many other countries, there is still room for improvement, and these countries continue to work on developing new policies and strategies to reduce the harm associated with opioid use. So, this research aims to address that void by comparing the wholesale statistics of Lithuania, Sweden, and Norway to identify any discrepancies in opioids between the three countries.

1.1 AIM

This research is aimed at the following objectives analyse opioid utilization rates in Lithuania, Sweden, and Norway between 2014 and 2021.

1.2 OBJECTIVES

- Assess if there are any differences in total use of opioids through comparing wholesale data in Lithuania, Sweden, and Norway.
- Examine the distribution of different substances (opioids) in Lithuania, Sweden, and Norway
- Assess sex- and age differences prescribing of opiods in Lithuania through comparison using two months for reference (2017-04 and 2017-06)

CHAPTER # 2. LITERATURE REVIEW

2.1 PAIN AND CLASSIFICATION

One of the most prevalent causes of medical attention-seeking is pain. According to statistics, 25-30% of people with pain in specific bodily parts report fair or poor health, 15-22% are unable to work, 12-17% sleep less than five hours per day, and 6-13% have psychological suffering (1). According to research, at least one-third of hospital patients report severe pain, and one-half of all patients report some level of pain. Inadequate pain therapy can significantly raise healthcare expenditures due to the enormous impact pain has on the patient's physical and mental health (16). Pain is responsible for around 10% of all medication sales by expenditure in the United States, and it costs an estimated $101 billion per year in healthcare costs and $61.2 billion in lost productivity. Pain that cannot be managed has been labelled "a serious worldwide healthcare concern" by the International Association for the Study of Pain (17). The good news is that effective pain management may have a positive impact on the patient's ability to go about their everyday life, which in turn can hasten their recovery and allow them to leave the hospital sooner. It might be difficult for doctors to find a way to alleviate pain quickly without worsening their patients' health (18).

2.1.1 DEFINITION

Pain is "an unpleasant sensory and emotional experience connected with existing or potential tissue damage, or characterized in terms of such damage," as defined by the International Association for the Study of Pain (19).

2.1.2 CLASSIFICATION

Pathophysiology (such as neuropathic or nociceptive pain), diagnostic purposes (chronic pain), aetiology (such as postoperative), and afflicted region are only some of the ways that pain has been categorized (e.g., headache, low back pain). Classifying pain as either nociceptive or neuropathic has proven to be more useful for therapy planning. Such categorizations help with treatment and medication selection (20). Diagnostically, pain can be either acute or chronic. Trauma, burns, infections, arthritis, and ischemia are all examples of injuries or inflammation that can cause nociceptive pain. Neuropathological pain is often treatable with standard analgesics. Trauma or malfunction in either the peripheral or central nervous system can lead to neuropathic pain (17). Nerve pain can be caused by a variety of conditions, including diabetes, herpes, and trauma. Unlike nociceptive pain, which often subsides on its own,

neuropathic pain syndromes can be chronic and challenging to manage. But other analgesics like tricyclic antidepressants and anticonvulsants could help them. Acute pain is characterized by a rapid start, a clear source, and a brief duration. Because it usually arises in the wake of an injury, its symptoms can be reduced or eliminated with successful treatment of the underlying condition (19). Stimulation of the autonomic nervous system is linked to symptoms including tachycardia, diaphoresis, and hypertension (16). Acute pain is a frequent response to an acute injury. In order to make diagnostic testing more manageable, it is crucial that acute pain be well managed. Managing acute pain can sometimes forestall the onset of chronic pain syndrome. In cases of chronic pain, it is not uncommon for psychological and behavioural elements to play a pivotal role (21). Chronic pain typically lasts longer than the typical recovery period. In some individuals, the threshold for activating primary afferent nociceptors can be lowered by severe, repetitive, or protracted stimulation (22).

2.2 OPIOIDS

"Opiate" is used to describe chemicals that are structurally similar to those found in opium (23). Papaver somniferum, more often known as the poppy, is harvested for its unripe seed capsules, which are processed and refined into opium. Powdered opium is made by drying the milky fluid, which is then processed into a powder that includes a variety of alkaloids (8). There are three distinct types of opioids: (i) opiates, which include morphine and codeine; (ii) semi-synthetic opioids, which include buprenorphine, oxycodone, and hydrocodone; and (iii) synthetic opioids, which include fentanyl, ketobemidone, and tramadol (24). The opioid agonist morphine is one example, but there are also opioids that operate as antagonists and agonists (buprenorphine). Opioids are the most effective pain relievers, but they also have the most prevalent negative effects (9).

Constipation, diarrhoea, itching, and nausea are the most common and most unpleasant side effects. Common analgesic dosages seldom cause life-threatening respiratory depression. Opioids' central nervous system (CNS) effects cause pain relief (25). By doing so, they indirectly suppress pain-transmission neurons while simultaneously activating pain-inhibitory neurons. Opioids are quite similar to one another pharmacologically. The primary areas where these drugs vary from one another are in terms of strength, length of action, and most effective delivery method (26). The quickest alleviation is achieved when given intravenously. There is a substantial inter-individual variation in the minimum effective dosage (MIC) and maximum tolerated dose (MTD) of opioids required to deliver the desired effects in any given patient (27).

Initiating treatment necessitates finding the best possible dose and time between treatments for patients with severe pain. The use of patient-controlled analgesia (PCA) is a novel method for providing effective pain management (28). Continuous PCA dosing is provided by the infusion device (29). By pressing a button, patients can give themselves extra dosages they've already programmed. Postoperative pain can be treated with PCA, and patients with metastatic disease can get short-term home care with this method (30). Alvimopan and methylnaltrexone, two peripherally acting opioid antagonists, have recently been added to the treatment arsenal for opioid-induced adverse effects. Alvimopan is a drug that may be taken orally but is only partially absorbed. Therefore its effects are confined to the digestive tract (31).

Opioids have several well-known physiological effects, including analgesia, altered body temperature, drowsiness, respiratory depression, hunger stimulation, slowed gastrointestinal transit, altered urine output, induced hyperalgesia, and euphoria or dysphoria. The three kinds of opioid receptors are principally responsible for these results: μ, κ, and δ. Among them, the μ-opioid receptor has received the greatest attention and research (24). Acute changes in neuronal excitability result from the activation of the G protein-coupled receptor. Opioid agonist activities at receptors are principally responsible for opioids' analgesic, antitussive, and antidiarrheal effects (32). Receptors also appear to be implicated in the misuse potential of several opioid medications. Some people with pain may be predisposed to or have a hereditary sensitivity to engaging in addictive behaviours. These behaviours may or may not include substances (24). Opioid addiction is linked to several signs and issues. While there has been widespread agreement in Western Europe over the past five years that substitution therapy is an important part of the treatment options available to people who are addicted to opioids, the efficacy of substitution treatment is still up for debate in Lithuania, where there is a severe lack of such facilities (33). The degree to which any given patient benefits from a given treatment may be moderated by their unique set of circumstances. Alterations to drug effectiveness and health status throughout therapy are crucial metrics for gauging the success of a program (32).

2.3 BRIEF HISTORY OF OPIOIDS

Opioids, a name derived from the Greek word opus, meaning "juice," refer to the alkaloid compounds in opium. It is extracted from the Papaver somniferum poppy and has been used for both recreational and medicinal purposes since ancient times (34). Poppies were initially cultivated by the Sumerians in approximately 3400 BC, according to historical records. Opium was widely adopted by Eurasia's major cultures due to its usefulness in medicine, particularly for the relief of pain (35). The active component was initially isolated from poppy seeds by a

German chemist named Friedrich Wilhelm Sertürner around the beginning of the nineteenth Century. He called the new substance morphine after the Greek deity of dreams, Morpheus (36). Opium use, especially for recreational purposes, spread throughout the West in the nineteenth Century, and opium dependency grew along with it. A hypodermic syringe and morphine were supplied to wounded Civil War soldiers. In the aftermath of World War II, widespread opioid addiction swept across American culture because of the careless distribution of narcotic painkillers to troops (37).

Table 1: Timeline of Important Events in Opioid History from Ancient to Modern Times

Historical Era	Events
5000 BC	Earliest reference to the growing of opium poppies
1500 BC	Opium usage for religious and medicinal purposes in Egypt and the Eastern Mediterranean
300 BC	In Greek medicine, opium is considered a narcotic
1660s	Sydenham's laudanum relieves pain
1803	Sertürner isolates morphine
1820	Merck commercializes morphine
1860s	Hypodermic syringe was discovered
1992-1993	Opioid receptors are cloned

Figure 1: "The countess, having taken a dose of laudanum nears death" Engraving by Louis Gérard Scotin after William Hogarth, 1745. (Welcome Collection gallery, CC-BY-4.0) (38)

Considering the widespread problem of morphine abuse, a replacement pain reliever was desperately sought. The first semi-synthetic opioid, heroin was developed in 1874 and given the brand name HeroinTM, derived from the Greek word for "hero," which refers to a powerful and heroic figure in mythology (39). Bayer marketed this respiratory medication as more efficient and less addicting than morphine. Heroin sales skyrocketed as its popularity grew around the globe. It wasn't until 1913 that its extreme addictiveness was discovered, at which point production was terminated (40). The tremendous addictive potential of opioids and their derivatives wasn't discovered until much later, when scientists could use new technologies to investigate the phenomenon. As a result, the first substance restrictions and control measures emerged around the turn of the twentieth Century. The availability of heroin and other opioids has been progressively curtailed (41). It was made illegal for doctors to prescribe opioids for the treatment of addiction by the 1914 Narcotics Tax Act in the United States, and the sale of heroin was outright banned by the League of Nations in 1925, both of which contributed to an increase in the illegal trafficking of precursor chemicals (42).

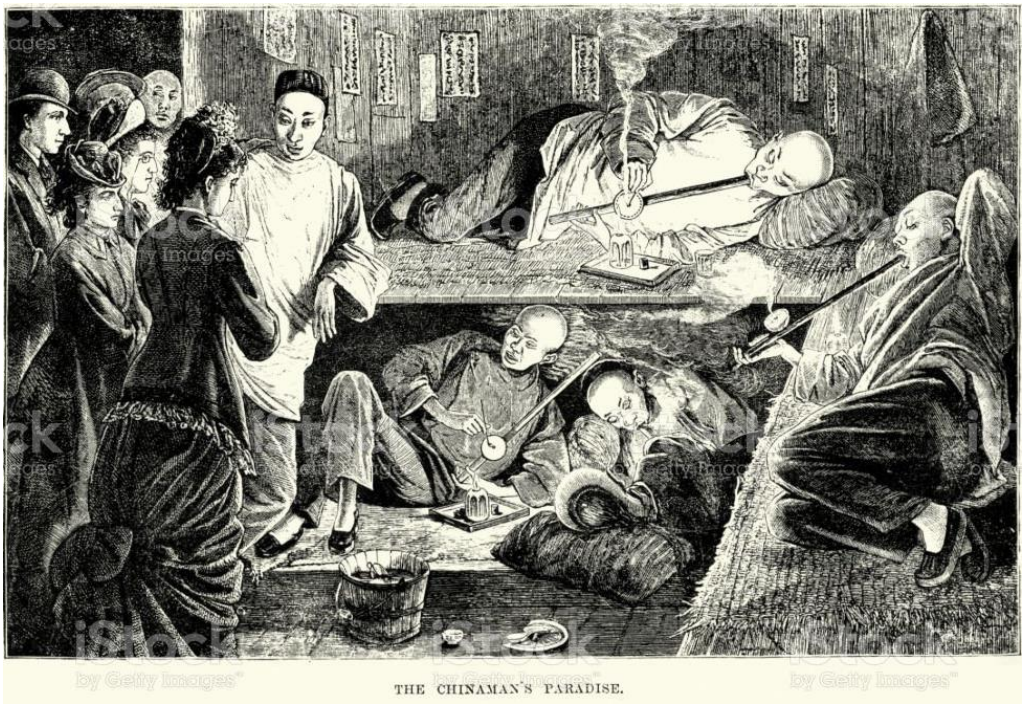

Figure 2: Chinese Opium Den San Francisco 19th Century (43)

Opioids were the standard treatment for cancer pain throughout the second half of the twentieth Century (44). Millions of people living with oncological pain have found that opioids have greatly improved their quality of life. Some writers argued that the widespread unfavourable perception of opioids was the result of both medical professionals' and patients' lack of familiarity with their proper usage (45). Historically, people have connected opioids with terminal illness, death, drug addiction, euthanasia, dangerous levels of drowsiness, panic attacks, and other negative emotions. The term "opiophobia" was coined to describe the widespread prevalence of false ideas and negative attitudes against the beneficial benefits of opioid administration for pain management. This is associated with doctors prescribing fewer of these medications and people taking fewer of them (23).

US healthcare systems began treating pain as a "5th vital sign" in the late 1990s. In 2001, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) made the prompt identification and treatment of pain a requirement for all healthcare facilities seeking accreditation (46). OxyContin is an extended-release version of oxycodone produced by the pharmaceutical corporation Purdue Pharma, which is notable because it was active in sponsoring and supplying teaching movies and materials about the need for better pain treatment (47). Initially touted as a less addictive substitute for traditional "narcotic" medications like morphine and heroin, OxyContin is a semi-synthetic opioid. It is being heavily promoted in the United States as an opioid-based treatment for moderate to severe pain caused

by different diseases (47). Most prescriptions for OxyContin were written by family doctors rather than pain specialists, and they were given to patients with a wide variety of pain conditions. Since 2010, sales of opioid analgesics in the United States have increased by a factor of four (48). Prescriptions for extended-release opioids, in instance, have skyrocketed from 9.2 million in 2012 to 22.9 million in 2019; that's an increase of 146% (49).

2.4 TYPES OF OPIOIDS

2.4.1 MORPHINE

It is reported to help with excruciating pain at a steady pace or via the intramuscular, intravenous, subcutaneous, or intrathecal routes. Morphine has a 10–15-minute onset and a duration of 2-4 hours, making it a complete OP3 agonist. It has the aforementioned negative consequences. This drug's active metabolite, morphine-6-glucuronide, is a glucuronide that the liver makes (morphine-3-glucuronide is also formed). Urine is the last destination for metabolites. Morphine does circulate from the intestines to the liver, although this is of no therapeutic significance (23). Morphine is Schedule 2 substance in Lithuania. Schedule 2 drugs include psychotropic compounds and narcotics, including plants, that are extremely harmful to human health in large doses. In the Republic of Lithuania, they are allowed to be used for health care purposes in compliance with the established ones.

2.4.2 BUPRENORPHINE

It is substance classified as Schedule 2 in Lithuania, that helps with mild pain. The drug can be administered intravenously, intramuscularly, subcutaneously, or orally, and it has a veterinary use authorization. There is an onset time of 45 minutes and its activities last 6-8 hours. This gives it a bell-shaped dosage response curve, with large experimental doses actually producing opioid receptor antagonism. It may consequently produce partial reversal of delivery of complete OP3 agonists such as methadone, morphine, fentanyl or pethidine (41).

2.4.3 BUTORPHANOL

It can be used to relieve slight pain. It doesn't do much to relieve pain, but it makes sleepy and helps stop coughing. Butorphanol is a mixed partial agonist that is used in veterinary medicine. It blocks signals sent by the OP3 receptor while acting as an agonist on the OP2 receptor. The effects of intravenous, intramuscular, or subcutaneous injection become noticeable within 15 minutes and continue for 2–4 hours (39). Currently is not indicated for human use in Lithuania, excluded only for animal use.

2.4.4 PETHIDINE

It is a complete OP3 agonist and used to treat moderate to severe pain. It can be administered i/m or s/c, but not intravenously because doing so will result in a significant release of histamine. The medicine takes 10-15 minutes to start working, and it lasts 30–60 minutes. Both chronotropic and spasmolytic, pethidine. In order to ease pain and enable rectal inspection of colicky horses, this medicine is an excellent choice (45). It is substance classified as Schedule 2 in Lithuania.

2.4.5 METHADONE

It is approved for use in both dogs and cats as a complete OP3 agonist and a restricted substance listed on Schedule 2 in Lithuania. Uses include i/v, i/m, and s/c. It is not advised to administer it as a continuous rate infusion since it builds up in the body over time. It is employed to treat pain ranging from mild to severe. Since it also functions as an N-Methyl-D-aspartate receptor (NMDAR) antagonist, it is thought to be more effective in relieving pain than morphine at the OP3 receptor. It has the benefit of seldom resulting in emesis. Following i/v, i/m, or s/c administration, effects begin to take action 15 to 30 minutes later and remain for around 4 hours (23).

2.4.6 FENTANYL

Fentanyl is a very powerful synthetic opioid and plays a crucial role in aesthetic combinations (50). It is also used recreationally, and is occasionally combined with other drugs such heroin, cocaine, benzodiazepines, and methamphetamine. Rapidly acting and short-lived, fentanyl's effects often wear off after two hours (51). It can also be taken via the cheek as a lozenge or tablet, and it is utilized in medicine as an injection, nasal spray, or skin patch (52). Nausea, vomiting, constipation, itching, drowsiness, disorientation, and injuries due to poor coordination are typical negative reactions to fentanyl. There may be certain serious side effects, including hallucinations, respiratory depression, low blood pressure, serotonin syndrome, and the potential for the development of an opioid use problem (53). Fentanyl is effective because it stimulates the -opioid receptors, as stated in. It has a potency around 50 times higher than heroin and 100 times higher than morphine (51). In 1960, Paul Janssen synthesized fentanyl, and by 1968, the drug had been licensed for medicinal use in the United States (54). Medical facilities throughout the world utilized 1,600 kilos (3,500 pounds) in 2015. In 2017, fentanyl surpassed all other synthetic opioids in medical use in 2019, it was the 278th most often prescribed pharmaceutical in the United States, with over 1 million prescriptions

(54). The majority of the 71,238 drug overdose deaths in the United States in 2021 were attributable to fentanyl and fentanyl analogues. It's more powerful than heroin, sells for more money, and is easier to transport due small size (52). In certain cases, it may be used to completely supplant illicit narcotics like heroin. Chinese fentanyl and fentanyl precursor plants are a major source of the global fentanyl supply, which is subsequently illegally exported to other nations for further manufacture and sale (51). More than 50 million fentanyl tablets were collected in 2022 by the US Drug Enforcement Administration (DEA), more than double the amount seized in 2021 and enough to kill everyone in the United States (50). It is also listed as Schedule 2 substance in Lithuania.

2.4.7 ETORPHINE

Etorphine, derived from morphine, is a powerful painkiller. It is an opioid with comparable effects to morphine, but it slows breathing quickly (55). The analgesic efficacy of etorphine (M99), a semi-synthetic opioid, is around 1,000-3,000 times that of morphine (56). Capacity to safely capture and restrain numerous species that had previously been unmanageable has been greatly expanded by the availability of etorphine since its first usage and description in the late 1960s (56). Etorphine has a very long half-life, and its recovery time is lengthened due to enterohepatic recycling. Diprenorphine, a particular antagonist, is used to counteract its effects, however relapsing into profound drowsiness is possible (57). Excitation precedes the onset of anaesthesia

because the medicine stimulates the central nervous system before it depresses it. Etorphine is sold in fixed-ratio combinations with tranquillizers such phenothiazines to combat this (58). Thiafentanil oxalate should be handled using the same procedures as etorphine and carfentanil. The handler should operate in tandem with another person who is familiar with the risks associated with handling powerful opioids (59) and who is likewise outfitted with protective gear like latex gloves and goggles. All capture workers should be aware that powerful narcotics are being employed (60). This substance is listed as Schedule 1 in Lithuania.

2.4.8 TRAMADOL

Tramadol is a recommended in the WHO for the management of pain (61). The metabolite O-desmethyltramadol, which is derived from tramadol, acts on the μ-opioid receptor, adding to the drug's multimodal effects on serotonergic and noradrenergic nociception. The signs of an overdose on tramadol are, however, similar to those of other opioid analgesics (62). Tramadol-related fatal overdoses are uncommon and are linked to extremely high dosages and the use of

other medications or alcohol. Tramadol's effectiveness in treating pain for more than three months is supported by just a small body of research, which is consistent with long-term usage of other opioids (63). Tramadol is the only opioid medicine that carries a risk of serotonergic syndrome due to its activity as a serotonin receptor agonist. When compared to other opioids like morphine, tramadol is still generally thought to have a reduced propensity for addiction (61). In the 1980s, tramadol was marketed as an opioid drug with a lower potential for addiction than other opioids, which may account for its meteoric rise in popularity (64). Similar concerns concerning the development of problematic opioid usage and overdoses have been observed for other opioids, and their use may generate similar concerns when it comes to tramadol, hence its rising popularity warrants more investigation (62). Despite having limited agonist characteristics at all opioid receptors, tramadol is particularly effective at OP3 receptors. The beginning of pain alleviation when ingested in an immediate-release formulation often starts within an hour. Additionally, it can be injected. It can be used in conjunction with acetaminophen (acetaminophen). It was accepted in the US and the UK in the middle of the 1990s. It is distributed globally under several brand names and is accessible as a generic drug. With more over 17 million prescriptions written in 2020, it ranked 35th among the most frequently prescribed drugs worldwide (63). It is substance classified as Schedule 2 in Lithuania.

2.4.9 CODEINE

Codeine, an opiate and prodrug of morphine, is frequently used to alleviate pain, suppress the cough reflex, and slow the transit time of diarrhoea (65). It is also widely used as a recreational drug. It occurs in nature as a component of the opium poppy (Papaver somniferum) sap. Regular patients take it to alleviate mild to severe pain. In contrast to synthetic opioids, codeine is a natural substance (66). It acts as a Mu opioid receptor agonist (MOR). While the MOR is highly responsive to codeine, the affinity between the two is low. Codeine acts as a prodrug of its primary active metabolites, morphine and codeine-6-glucuronide, which are far more effective MOR agonists than codeine itself (67). Both morphine and codeine have been identified as endogenous compounds in the depolarized neurons of nonhuman monkey brains. It suggests that codeine may play a role in the central nervous system as a neurotransmitter or neuromodulator (67). Codeine, similar to morphine, triggers TLR4 (Toll-Like Receptor 4**)** signalling, which in turn produces allodynia and hyperalgesia. As a natural pain reliever, it doesn't require further processing into morphine (65). To put it simply, codeine is an opioid and a MOR agonist. It has an analgesic effect by acting on the central nervous system. Through hepatic metabolism, it becomes morphine, which is 10 times more powerful than opiate

painkillers at binding to the Mu receptor (68). G protein-coupled opioid receptors are involved in both positive and negative regulation of synaptic transmission through intracellular signalling. Codeine and morphine bind to the MOR and cause a neuron to hyperpolarize. Reduced neural excitability causes an analgesic effect and enhanced pain tolerance (66). Codeine is listed as Schedule 3 substance in Lithuania and it is available both as OTC drug, as well as prescription only drug. In Norway codeine is available in combinations with paracetamol or acetylsalicylic acid. In Sweden codeine is available in combinations with paracetamol or ibuprofen.

2.4.10 OXYCODONE

To alleviate moderate to severe pain, doctors often prescribe oxycodone, a powerful, semi-synthetic opioid. It is a widely misused and addictive substance (69). It is used orally and comes in both rapid-release and extended-release forms. In order to have an effect, oxycodone must first activate the -opioid receptor. When used orally, it has around 1.5 times the potency of morphine (70). For the pain treatment brought on by disease or trauma, OxyContin works just as well as fentanyl. Children who are currently receiving opioid treatment and can take at least 20 mg of oxycodone daily can also use it well during major surgery (69). Constipation problems are more likely to last during treatment, but most adverse effects subside over time. Managed-release tablets containing oxycodone and naloxone have been developed to prevent opioid misuse and alleviate the gastrointestinal side effects of opioids, such as nausea and constipation (71). Individuals who abuse oxycodone or who take more than the recommended amount are at increased risk to experience severe signs of withdrawal (70). It's possible to have "anxiety, panic attack, nausea, sleeplessness, muscular soreness, muscle weakness, fevers, and other flu-like symptoms" after withdrawing from oxycodone, as is the case with other opioids. Semi-synthetic opioid oxycodone is a potent, selective full agonist of the MOR (72). This is where the body's own endocannabinoid opioid neuropeptide -endorphin mostly functions biologically. Oxycodone is a weak agonist at both the delta-opioid receptor (DOR) and the kappa-opioid receptor (KOR) (73). Inhibition of neurotransmitter release occurs when oxycodone binds to the MOR, releasing a G protein-complex that blocks calcium entry into the cell and opens potassium channels (71). The analgesic effects of opioids like oxycodone are caused by their activation of the MOR in the rostral ventromedial medulla (RVM) and the periaqueductal grey (PAG) of the midbrain (74). It is substance classified as Schedule 2 in Lithuania.

2.4.11 TAPENTADOL

Benzenoid opioid analgesic tapentadol is a dual-acting mu-opioid receptor agonist and antagonist and a norepinephrine reuptake inhibitor (NRI) to alleviate pain (75). Like tramadol, its dual mechanism of action consists of stimulating the mu opioid receptor and inhibiting the uptake of norepinephrine. It is a far more powerful opioid than tramadol and has no known active metabolites, however it has fewer effects on serotonin reuptake (76). Tapentadol does not require metabolism to exert its therapeutic benefits, as it is not a pro-drug (77). Accordingly, it can be an effective alternative to high-potency opioids for individuals who have not responded well to other pain relievers (78). This is because of the patient population's genetic predisposition (few CYP3A4 and CYP2D6 metabolizers) and because it provides a more uniform dosage-response range (79). Tapentadol's analgesic effectiveness is equivalent to that of oxycodone despite a decreased frequency of adverse effects, placing its potency halfway between that of tramadol and morphine (80). It is considered an opioid of moderate potency, by most accounts. Classified as a Category C drug for use during pregnancy, tapentadol is safe. It is not suggested that women use tapentadol during labour or in the hours leading up to delivery because there have been no well-controlled trials of its usage in pregnant women (81). Tapentadol, like other mu-opioid agonists, has the potential to produce spasms of the sphincter of Oddi, and is hence not recommended for individuals with biliary system illness, including acute and chronic pancreatitis. Patients' seizure thresholds have been shown to be lowered with tapentadol (82). Patients with a history of seizures or who are taking other medications known to lower the seizure threshold should use caution when using tapentadol (83). Patients with a history of head trauma, metabolic abnormalities, and/or who are in the process of alcohol and drug withdrawals are also at increased risk, as are those who are on various serotogenic and adrenergic drugs (84). It is also listed as Schedule 2 substance in Lithuania.

2.5 OPIOID THERAPY

Opioid therapy is linked to a considerable series of unfavourable outcomes; yet, opioids are still widely used in the treatment of pain (85). The successful application of opioid therapy to the management of chronic pain has paved the way for generalizing these methods to other chronic pain conditions. Chronic disease trajectories are on the rise due to improved treatment options, pain and chronic pain are of particular importance (86). However, the present US pandemic of prescription opioid addiction and fatalities may be traced back to the dramatically increasing prescribing of opioid analgesics beginning in the 1980s (87). When all other options for relieving pain have been explored, opioid medication may be beneficial for certain carefully

selected and properly managed individuals with pain and confirmed opioid-responsive pain syndromes (88).

Almost the past few decades, opioids have been a common treatment for pain, accounting for over 80% of all prescriptions filled globally and 20% other NSAIDs (56). The use of both strong opioids and moderate opioids like tramadol has increased, although the latter has seen a much higher growth in popularity. Opioid-responsive chronic pain often only responds well to opioids in the early stages of therapy due to the unpredictable and nonlinear nature of pain, in contrast to acute pain (3). Disposition, context, stress, length, significance, acceptance, anticipation, and fear all play a role in how chronic pain is reported and experienced. As a result, there is no uniform pattern to the way in which opioids affect chronic pain ratings. To the contrary, there has been an increase in the misuse of opioids in an effort to reduce chronic pain ratings (88). As per WHO's stepladder method, people with pain now believe that opioids may reliably alleviate their pain and boost their quality of life. This strategy not only puts pain patients at risk, but also sets them up for disappointment on the part of their doctors as a result of inadequate therapy (88).

2.6 PERIPHERAL OPIOID ANALGESIA

The expression of opioid receptors varies in different kinds of cells and organs. Human synovia, dental pulp, dermal and epidermal nerve fibres have all been shown to contain opioid receptors, proving that these receptors are not limited to central nervous system tissues (89). It was once believed that the only way μ-opioid could have an impact is via attaching to opioid receptors in the brain (90). Several investigations over the past two decades have established that μ-opioid receptors on peripheral sensory neurons mediate the analgesic effects of opioids. It has been established via a variety of investigations that neurons of varying sizes in the dorsal root ganglia express μ-opioid receptors (91). It has been hypothesized that sensory neurons in the dorsal root ganglia produce these receptors, which are then delivered to both central and peripheral nerve terminals. As with CNS receptors, it has been hypothesized that they act by blocking ion channels to produce their effect (92).

Amplification of opioid receptors, especially the μ-opioid receptor, can occur as a result of painful inflammation in peripheral tissue. A key mediator of overexpression of opioid receptors is the length of inflammation. Even after 30 minutes of inflammation, no changes were seen in the expression of opioid receptors in sensory nerve endings (93). Dorsal root ganglia neurons had more μ-opioid receptor-expressing neurons and binding sites. Quantity of μ-opioid

receptors per neuron, but not opioid agonist affinity (90). Overexpression of opioid receptors may result from cytokines' stimulation of transcription factor binding to the opioid receptor gene. It has also been postulated that inflammatory mediators like bradykinin and cytokines facilitate G-protein coupling on the dorsal root ganglion -opioid receptor and boost its peripherally directed axonal trafficking (94).

Additionally, inflammation can break down the perineural barrier, making it easier for opioid agonists to reach their receptors (95). Patients with an extensive variety of pain conditions, including those with chronic rheumatoid arthritis, complex regional pain syndrome, oral mucositis, osteoarthritis, bone pain, and following urinary bladder, knee surgery, and dental have shown that these receptors mediate analgesia (96). The analgesic effects of systemically delivered opioids are mediated, according to a large body of research, in large part via peripheral opioid receptors. One of the most researched procedures and the most effective use of peripheral opioid analgesia is intra articular injection of morphine into inflamed knee joints. Further, individuals who had knee surgery and then had a local injection of naloxone to inhibit intra articular opioid receptors reported much higher postoperative pain (95).

2.7 AVAILABILITY OF OPIOIDS FOR TREATMENT

Defined daily dose (DDD) is the average maintenance dose (long term therapeutic dose) per day for medications with an Anatomical Therapeutic Chemical (ATC) categorization code and is used as a proxy for the accessibility of pharmaceuticals in the general population (97). Each ATC code and each administrative route is given a unique DDD. The DDD is employed as a fixed unit, especially for making comparisons between populations, despite the fact that it will only provide an approximate estimate of consumption (98). International Narcotics Control Board (INCB) use the word DDD as a technical unit of measurement for comparing, for example, narcotic medications of varying strength. Data shows that opioid availability has generally increased throughout this time period, but also highlights a global distribution mismatch. Morphine is widely accessible in primary care settings in high-income regions like Europe and North America, but not in low-income regions like South America and Africa (97).

The availability of opioid analgesics peaked between 2016 and 2018 in the Canada, United States, Australia, and Europe with further developed nations like Norway, UK, and New Zealand (99). The availability of opioids for consumption, on the other hand, remains inadequate or, in some situations like Namibia or South Africa, has dropped. These low-income nations are concentrated in Africa, Asia, Eastern Europe, and South America (100). One of the

medicines linked to overdose deaths from prescription drug usage is oxycodone, and its use has climbed dramatically in recent years, making it the second most commonly used opioid worldwide. In contrast, morphine use has been relatively steady since the late 1990s, with just a little rise (101). Only opium, methadone, and heroin are classified uniquely among opioids (102). Therefore, the NCoDR's overdose data is broken down into a number of "aggregated groupings," such as "other opioids," which includes codeine, morphine, and oxycodone, and "other synthetic narcotics," which contains, among other things, tramadol, buprenorphine, pentazocine, and fentanyl (102). Prescription opioid dispensing patterns in Sweden, Denmark, and Norway revealed an uptick in the distribution of oxycodone between 2006 and 2017 and a decrease in the distribution of tramadol in Norway (103). In 2016, 12.2% women and 9.2% men in Norway were prescribed and received opioids as an outpatient, making Norway the country with the highest prevalence of all prescription opioids (104).

2.8 LONG-TERM OPIOID THERAPY FOR CHRONIC PAIN

Opioid maintenance treatment is commonly used for people with pain. Three studies with follow-up periods ranging from 7 to 24 months were reported in a review, and their results revealed that 44 percent of patients were still on long-term opioid treatment (105). In another research, it was discovered that just 24% of new heavy opioid users were still receiving opioid therapy at the 5-year follow-up (85). Population-based research makes up the bulk of the evidence concerning the efficacy of long-term opioid treatment for pain. Due to the limited time available for follow-up, RCTs have been used to study the efficacy of opioid therapy over the long term (87). Because of the high prevalence of opioid-related adverse effects and the high likelihood of participant attrition, randomized controlled trials (RCTs) of long-term opioid medication can be challenging to perform (105). Various studies documenting the long-term safety and efficiency of opioids for pain are few. Similar results were seen in two trials comparing long-term opioid medication to other therapeutic options (106). There is insufficient data to establish that long-term opioid medication effectively reduces pain and boosts QOL. Several studies have revealed that there a higher risk of dosage escalation while using opioids for extended periods of time (24,107). From a societal point of view, the majority of opioids prescribed are part of higher-dose regimens; therefore, judicious dosage may limit both the potential for diversion and the risks of side consequences (63).

2.9 LONG-TERM OPIOID THERAPY AND SIDE EFFECTS

Administering opioids has a number of negative effects like the majority of pharmacological medicines. Both natural and artificial opioids bind to the respiratory centres and opioid receptors in the brain (108). Nevertheless, the stem, gut, and chemo trigger zone all have μ receptors, and adverse effects frequently arise when the μ receptors in these regions are activated. Common adverse reactions when taken as directed include nausea, sedation, vomiting, constipation, sleepiness, and disorientation (108). Adverse effects from excessive dosages might include circulatory collapse and respiratory depression. 15 to 30 percent of patients who are on opioid treatment for nausea say they experience it, although tolerance frequently sets in (28). Approximately 20–60% of patients experience sedation; however, tolerance often grows quickly as well. Constipation is a side effect that affects up to 70% of individuals receiving opioid medication, however tolerance relatively rarely develops (109).

These negative effects of opioids might cause people who don't build tolerance to stop taking them, reduce their dosage, and get subpar pain relief. Because of these differences in biology, the available opioids for therapy have varying degrees of negative effects for different people (30). In order to optimize the efficacy of opioid treatment while minimizing the severity of side effects and adverse events, it is imperative that clinical personnel be well-educated to commence preventative treatment of anticipated side effects, to switch and cycle opioids or the route of administration (110). Tolerance, hyperalgesia, dependency, and addiction are other negative outcomes associated with opioid analgesics. The latter are arguably the most dreaded and well-known side effects of opiate addiction at now (29). Tolerance to the analgesic effect, defined as decreased sensitivity to therapeutic opioid dosages, probably arises as a result of either decreased receptor activation or decreased cellular expression of the targeted opioid receptor. A higher and higher dose of the medicine is required to provide the same level of analgesia (109).

Recent research on the efficiency of opioids to treat neuropathic pain has revealed that the most common side effects are constipation, drowsiness, nausea, and vomiting (31). Opioid use, and specifically chronic opioid use for pain, can have negative effects on the gastrointestinal, respiratory, musculoskeletal, immune, cardiovascular, central nervous, and endocrine systems. Possible unwanted effects include tolerance to the drug, hyperalgesia, hypogonadism, erectile dysfunction, and immunosuppression (111). Long-term opioid users have been shown in previous epidemiological studies to be at a significantly higher risk of all-cause mortality, as well as an increased risk of poisoning/toxicity and injuries leading to hospital impatience, and

to experience moderate/severe pain, poor self-rated health, unemployment, higher costs of healthcare system, a significantly higher risk of all-cause mortality, and a devastating effect on quality of life (112).

The endocrine effects of opioids, which have been shown to manifest rapidly after opioid administration but have received little attention, are unintended consequences of opioid therapy (113). Long-term suppression of adrenal-related hormone production by opioids can result in hypogonadotropic hypocorticism and hypogonadism. As a result, opioid-induced suppression of hypothalamic-pituitary function may lead to endocrine dysfunction in many patients with pain using opioids (86). Because low testosterone levels in both sexes have a negative effect on sexual desire and fertility, a drop-in sex hormone production can have a detrimental effect on patients' sex lives. Despite this, there is a dearth of research on the links between pain, opiate abuse, and sexual activity (105).

A population-based study found that the risk of overdose, as well as addiction, fractures, intestinal obstructions, and sleepiness, rose when patients were prescribed opioids at higher daily dosages (87). Ischemic heart disease, heart failure, and pneumonia are all more likely to strike the elderly, have all been linked to immunosuppression. It was shown that long-term opioid therapy among patients with pain may have a negative effect in the form of an increase in the incidence of fatalities due to opioid overdose. Another study showed that the growing death toll from opioid pain medications generally parallels the increased sales of these pharmaceuticals (32). Authorities advise limiting opioid prescriptions to a select few patients. One of the most important things that can be done for patients with pain is to provide an early and accurate diagnosis, as well as vigilant monitoring for signs of opioid addiction (106).

2.10 DEPENDENCE AND TOLERANCE

Addiction is a condition that can manifest on its own. When people use opioids for a long enough time or at high enough dosages, they develop an addiction (109). Every patient receiving long-term opioid therapy is potentially at risk and should be closely watched, even if some individuals appear to be more prone to opioid addiction than others. However, over ninety percent of those with chronic pain who are prescribed opioids do not become addicted to them (29). Opioid diversion, in which a patient illegally shares and sells their medicine, and opioid misuse, in which the substance is used to purposefully generate feelings of euphoria, are not to be confused with opioid addiction as a chronic condition. It is possible that anxiety over the

potential for addiction and physical reliance will lead to a doctor's prescribing the wrong medication, leading to subpar pain relief (110).

About 3%-19% of people taking opioids long-term for pain management develop opioid abuse or dependency, but opioid treatment for acute pain is seldom related with the development of opioid abuse/dependence (63). Some estimates place the percentage of long-term opioid users who engage in risky practises such as getting opioids from multiple prescription, stealing opioids, forging prescriptions, or administering oral opioids via intranasal or intravenous routes at 40% (61). As there is a lack of epidemiologic data that precisely defines risk factors for opioid addiction among patients with pain, the characteristics that predict opioid misuse continue to be a source of contention. However, a history of substance abuse, either personal or familial, cannabis use, psychiatric morbidity, psychosocial comorbidity, young age, multiple pain complaints, back pain, increased subjective pain, functional impairment, and, most likely, heredity are all risk factors for opioid addiction and misuse.

Both doctors and patients can suffer from opiophobia, or a fear of using opiates to manage pain. This apprehension can arise from a number of sources, including physicians' lack of knowledge about the risks and consequences of opioid use, patients' lack of knowledge, and clinicians' own anxiety about inducing or experiencing opioid addiction among their patients (34). Since opioids are restricted medicines with a well-known potential for misuse, opiophobia (the dread of opioids) may have cultural roots in the anticipation of legal action or disciplinary consequences for using opioids inappropriately (114). Initially proposed in the late 1980s, the term "Pseudoaddiction" refers to the phenomenon whereby people abusing opioids exhibit abnormal behaviour due to inadequate pain management, despite the absence of true addiction (115). Improving pain management can help alleviate this condition, which displays similar behavioural signs to addiction. Certain criticisms have been levelled at this idea, however, because objective symptoms and a definitive treatment plan are lacking at the present time to help doctors make informed decisions (114).

2.11 PREVALENCE OF OPIOID-RELATED HARMS

The size of the worldwide opioid market was estimated at 18.5 billion US dollars in 2018, and in 2019 it will be worth $19,007.2 million (116). Forecasts predict a consistent increase in demand for opioid medications as analgesics and for pain management, particularly in the oxycodone and fentanyl markets, leading to a market size increase of up to $22,387.2 million by 2026 (117). With current growth rates of 3% in India, China, Australia, and South Korea

and an anticipated growth rate of up to 5% in the future years, the Asia-Pacific area is home to emerging markets. However, it has been demonstrated that the opioid crisis and increasing mortality from opioid overdoses have a negative influence and lower growth rates (118). Around 8 900 persons were thought to be injecting opioids and stimulants (4.63 per 1 000 aged 15-64 years) (118). Opioids, primarily heroin, were the most often reported primary drug for first-time entry into treatment in 2017, according to data from specialized treatment centres (33).

In recent years, various nations, including the USA and Canada, saw a surge in opioid-related side effects up to opioid-related fatalities, and this raised serious public health concerns (119). These nations showed a surge in the availability and prescription of opioids, which was implied in various media reports to be directly connected to the risks associated with opioid use. Without seeing any indications of rising opioid-related problems, other nations also exhibit increased opioid availability (118). With 19.4 million users worldwide in 2016, the illegal opioid industry has grown significantly over the past several years, mostly driven by heroin but also including the morphine market. Asia accounts for 58% of illegal opioid users, followed by Europe with 17% and America with 15%. With 86% of Americans using illegal opioids, North America has the highest incidence (120). Total first-time treatment clients reporting opioid or amphetamine/methamphetamine main use decreased between 2015 and 2017; there was no continuation in 2017 of the previously recorded increase in cannabis users pursuing medical treatment for the first time (120).

In recent years, illegal opioid usage has become more common in Europe, particularly in Poland. Between 2012 and 2016, drug-related deaths—mostly those caused by heroin and morphine—rose by 58% in England and Wales and by 70% in Germany (121). The market for prescription opioids used for non-medical purposes is also growing. Data on illegal prescription opioids collected in 2016 show an increase in the usage of tramadol in Africa, buprenorphine and fentanyl in Europe, and hydrocodone, oxycodone, codeine, and tramadol in North America (122). Prescription opioid analgesics, illegal opioids, or both can all cause opioid-related fatalities. When heroin and amphetamine addicts begin treatment, injection is still the preferred method of drug delivery. Depending on the major medication administered, around one-fifth of patients beginning therapy are female (10). The distinction is made much more difficult by the availability of illegally produced opioids like fentanyl which were once prescribed drugs (123). For instance, the Centres for Disease Control and Prevention (CDC) calculates prescription opioid mortality by including deaths involving synthetic opioids from illegally made opioids like fentanyl, which might have a major impact on the numbers (116).

2.12 REGULATORY BARRIERS TO OPIOID ACCESSIBILITY

Opioids for pain treatment are not distributed uniformly over the world for a variety of reasons (101). When asked why pain treatment is still subpar in many parts of the world, the International Association for the Study of Pain (IASP) cited the following factors:

- A lack of convenient options for relieving sudden pain.
- Professionals' insufficient understanding of pain's causes and treatment.
- Having chronic pain is stigmatized.
- Weak or non-existent national policy for dealing with pain as a public health issue.
- Strict regulations on access to opioids and other life-sustaining drugs.

The stigmatization of patients who use opioids and the fear of prescribing opiates to control pain are two examples of cultural factors that contribute to the wider discussion of the use of opioids for pain management, which also includes the legal limits due to restrictive policies and laws and the knowledge and acceptance of healthcare providers.

2.13 OPIOIDS FOR PAIN MANAGEMENT IN LITHUANIA, SWEDEN, AND NORWAY

Lithuanian approaches to pain control and palliative care are fairly comparable to those in other Eastern and Central European nations (15). Due to the large number of cancer patients who still have advanced disease (stage III-IV), a deficient palliative care and pain management system, and a lack of medical professionals with the necessary training to treat these patients, the percentage of cancer patients who experience pain is still higher. Despite the lack of a competent pain management system, Lithuania has a good supply of opioids and other analgesics. In Lithuania, the pharmacovigilance system is still in its infancy. In a recent study, it reported 476 negative side effects that were recorded in Lithuania (2,888,558 residents), and only 3% of these were related to medications that impact the musculoskeletal system, while the Danish government reported a total of 1,080 adverse reactions (5,681,810 inhabitants) (124). In the same year, 7538 complaints of adverse medication reactions were received by the Medicines Agency. Another study analysing adverse reaction reports from the French pharmacovigilance database may provide light on the inefficiency of the Lithuanian pharmacovigilance system. Significant adverse responses to opioids were reported 42,389 times (125). There is no denying that not everyone in Lithuania had a bad experience. There is a misperception that because current opioids use, patterns are suitable, there is no need to alter

long-standing practices or implement fresh, evidence-based recommendations in actual clinical practice.

One in five Europeans have moderate to severe chronic pain, according to a recent poll, and it has been stated that pain is the major reason people in Sweden visit their doctor. Another study indicated that over-prescribing opioids for pain management and increased use of prescription opioids by those with a history of drug abuse may both contribute to the rise in opioid-related fatalities in Sweden (126). In Sweden, access to powerful opioids has increased since 2006. This is due to two factors. First, stronger opioids were administered for chronic pain more frequently over the time period as a result of more widespread treatment techniques. Second, once the OAT regulations were revised in 2005, more treatment programs were launched. Methadone and buprenorphine augmentation therapy (OAT) admissions increased (127).

In another Swedish study, 54% of first-time painkiller prescriptions were for oxycodone, compared to 19% for fentanyl, 14% for buprenorphine, and 13% for morphine. Within 6 months, 63 per cent of patients who were prescribed slow-release strong opioids (SRSOs) also filled their prescriptions, whereas 12 per cent switched to fentanyl most often. After 3 years, 51% of patients with cancer and 27% of patients without cancer who continued to have contact with health care were still taking some kind of SRSO. Thirty-five per cent of those who didn't have cancer were also taking medicine for their mental health (SSRI or benzodiazepine). Overall, fewer patients continue to take SRSO over the long term in clinical practice than were seen in clinical trials. First, SRSO prescriptions are most commonly for oxycodone, and one-third of patients obtain a prescription suggesting mental comorbidity (128). Based on these findings, greater effort is needed to enhance treatment standards and guarantee that they are followed in order to satisfy the requirements of these individuals.

In another study, when DDDs were used as the unit of measurement, the disparities between Denmark, Sweden, and Norway in terms of consumption per 1,000 people were minimal, while when mg Omeqs were used, the differences between the nations were noticeable. In comparison to Sweden and Norway, Denmark had substantially greater usage of Omeqs per 1,000 people. In Norway, Sweden, and Denmark, the average yearly intake was 1979, 3615, and 6025 mg Omeq/user, respectively. In all three nations, the preferred opioid-type options were altered throughout that time. In contrast to Denmark, Norway and Sweden saw more pronounced shifts in the balance between the use of mild and powerful opioids (129). In Sweden, drug-related fatalities rose from 7.3 per 100,000 people in 2006 to 11.6 per 100,000 in 2017. Opioids are to blame for almost 80% of these fatalities. From 2000 to 2018, the total number of people in

Sweden having opioid prescriptions remained stable (26). Tramadol and codeine/morphine prescriptions are declining, but oxycodone prescriptions are increasing, according to prescription data (9). While this time has passed, there has been no rise in the morphine equivalent dosage.

However, in 2014 and 2015, opioid prescription rates were extremely high in the southernmost county of Sweden among people with hip and knee osteoarthritis. Rates of at least one opioid prescription being filled each year were 23.7% (8). In another study, 85% of 14,477 persons with chronic nonmalignant pain didn't take opioids, 3% did continuously, and 12% sometimes. Even among those with severe or very severe chronic pain, substantially more did not take opioids. Despite utilising opioids, 75% of patients felt significant or very intense pain. Increased risk of long-term opioid dependence reported to be associated with individuals with chronic pain who were not consistent opioid users at baseline were >100 specified annual regular doses of benzodiazepines, occasional opioid use, severe pain intensity, and physical inactivity. With even extreme pain, most people with chronic nonmalignant pain do not use opioids. Most opioid-dependent individuals experience high or extremely intense pain despite therapy (18).

Study Gaps

While studies have examined opioid usage rates in a number of nations, including Lithuania, Sweden, and Norway, there is a gap in the research when it comes to contrasting these nations and looking at the variables that could explain variations in opioid usage rates across them. It is unclear how these policies compare to those in Lithuania and whether policy differences or other factors may be responsible for differences in opioid utilization rates, despite some evidence suggesting that strict regulatory systems and policies in Sweden and Norway may have contributed to lower rates of opioid use and overdose deaths in these countries. Hence, research comparing the rates of opioid use and the laws governing it in Lithuania, Sweden, and Norway might provide insight into the elements that contribute to the variations in opioid use and overdose rates across these nations. The regulatory frameworks and policies in place in each nation, as well as socioeconomic and demographic variables that may have an impact on variations in opioid consumption rates, might all be the subject of such a study. Knowing these characteristics might aid healthcare professionals and politicians in all three nations in creating more efficient plans for restricting opioid usage and minimizing the harm brought on by opioid addiction and overdose.

CHAPTER # 3. METHODS

3.1 STUDY DESIGN

This was a cross-national, cross-sectional analysis of opioid utilisation rates in Lithuania, Sweden, and Norway between 2014 and 2021.

3.2 SETTING

The Republic of Lithuania is a Baltic country of North Eastern Europe with a population of 2.8 million permanent residents (130). In Lithuania, the infant mortality rate was 2.99 per 1,000 births as of 2019, while the country's life expectancy at birth was 76.0 (71.2 years for men and 80.4 years for women). The Kingdom of Sweden is a Nordic country in Northern Europe with a population of 10.3 million people (131). Sweden is among the European nations with the highest drug-related death rates, according to international data (132). The Kingdom of Norway is a Nordic country in Northern Europe with a population of 5.43 million people (133). In 2016, women in Norway could expect to live an average of 84 years, while males could expect to live an average of 81 (134). The Norwegian Cause of Death Registry (NCoDR) is a general mortality record which tracks overdose fatalities annually based on diagnostic codes (GMR) (135). In comparative demographic and geographical position, Lithuania is located in Northeastern Europe, Sweden in Northern Europe, and Norway in Northern Europe. Among three of these countries, population wise largest country is Sweden with 10.3 million population following Norway and Lithuania with 5.43 million and 2.8 million population respectively.

Table 2: Demographic and socioeconomic context in Lithuania, Sweden, and Norway

Population (2021)	2.8 million		10.3 million		5.41 million	
Share of population under age 18 (%) (2020)	17.9		21.1		12.4	
Share of population aged 65 and	19.9		20.0		17.79	
Life expectancy at birth (years)	81.2 Females	71.6 Males	84.8 Females	81.5 Males	84 Females	81 Males

Standardised preventable and treatable mortality (2017)	492.63	184.63	133.23
GDP (2021)	$65.5 billion	$ 627.4 billion	$482.4 billion
GDP per capita (2021)	$23,433.39	$60,238.99	$89,202.75
Poverty (population at risk) (2015)	1.4%	0.60%	0.30%
Total health care expenditure (2019)	$1370 per capita	$5671 per capita	$8,007 per capita

In Lithuania, the Supreme Council, or "Seimas," enacted the National Health Concept in 1991 (136). It prioritised illness prevention and basic care and implemented health insurance. Compared to 1990, there were 52 fewer hospitals in 2012. In addition to 49 nursing hospitals, there were 26 secondary hospitals, 66 general hospitals, and 4 rehabilitation facilities (137). The State Public Health Centre, which oversees the public health network that consists of 10 county public health centres and their local branches, is under the purview of the ministry (136). The county hospitals and other specialised medical institutions are managed by the 10 counties. In 2013, 6.2% of GDP was spent on healthcare overall, or $1,579 per person (138). In 2009, there were 12,191 doctors in the nation, or 36.14 per 100,000 people. 225,510 persons, or roughly 8% of the population, were believed to be outside the nation when it came to paying their National Health Insurance fund payments in 2016, however this was not confirmed (139). Outpatient prescription medications are not covered by the insurance plan. All citizens get free access to emergency medical care. Typically, a general practitioner may refer patients for hospital care (138).

Although private health care is also available, the Swedish health care system is mostly government-funded, available to all people, and decentralised (140). Swedish regions and local governments largely levy taxes to fund the country's healthcare system. The country's primary and hospital care is overseen by a total of 21 regions (previously called councils) (132). Three levels—national, regional, and local—are used to structure and operate the Swedish healthcare system (132). The Ministry of Health and Social Affairs sets the political agenda for health and medical care on a national level as well as the standards for prescriptions and treatment (141). Along with other government agencies, the ministry oversees lower-level operations, distributes funding, and regularly assesses services to ensure compliance with overall

objectives. The 21 regions are given decentralised control over funding and delivering healthcare at the regional level (131). They are also responsible for the drug budget for their citizens and regional Drug & Therapeutics committees, mandated by law, produce guidelines for rational use of drugs (142).

Regional governments also control the costs and calibre of services provided by independent contractors. Contracts between private service providers and county authorities are necessary (140). Private service providers without a contract with the county councils are not compensated by the government for their services to patients (143). These are, however, rare in Sweden since most providers operate under contract with the region. Furthermore, even drugs prescribed from private providers without contract are covered within the same national reimbursement scheme. Every county council in Sweden is required to offer inhabitants access to high-quality medical care and health services, as well as to work to promote overall population health, in accordance with the country's health and medical care policies. About 9% of Sweden's GDP was spent on health and medical expenses in 2005, a percentage that has mostly stayed constant since the early 1980s (143). The costs has increased to 11.9% of GDP by 2015, the highest in Europe (143). County councils are authorised to collect income tax, and local taxes account for 71% of the cost of healthcare. The majority of healthcare expenses are covered by the government, with the patient just having to pay a minor examination charge. The state covers over 97% of medical expenses (144).

In Norway, four Regional Health Authorities (RHA) under the Ministry of Health and Care Services are responsible for managing all public hospitals (145). There are modest number of privately-operated health clinics in operation in addition to these governmental hospitals. There are certain payment requirements even though Norway has universal access to public healthcare (146). Children under the age of sixteen, along with a variety of other categories (including elders and nursing mothers), are guaranteed free healthcare regardless of their previous coverage status. Norway routinely ranks at the top of global health care performance rankings (147). Unique to Norway is its universal healthcare system, in which the state pays for nearly all of a patient's expenses. Extra expenses incurred by a patient due to a chronic disease may qualify them for a tax credit (148). Health care costs in 2020 amounted to only around 14% of GDP, or 11.3%, indicating low patient contributions. The public sector receives just around 17% of total government spending for health (135). The government traditionally creates a health budget for the next year in the month of December. The Norwegian healthcare system is fully funded by this budget. Extra financing for the rest of the year, notably for hospitals, has

been allowed by parliament only on a handful of occasions (133). The welfare state is quite costly to maintain after you include in inflation and the cost of living for the year (133).

3.3 DATA COLLECTION

In this study, drug use was measured by compiling and analysing sales and dispensing information for opioid analgesics in Lithuania, Norway, and Sweden. State Medicines Control Agency of Lithuania, Norwegian Drug Wholesale Statistics, - the Norwegian Institute of Public Health (NIPH), and the Swedish E-health Agency were consulted for wholesale data for 2014-2021. Information from both inpatient and outpatient settings was used. This analysis used data on sales to pharmacies and other healthcare institutions. Among the several sales characteristics that were retrieved were:

- Unique identifier of the drug
- Drug's generic and brand names
- Dosage (strength and package size)
- Pharmaceutical form
- A monthly number of packages are sold to pharmacies and personal healthcare institutions.

Swedish statistics offered the same information on sales patterns as those of Lithuania and Norway. Additionally, it included data on the number of DDDs for each medication class. Defined Daily Dose per 1000 Residents Per Day (DDD/TID) is the unit of measurement to allow for comparisons between the three nations. This study analysed the opioid analgesics following worldwide standards and their availability in the markets of Lithuania, Norway, and Sweden.

In order to to analyse Lithuanian opioid utilization trends by comparing age and sex, it was needed to collect information from ESPBI IS electronic prescription subsystem data on prescribed drugs. In other sections of this master thesis ESPBI IS electronic prescription subsystem data will be called Lithuanian prescription data. Mentioned data showed all prescribed drug classes for the patients and did not exclude opioid drug prescriptions only. Collected data offered most relevant information for this study, which was sex, generic name of the drug, patient age and DDD/TID. For comparison it was decided to pick two months from 2017 to analyze and compare most relevant data. Months selections for comparison were April and June.

3.4 METHOD OF ANALYSIS

The ATC/DDD technique, regarded by the WHO as the gold standard for international research, was used to analyse and compare the patterns of use of opioid analgesics. The system's reliability depends on efforts made to maintain consistent ATC codes and DDDs over time. Only one DDD is assigned inside an ATC code per method of pharmaceutical delivery. Despite the number of active ingredients in combination products, DDDs are allocated based on the idea that the combination constitutes one daily dose (149).

DDDs were manually estimated for this study using wholesales data from Norway, Sweden, and Lithuania. Opioid analgesic wholesales totals were calculated as specified daily doses (DDD) per 1,000 people per day (DDD/TID). The DDD/TID metric, also called the "therapeutic intensity" is especially helpful for evaluating the use of medications that are taken on a regular basis. In this study, it served as an approximate gauge of the population's daily opioid analgesic treatment rate. Inferred from 10 DDDs/TID is that 1% of people take this medication daily (150). Utilising ratios and proportions, descriptive statistical techniques were used and MS excel form were used for calculations and data management. Same techniques have been applied for analysis of Lithuanian prescription data.

$$= \frac{\text{DDDs/1000 people/day were calculated in the following way: Amount of drug sold (mg) in 1 year}}{\text{WHO recommended DDD(mg)x number of days per year x number of people}}$$

3.5. ETHICAL CONSIDERATIONS

The major goal of this study is to analyse opioid utilisation rates in Lithuania, Sweden, and Norway between 2014 and 2021. In this study wholesale data and prescription data, which did not contain any personal patient details, was used, which is why it is impossible to identify a specific individual. It is hard to pinpoint a single person since we used aggregated data. Due to the absence of (known) harm, the use of opioid analgesics was explored in this study, which should not raise confidentiality concerns. The Bioethics Committees did not need to approve this study. Stakeholders and practitioners in pharmaceutics and medicinal community would also be considered to add as expected beneficial bodies of this research.

CHAPTER # 4. RESULTS

During the study period of 2014-2021, the data suggests remarkable differences in the total sales of opioid medicines between Lithuania, Sweden, and Norway. In Lithuania, the usage of opioid medicines has been shown to increase progressively from 2014-2021, as it was lowest in 2014 (1.71 DDD/TID) and highest in 2021 (3.26 DDD/TID). In contrast, opioid usage showed to be decreased significantly in Sweden from 2014-2021, while it only decreades slightly in Norway. In Norway, its use was highest in 2021 (19.93 DDD/TID) and lowest in 2021 (18.22 DDD/TID). In Sweden, opioid use was also highest in 2021 (17.67 DDD/TID) and lowest in 2021 (10.65 DDD/TID) (Figure 3).

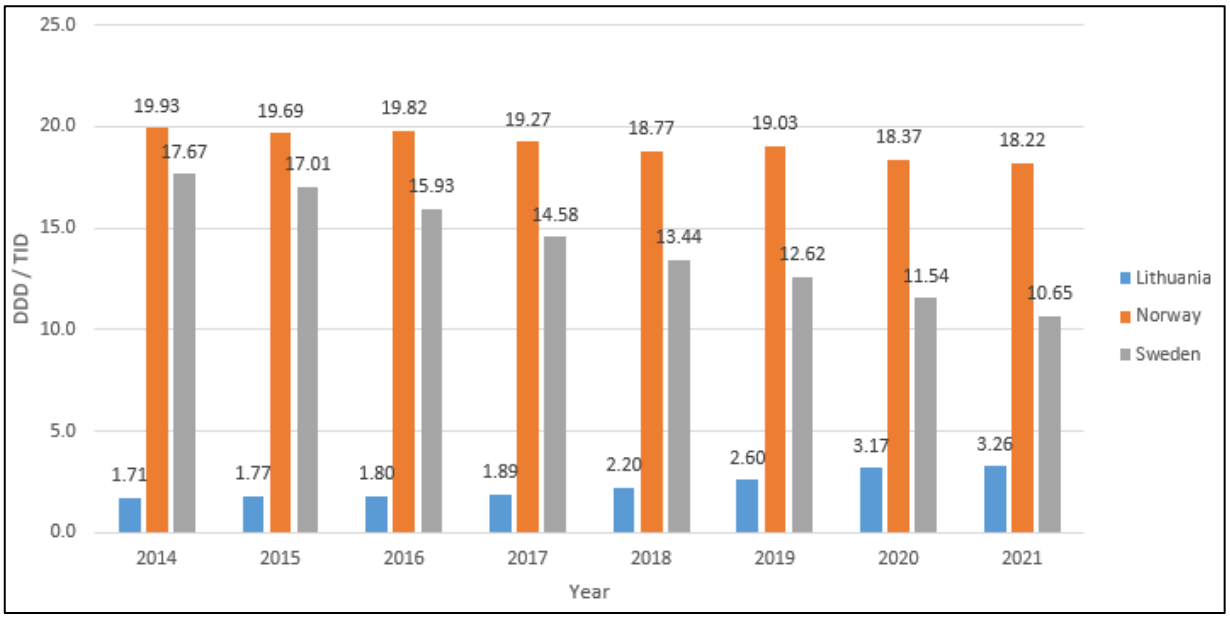

Figure 3: Most common opioids use trends Lithuania, Sweden, and Norway (2014-2021)

In Sweden, the fixed combination of codeine and paracetamol accounted for the highest volumes in 2014 (6.37 DDD/TID) that became lowest in 2021 (3.86 DDD/TID). Similarly, tramadol was reported to be highest in 2014 (4.66 DDD/TID) and it decreased substantially lowest in 2021 (1.70 DDD/TID). However, oxycodone increased sigthly from 1.82 DDD/TID in 2014 to 2.24 DDD/TID in 2021. There was a slight reduction reported in codeine and other non-analgesics from 2014 to 2021 (1.10-0.46 DDD/TID). Likewise, morphine also showed a similar pattern of reduction from 2014 to 2021 (1.01-0.26 DDD/TID) (Figure 4).

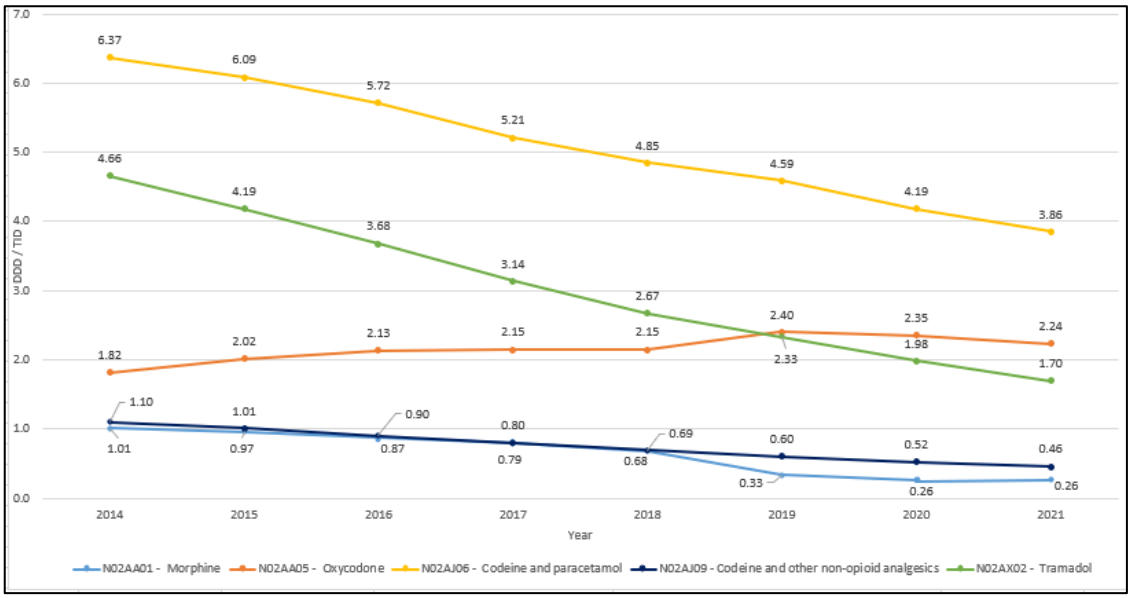

Figure 4: Most common opioids use trends in Sweden from 2014-2021

In Norway, the fixed combination of codeine and paracetamol accounted for the highest volumes in 2014 (9.90 DDD/TID) and slightly reduced in 2021 (7.72 DDD/TID). Similarly, tramadol was also reported to be slightly reduced from 2014-2021 (4.09-3.94 DDD/TID). Compared to tramadol, codeine and paracetamol were more commonly used, particularly from 2015 to 2017. However, oxycodone was reported to be the lowest in 2014 (1.94 DDD/TID) that increased substantially in 2021 (2.45 DDD/TID). There was a slight reduction reported in fentanyl from 2014 to 2021 (1.36-1.29 DDD/TID). Likewise, morphine also showed a similar pattern of reduction from 2014 to 2021 (1.17-1.06 DDD/TID) (Figure 5).

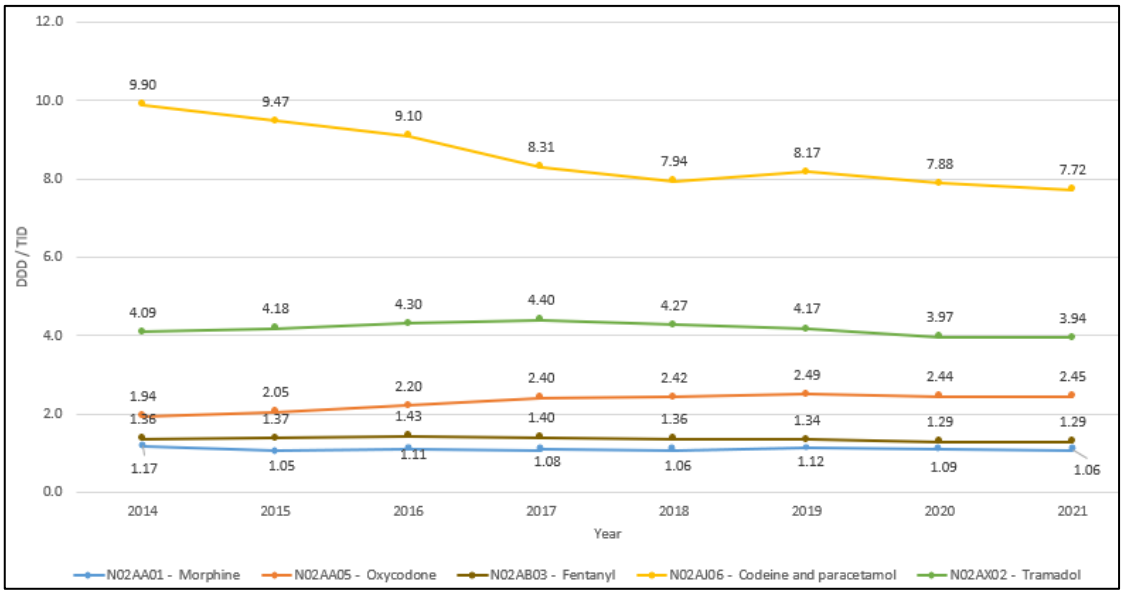

Figure 5: Most common opioids use trends in Norway from 2014-2021

In Lithuania, the fixed combination codeine and paracetamol were not that commonly used with low volumes in 2014 (0.16 DDD/TID), which slightly increased till 2021 (0.38 DDD/TID). Tramadol was the most common opioid, reported to be almost constant throughout 2014-2021 (0.93 DDD/TID). However, the lowest use was reported in 2019, with 0.91 DDD/TID and the highest in 2020, with 1.00 DDD/TID. There was a slight increase reported in fentanyl from 2014 to 2021 (0.36-0.44 DDD/TID). However, morphine showed a slight reduction from 2014 to 2021 (0.23-0.19 DDD/TID) (Figure 6).

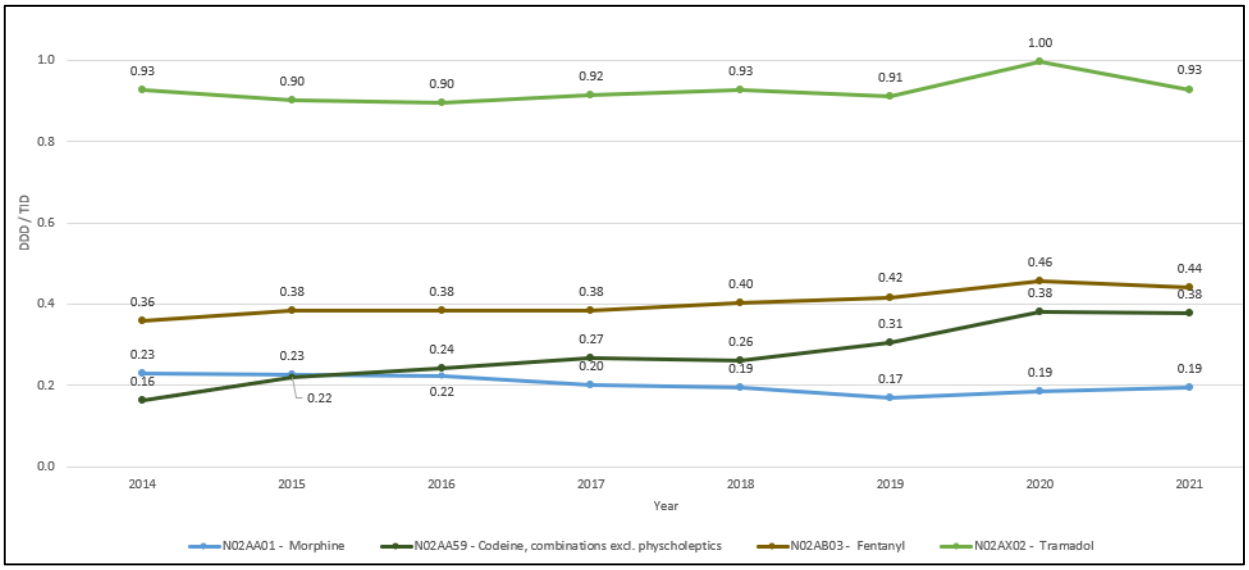

Figure 6: Opioids use trends in Lithuania from 2014-2021

4.1. Comparison Between April, 2017 AND June, 2017:

The graph below shows the difference in the prescription amount for the male and female patients in Lithuania for two different months, which is April and June 2017. The comparison shows an interesting narrative whereby it may be seen that the prescription amount for the females is quite higher than that of the males. Furthermore, there was a marked increase in the prescription amount between April and June as well. The overall comparison of the prescription amount by sex shows a marked increase, with the female prescription growing by almost 92 %, while the male prescription amount has increased by a percentage of nearly 96.

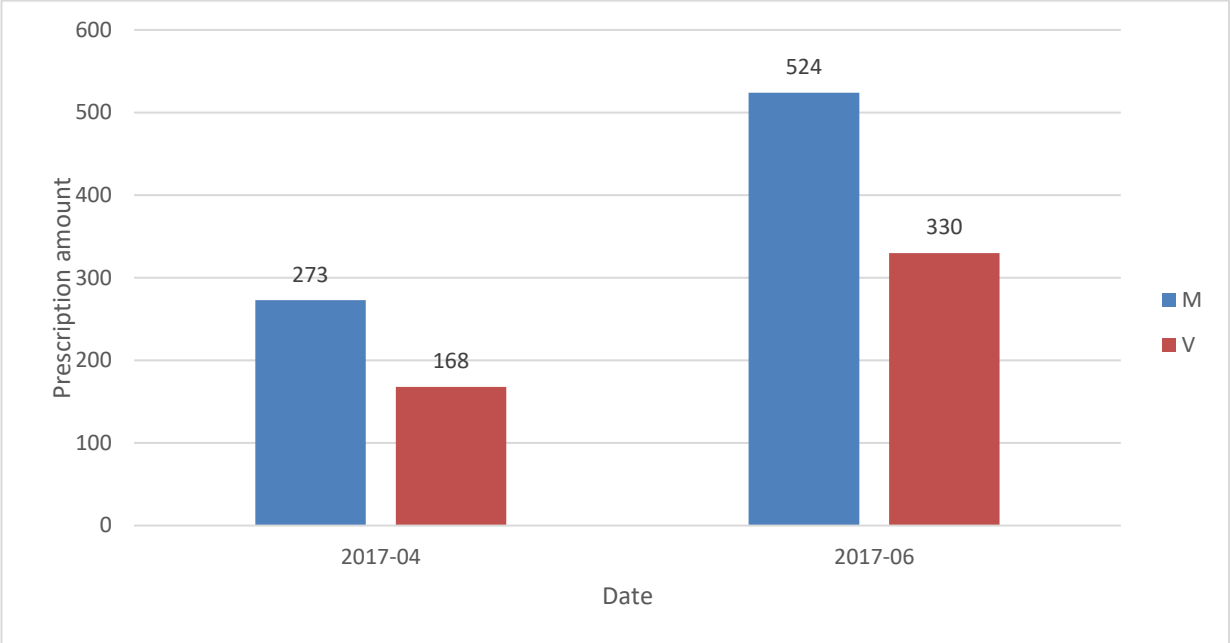

Figure 7: The prescription amount by patient sex comparing two different months (2017-04 and 2017-06)

The Figure below shows the prescription amount for some of the most common opioid medicine in the world. There is a consistent trend whereby the drug prescription amount was higher in June than in April, with all the drugs in the sample showing an elevated prescription level. The most significant change may be observed in the prescription of Tramadol Hydrochloride, which saw an increase of about 86 per cent.

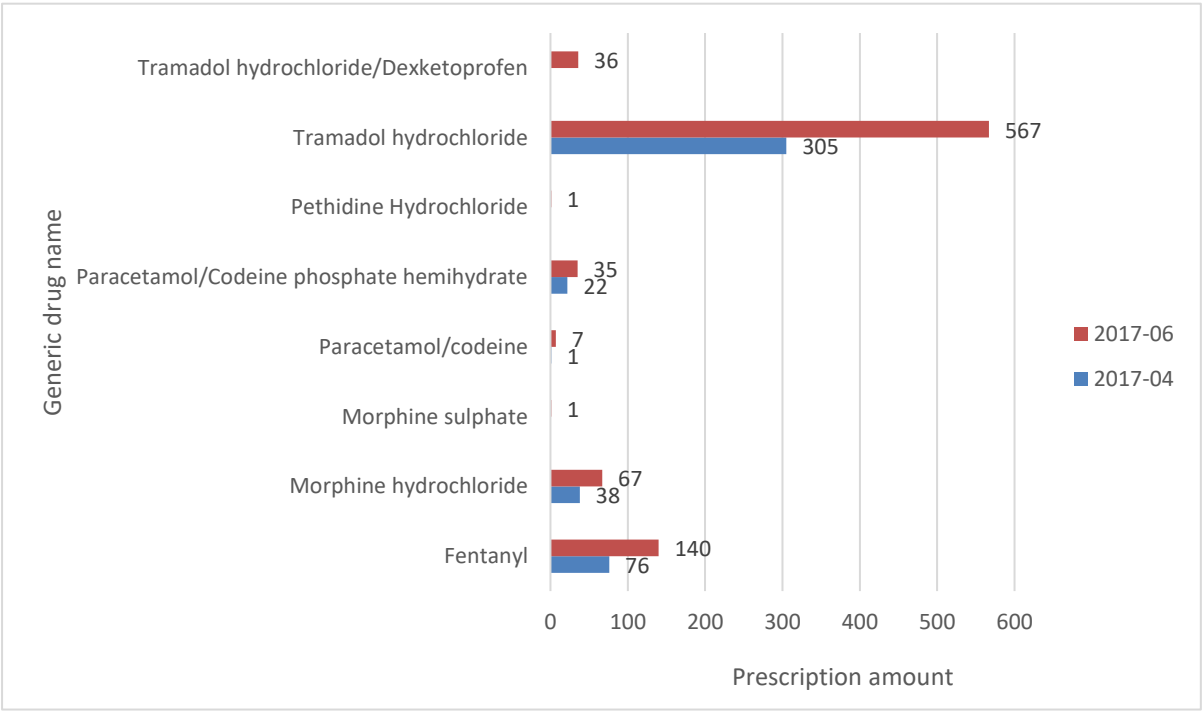

Figure 8: Amount of prescriptions by the generic name of the drug comparing two different months (2017-04 and 2017-06)

Figure – 9 shows the number of opioid prescription in Lithuania by age in the months of April and June 2017. The 15–44-year age bracket has increased from 15 to 38. Likewise, the 44–64-year age span have higher volumes of drugs in June compared to April from 73 to 159. Lastly, the above 65-year age bracket has seen an increase from 353 to 657. It may be seen that the volumes almost doubled for all the age demographics that have been analysed. This is partially consistent with the data above.

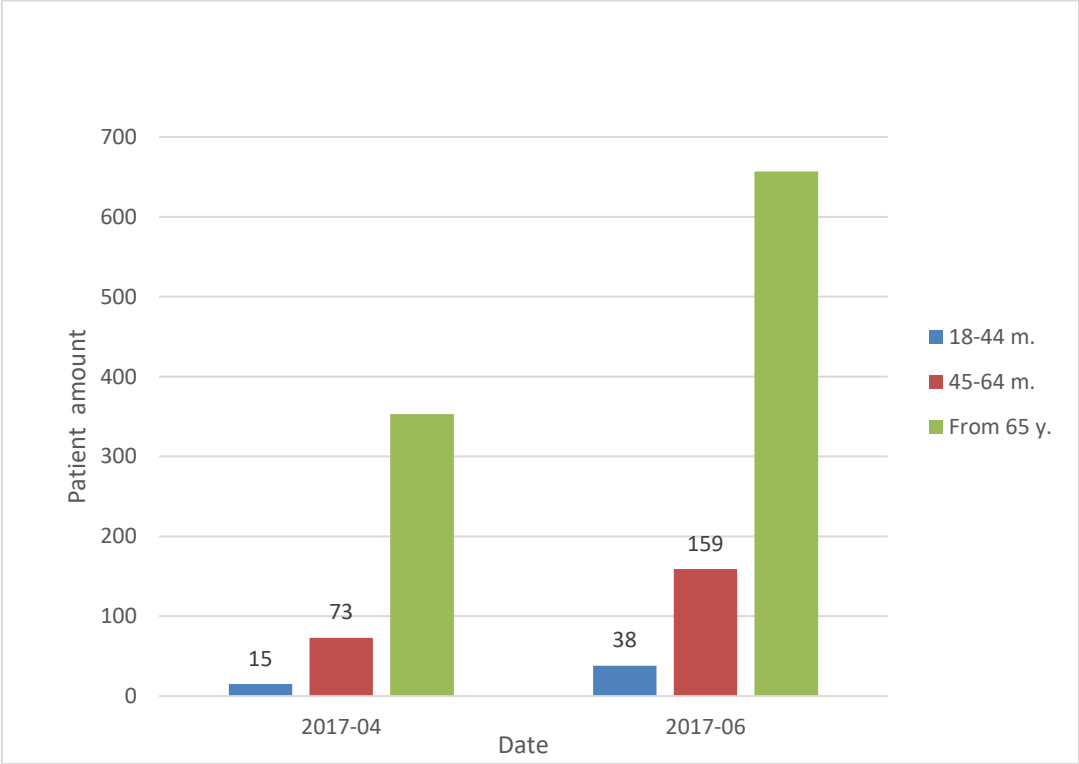

Figure 9: Patients amount by patient age comparing two different months (2017-04 and 2017-06)

CHAPTER # 5. DISCUSSION

This chapter critically analysis the results that have been obtained as a result of the implementation of the research methodology and the presented in the previous section. It is imperative to perform a critical evaluation of the results to understand and interpret their meaning, along with the concurrence of these studies with the literature and academic research available to evaluate its convergence with the present and emerging theories and ideas presented. The results of the study have been presented above with graphical interpretations. The main questions that were to be answered included an assessment of the differences in Opioid use through the wholesale data in Lithuania, Sweden, and Norway. In addition, some data on age and sex were presented for Lithuania specifically.

5.1. DIFFERENCES IN USE BETWEEN COUNTRIES

Opioids can cause addiction, overdose, and other health issues, making them a concern for decades. Opioid overdose kills many globally (151). Population, medical needs, and regulatory regulations determine a country's safe Opioid DDD/TID. To reduce harmful effects and addiction, the WHO recommends "start low and go slow" opioid use.

Between 2014 and 2021, wholesale opioid data from Lithuania, Sweden, and Norway shows significant disparities in opioid drug sales. Lithuania had a steady increase in opioid use, while Sweden had a large decline and Norway had a minor decline. Sweden and Norway used the most opioids, while Lithuania used the leasteven after the high increase over the period. In Norway and Sweden, codeine in fixed combination with paracetamol was the most widely utilised opioids, whereas Lithuania preferred tramadol. Opioids are mostly used to relieve pain in Lithuania, and their rising use may imply a rise in chronic pain problems that require long-term treatment. As in other countries, increasing opioid use may lead to addiction and overdose (152).

Prescription medication monitoring programmes also help identify and treat opioid use issues. These advancements support international and national opioid reduction efforts. After the EMA safety recommendations, NSAID use dropped significantly (124). NSAID use dropped from 34.1% to 30.1% after the recommendations. The suggestions raised paracetamol use from 25.8% to 27.6% (124). Opioid use increased slightly from 5.5% to 6.4% after the recommendations. NSAID and Opioid use dropped from 4.4% to 2.8% after the guidelines (124).

These countries use different opioids, according to the data. OUD prevalence was higher in men, those with psychiatric or substance use issues, and those with criminal records (153). Due to a lack of regulation and risk knowledge, this opioid use pattern may signal a shift towards heavier opioids.

Opioid dose and duration increased Opioid use disorder (OUD) risk. Opioid prescriptions for acute or cancer pain had a lower incidence of OUD than those for non-cancer chronic pain. OUD treatment with buprenorphine or methadone reduced the likelihood of OUD.(153) Opioid use is advised by international medical organisations. These guidelines emphasise monitoring and assessing patients' treatment response and risk of misuse, addiction, and overdose. They advocate non-opioid pain treatments first and prudence when giving opioids at greater doses. To lower opioid doses, the guidelines recommend multimodal analgesia, which combines opioids with non-opioids.

The healthcare system, prescribing practices, and pain management cultures in the three nations may explain the opioid use disparities. Norway and Sweden have universal healthcare systems that emphasise pain management. Lithuania's healthcare system is less developed; therefore, pain management is less important. Opioid use in the three countries may be related to healthcare systems (151).

Prescription practices may potentially affect opioid use. Opioids are tightly regulated and monitored in Norway and Sweden. Prescribers must follow tight criteria to protect patients from addiction and overdose. Opioids are prescribed more freely in Lithuania, which increases use. Opioid use may also vary by culture. Norway and Sweden emphasise self-reliance and reluctance to seek medical care for mild ailments (153). Patients may be more willing to explore other pain treatment approaches before using opioids due to this cultural mindset. However, Lithuanians may use more opioids because pain treatment is less stigmatised.

The three countries use different opioids. Codeine in fixed combination paracetamol were the most used opioids in Norway and Sweden, whereas Lithuania used tramadol. The varied opioids available on the market in the three countries may explain the differences in opioid use. In Lithuania, tramadol may be more accessible, increasing use. The wholesale opioid usage data from the three nations provide vital insights into opioid usage variances, but it does not include information on opioid usage reasons or patient characteristics. Reporting practices in the three nations may potentially affect data consistency (153).

The data does not include opioid addiction rates or opioid-related harm in the three countries. Lower opioid use may indicate a lower chance of addiction and overdose, but other factors like harm reduction, access to addiction treatment, and illicit opioid use must be considered. Opioid sales in Lithuania, Sweden, and Norway between 2014 and 2021 differed significantly, according to wholesale data (153). Norway and Sweden saw opioid use drop, whereas Lithuania saw it rise. The three countries' healthcare systems, prescribing practices, cultural attitudes towards pain management, and availability and accessibility of different opioids may explain the opioid consumption discrepancies. While the data is useful, other factors like opioid-related harm and addiction rates should be considered when assessing opioid use in the three countries.

5.2. SPECIFIC DRUG USAGE AND COMPARATIVE GUIDELINES:

Over-prescribing, cheap synthetic opioids, and a lack of effective opioid addiction therapy contribute to the opioid crisis (151). Wholesale opioid consumption data from Lithuania, Sweden, and Norway from 2014-2021 shows significant disparities in drug distribution. Opioid drug use climbed steadily in Lithuania from 2014 to 2021, but it declined dramatically in Norway and Sweden. Codeine, paracetamol, and tramadol were the most often used opioids in Norway, Sweden, and Lithuania, respectively. This is inline with the other studies that have been conducted (157).

The WHO recommends opioids for moderate to severe pain. The WHO emphasises monitoring and assessing the patient's response to therapy and the risk of misuse, addiction, and overdose. The WHO advises using non-opioid analgesics, light opioids, and powerful opioids if needed. The WHO advises prescribing opioids at the lowest effective dose for the shortest time (157).

In 2014, codeine and paracetamol were Sweden's most utilised opioids. From 2014 to 2021, tramadol use dropped. Oxycodone use rose from 2014 to 2021. During the study, codeine, non-analgesics, and morphine use decreased slightly. Sweden's opioid use decreased due to growing awareness of opioid addiction, tougher Opioid prescribing restrictions, and a focus on alternative pain care (154).

In 2014, codeine and paracetamol were Norway's most utilised opioids. Tramadol use dropped somewhat from 2014 to 2021. Codeine in fixed combination with paracetamol outsold tramadol, especially from 2015 to 2017 (157). Oxycodone use climbed significantly from 2014 to 2021. Fentanyl and morphine use decreased from 2014 to 2021. Norway, like Sweden, reduced opioid use due to increasing awareness of opioid addiction, stricter opioid prescribing rules, and a focus on alternative pain care (154).

Norway's opioid use has decreased due to its harm reduction methods, such as widespread naloxone distribution and needle exchange programmes, to combat the opioid overdose crisis (154). Norway offers methadone and buprenorphine-assisted treatment for OUD in primary care. Low-threshold, patient-centred care meets the multifaceted needs of substance use disorder patients in Norway (154).

Public education efforts in Norway aim to lessen the social and economic marginalisation of people with substance use problems (154). Norway's harm reduction and treatment strategies could help other countries combat the opioid overdose problem and increase access to evidence-based addiction treatment (154).

In Lithuania, tramadol was the most often used Opioid. 2019 had the lowest usage, and 2020 the most. Codeine and paracetamol use dropped in 2014 but rose through 2021. From 2014 to 2021, morphine use decreased, but fentanyl use grew. Tramadol and fentanyl use in Lithuania has increased due to a lack of understanding about opioid addiction, looser opioid prescribing rules, and less attention on alternative pain care (155).

Opioids are distributed differently in several nations according to prescribing practices, opioid prescription restrictions, patient preferences, and cultural variables. Norway and Sweden have restricted opioid prescriptions and prioritised alternative pain therapy. Lithuania has been slow to regulate opioid prescription and promote alternate pain management (153).

However, wholesale opioid use data does not fully depict the opioid crisis in these countries. It only accounts for opioids prescribed by doctors, not misuse, illegal sale, or other opioid use. To understand the opioid problem in these countries, this data must be combined with data on opioid-related deaths, hospitalisations, and abuse surveys (154).

5.3. COMPARATIVE ANALYSIS WITH LITERATURE:

It is estimated that 1.1% of Lithuanian adults used problem drugs (156). Respondents injected drugs most often. Problem drug use was highest in 20-24-year-olds. In Lithuania, injecting drug use causes serious harm. HIV and hepatitis C are common among injectors, and overdose is a risk, according to EMCDDA. EMCDDA recommends providing clean needles and syringes and opioid substitution treatment (155). Reliance on a single usage matrix may not be ideal for analysing the whole situation as there are many other factors that interplay into the indicators of an opioid crisis. It also highlights the situation in Lithuania is far from ideal (156).

It is recommended the need for more effective drug prevention and harm reduction measures. It suggested that a comprehensive approach is necessary for tackling the problem of drug use, which should involve not only law enforcement but also health and social services (14). There is a need to implement evidence-based prevention programs and harm reduction measures such as needle and syringe programs, opioid substitution therapy, and HIV prevention measures for people who inject drugs (157). One of the most important and interesting relationship is the correlation between the illegal and legal use of opoiod drugs. The comparative analysis between the different studies can be invaluable in determining the interrelationship between medical uses that may lead to addiction in the long term.

The three countries also distributed opioids differently. Codeine and paracetamol were the most often used opioids in Sweden in 2014, but their use fell considerably by 2021. Sweden also utilised tramadol, but use decreased dramatically over the research. Swedish oxycodone use increased considerably during the research. Codeine and paracetamol were the most often used opioids in Norway in 2014, but their use dropped by 2021. Over the study period, Norway used less tramadol and more oxycodone. Olsson et al. used hair analysis to assess non-medical tramadol usage in Malmö, Sweden, treatment-seeking teenagers (158). 60% of individuals' hair samples included tramadol, the most common non-medical prescription medication (158).

Polydrug use was also common, with 87% of the participants testing positive for at least one additional substance (158). Fentanyl and morphine usage declined slightly in Norway over the study period. Cannabis was the most commonly detected illicit drug, followed by benzodiazepines and amphetamines (158).

In Lithuania, codeine and paracetamol were the least commonly used opioid substances, and their usage remained relatively constant over the study period. Tramadol was the most commonly used opioid substance in Lithuania, and its usage remained relatively constant over the study period. Fentanyl usage increased slightly in Lithuania over the study period, while morphine usage declined slightly (158).

Iqbal et al. reported that unspecified opioids were identified in 15% of all opioid overdoses in Oslo. The majority of these cases were male, with a median age of 37 years. The most common co-ingested substance was benzodiazepines. The mortality rate among unspecified opioid overdoses was higher compared to overdoses involving known opioids (159). However, this does not align with the other findings where the gender population distribution for opioid consumption is similar among males and females.

The reasons for the differences in opioid use among Lithuania, Norway, and Sweden are not entirely clear. However, it is likely that various factors have contributed to these differences, including differences in prescribing practices, healthcare policies, and cultural attitudes towards pain management (159). In Sweden and Norway, it is likely that efforts to reduce opioid use and promote alternative pain management strategies have been successful. In Lithuania, it is possible that opioid use is increasing due to factors such as an ageing population, an increase in chronic pain conditions, or changes in prescribing practices (159).

The trends in opioid use in Lithuania, Norway, and Sweden suggest that efforts to reduce opioid use and promote alternative pain management strategies may be effective in reducing opioid addiction and overdose. Olsson et al. suggests that tramadol use among treatment-seeking adolescents is a significant concern in Sweden (158). There is a need for targeted interventions to address non-medical prescription drug use among young people, with a particular focus on tramadol (158). Polydrug use among adolescents should also be addressed, and interventions should consider the potential for combinations of prescription drugs, illicit drugs, and alcohol to cause harm (158). However, the differences in opioid use among the three countries also highlight the need for continued research and monitoring of opioid use and prescribing practices to identify effective strategies for reducing opioid-related harms while ensuring that patients receive appropriate pain management.

5.4. POSSIBLE FACTORS THAT INFLUENCE THE USE CULTURE OF OPIOIDS

The use of opioids for the management of pain has been a subject of debate and discussion for years. While opioids are considered effective pain relievers, their misuse, overuse, and abuse can lead to addiction, overdose, and death (159). Thus, international healthcare bodies and medical institutions have provided recommendations for the safe use of opioids. There can be multiple factors responsible for the differences in opioid use in Lithuania, Sweden, and Norway. One possible explanation for the diverging trends could be the differences in healthcare policies, prescribing practices, and regulations regarding opioids (160).

The American Society of Anesthesiologists (ASA) has developed guidelines for the safe use of opioids in the management of acute and chronic pain. The guidelines recommend that opioids be used only when non-opioid therapies have been ineffective or are not appropriate. The ASA also recommends the use of multimodal analgesia, combining opioids with other non-opioid analgesics, to reduce the need for high opioid doses. The ASA also advises providers to monitor patients for signs of opioid misuse, addiction, and overdose (159).

Sweden and Norway have well-established and regulated healthcare systems with guidelines and policies regarding the prescription and use of opioids. In Sweden, rules for how to prescribe opioids are regulated by the Swedish National Board of Health and Welfare and additional guidance are provided by the regional Drug and Therapeutics committees. Opioids are mainly recommended for patients suffering from cancer or other severe illnesses. Moreover, there is a strong emphasis on non-pharmacological pain management techniques, and opioids are not considered the first line of treatment for chronic pain. Similarly, in Norway, the use of opioids is tightly regulated by the Norwegian Directorate of Health, and healthcare providers are required to follow specific guidelines for opioid prescription, including regular assessment of patients and consideration of alternative treatments. Norway also has a national registry of opioid prescriptions, which can help monitor and prevent the misuse of opioids (160).

In contrast, Lithuania does not have a well-established healthcare system and lacks specific regulations and guidelines for opioid prescription and use. This may result in an over-reliance on opioids as a pain management solution and a lack of awareness among healthcare providers regarding the risks associated with opioid use. Additionally, there may be cultural factors at play, such as a general acceptance of pharmacological interventions for pain management, which could lead to higher rates of opioid use (156).

The comparative analysis of opioid use considers only the wholesale data for the country, where the arguments may be raised that the complete picture may not be available, for there may be informal or illegal supply chains for the opioid drugs present. EMCDDA provides an overview of the situation regarding drug use in the country, including data on prevalence, trends, and patterns of use, as well as information on the harm associated with drug use and related responses (155).

EMCDDA identifies heroin as the most used drug in Lithuania, although cannabis and amphetamines are also prevalent. In recent years, there has been a significant increase in the use of new psychoactive substances (NPS), which are often marketed as "legal highs." EMCDDA notes that these substances are difficult to regulate, and their effects can be unpredictable and potentially dangerous (155).

In the United States, the CDC has issued guidelines for the safe prescribing of opioids. These guidelines recommend non-opioid therapies as the first-line treatment for chronic pain and advise that opioids be used only when the benefits outweigh the risks. The CDC also recommends that providers use caution when prescribing opioids at higher dosages, particularly

for patients at risk of overdose or addiction. The guidelines also suggest monitoring and assessing patients' response to treatment, as well as the potential for misuse, addiction, and overdose (160).

Another possible factor that may be contributing to the differences in opioid use is the availability and accessibility of opioids in the three countries. Sweden and Norway have lower rates of opioid availability compared to Lithuania, which could be due to stricter regulations and monitoring of opioid distribution. In Lithuania, there may be easier access to opioids, leading to higher rates of unofficial or illegal use (155). As such, the wholesale data may not be a proper indicator for the opioids use in Lithuania as the major market for the drugs may be unregulated and not recorded under the wholesale data that has been used for this study.

Finally, societal and cultural factors may also be at play, such as differences in attitudes towards pain and pain management and overall levels of healthcare literacy among the general population. These factors can impact the willingness of patients to seek alternative pain management solutions and the prescribing practices of healthcare providers (160). Addressing the underlying factors contributing to opioid use in each country is crucial for reducing opioid-related harms and promoting safer and more effective pain management practices

5.5. **PAIN MANAGEMENT, SEX AND AGE:**

One of the most important factors to be considered is the role of pain management following medical procedures. Economic factors may be analysed for their role in predicting opioid use. Economic factors such as employment, poverty, and healthcare can also influence opioid use. Individuals with lower education, income, and social class were more likely to report pain and chronic pain (4). In Lithuania, there is a high level of unemployment, and this could contribute to the high rates of opioid use observed in the country. The specific circumstances for the massive growth in prescription amount between April 2017 and June 2017 is not known.

According to Eurostat, Lithuania has one of the highest unemployment rates in Europe. Unemployment can lead to economic hardship, social exclusion, and poor mental health, which could increase the risk of opioid use. In contrast, Sweden and Norway have lower levels of unemployment, which could explain the lower rates of opioid use observed in these countries. Additionally, the healthcare systems in Sweden and Norway are more developed than in Lithuania, and this could contribute to the lower rates of opioid use observed in these countries. However, it must be kept in mind that this may not consider the wholesale data and the opioid use epidemic recorded in this discussion may hold true for unregulated use.

There was a significant association between pain and poor self-rated health, psychological distress, and limitations in daily activities (4). Numerous studies have demonstrated the impact of pain on health outcomes. For instance, a cross-sectional study conducted by Hammerlid et al (161), found that patients with chronic pain reported poorer self-rated health compared to those without pain. Similarly, a longitudinal study by Derks et al. (162), found that patients with chronic back pain reported greater levels of depression and anxiety than those without pain. Moreover, a study by Nayback-Beebe et al. (163), found that pain severity was a significant predictor of limitations in daily activities, such as work, leisure activities, and social interactions.

While the statement is supported by research, it is important to acknowledge that the relationship between pain and poor health outcomes is complex and multifactorial. Other factors, such as social support, coping strategies, and underlying medical conditions, can also influence health outcomes in individuals with pain. Furthermore, it is crucial to recognise that pain is not a uniform experience, and different types of pain may have different effects on health outcomes. For example, chronic neuropathic pain may have different impacts on daily activities compared to acute musculoskeletal pain (164).

One of the most important aspects is the proposal of the revised reporting framework that could effectively provide a more streamlined and uniform comparison for cross-national analysis. The POINT study is a large-scale, population-based study that will provide important insights into the use of long-term opioid therapy for chronic non-cancer pain in Norway (165). Hamina et al**.**'s proposed study will provide data on the prevalence of opioid use in Norway, as well as the characteristics of patients who are prescribed opioids for chronic non-cancer pain. The study will evaluate the effectiveness and safety of long-term opioid therapy for chronic non-cancer pain, including the risk of opioid-related adverse events and the potential for opioid misuse and addiction. The study will also assess the impact of various interventions aimed at reducing the use of opioids for chronic non-cancer pain, including the use of alternative pain management strategies and the implementation of guidelines and policies aimed at reducing opioid prescribing (166).

The POINT study highlights the need for ongoing monitoring and evaluation of opioid prescribing practices, particularly for chronic non-cancer pain. The study emphasises the importance of developing and implementing evidence-based guidelines for the management of chronic non-cancer pain, with a focus on non-opioid pain management strategies. There is a dire need for increased awareness among healthcare providers and patients regarding the

potential risks associated with long-term opioid therapy, including the risk of opioid-related adverse events and the potential for opioid misuse and addiction. Moreover, it is critical under the ongoing efforts to reduce the availability of prescription opioids and to implement policies and programs aimed at preventing opioid misuse and addiction (166).

The prevalence of long-term opioid therapy (LTOT) was found to be high among patients with CNCP attending a university-based tertiary pain clinic in Sweden, with 45.8% of patients being prescribed opioids for longer than 3 months (167). LTOT was found to be associated with older age, lower educational level, and higher pain intensity. Patients on LTOT had significantly higher levels of depression and anxiety compared to patients not on opioids. A significant proportion of patients on LTOT had opioid-related adverse events, with constipation being the most common. They also suggest the need for more research into the effectiveness of LTOT in CNCP, as well as the development of guidelines for tapering and discontinuing opioid therapy (167).

Countries could prioritise harm reduction strategies, including widespread distribution of naloxone and needle exchange programs, to reduce opioid-related harm and fatalities (154). Treatment of OUD should be integrated into primary care and made more widely available and accessible, particularly medication-assisted treatment (MAT) with methadone or buprenorphine. The national healthcare system should adopt a low-threshold, patient-centred approach to addiction treatment that addresses the complex needs of individuals with substance use disorders.

Amundsen et al. included 77,155 individuals admitted to substance use disorder treatment in Norway between 2008 and 2017. The most common substances of abuse were alcohol (51.4%), followed by opioids (22.4%) and amphetamines (13.1%). The study found a significant gender difference in substance abuse, with men being more likely to abuse alcohol and women being more likely to abuse opioids and benzodiazepines (160).

Amundsen et al. also found significant age differences in substance abuse, with younger individuals more likely to abuse amphetamines and older individuals more likely to abuse opioids and benzodiazepines. Individuals who were admitted to treatment for opioids were more likely to have a criminal history and a history of mental illness compared to those who were admitted for alcohol or amphetamines. Individuals who were admitted for alcohol abuse were more likely to have a higher education level and a higher income compared to those who were admitted for other substances of abuse (160).

IMPROVEMENT EFFORTS:

Healthcare providers should be cautious when prescribing opioids to older adults, considering the potential for adverse effects, drug interactions, and falls (154). Alternative pain management strategies, such as non-opioid medications, physical therapy, and cognitive behavioural therapy, should be considered before opioids are prescribed. Policies and interventions should be implemented to reduce the overall use of opioids and prevent opioid-related harm among older adults.(152)

The COVID-19 pandemic has exacerbated the opioid crisis by disrupting drug supply chains and increasing social isolation, leading to increased drug use and overdose. The opioid crisis is not limited to high-income countries, and low- and middle-income countries are also affected (153). Efforts should be made to reduce the number of opioid prescriptions and to limit their duration, especially for those with high-risk factors. Screening for psychiatric and substance use disorders should be conducted before prescribing opioids. Those at higher risk for OUD should receive closer monitoring, and alternative pain management strategies should be considered. Greater access to MAT for OUD, such as buprenorphine and methadone, should be provided to those in need (153).

The stigma associated with opioid addiction is a significant barrier to treatment and harm reduction efforts (151). Efforts should be made to reduce inequalities in pain prevalence across socioeconomic groups and countries (4). Increase access to naloxone, a life-saving medication that can reverse opioid overdose (151). Addressing the social determinants of opioid addiction, including poverty, social inequality, and trauma, may have a positive impact. Improve opioid prescribing practices to prevent over-prescription and minimise the risk of addiction (151). Additionally, addressing the stigma associated with opioid addiction and promoting harm reduction strategies, including safe injection sites and needle exchange programs, can also improve the situation (151).

EMCDDA highlights the need for greater efforts to prevent drug use among young people, as well as measures to address the social and economic factors that contribute to drug use. The report notes that poverty and social exclusion are significant risk factors for drug use and suggests that addressing these underlying factors could help to reduce the harm associated with drug use in the long term (155). In terms of responses to drug use, EMCDDA notes that Lithuania has a well-established system of drug treatment services, including both inpatient and outpatient services. However, the report also highlights the need for greater coordination

between different services and for the provision of more effective and evidence-based treatment options (155).

It is necessary to increase funding for research into the prevention and treatment of opioid addiction. It may be useful to develop international collaborations to address the global nature of the opioid crisis (151). Greater attention should be paid to chronic pain, as it is a significant burden on individuals and society. Multidisciplinary approaches to pain management should be promoted, with a focus on non-pharmacological interventions and patient-centred care. Further research is needed to understand the underlying mechanisms of pain and the factors contributing to pain inequalities (4).

The WHO also provides guidelines for the use of opioids in the treatment of pain, including recommendations for dosing, titration, and monitoring. The guidelines emphasise the importance of individualised treatment and regular reassessment of patients to ensure that the benefits of opioid therapy continue to outweigh the risks. It is also important to note that the safe level of opioid use can be influenced by factors such as age, medical history, concurrent use of other medications, and individual tolerance to opioids. Therefore, it is crucial for healthcare professionals to carefully evaluate each patient's needs and risk factors before prescribing opioids and to monitor their use closely (152).

Kasciuškevičiūtė et al. recommend that physicians in Lithuania should consider alternative pain treatments, such as paracetamol, before prescribing NSAIDs or opioids, especially in patients at risk for cardiovascular events or gastrointestinal bleeding (124). Physicians should carefully evaluate the risks and benefits of prescribing NSAIDs or opioids and should consider other pain treatments or non-pharmacological interventions if appropriate. Future research should investigate the long-term impact of the EMA safety recommendations on NSAID use and patient outcomes in Lithuania (124).

CHAPTER # 6. CONCLUSION:

This chapter summarises and concludes upon the research questions set out in the first chapter, using the data and discussion in the preceding chapters. Opioids have become a global health issue due to their potential to cause addiction, overdose, and other health problems. This article examines wholesale opioid data from Lithuania, Sweden, and Norway from 2014 through 2021, revealing significant differences in opioid drug sales and Lithuanian prescription data, which reveals opioid prescription patters via analysis by patient sex and age. The following conculsions could be drawn:

1. The total sales of opioid medicines have remarkable differences in Lithuania, Sweden, and Norway. Lithuania shows progressive increases in opioid usage, Sweden decreased opioid usage over time and Norway remained at a high level. In Sweden, codeine in fixed combination with paracetamol was the most commonly used opioid in in 2014 but it decreased significantly in 2021. Tramadol also decreased over the study period, while oxycodone increased substantially. Codeine and other non-analgesics, as well as morphine, also showed reductions. In Norway, codeine in fixed combination with paracetamol were reported to be highest in 2014 but slightly reduced in 2021. Tramadol also slightly decreased, while oxycodone increased substantially. Fentanyl and morphine also showed slight reductions. These patterns suggest that there may be differences in opioid prescribing practices and regulations between these countries. For example, the increased usage of oxycodone in Sweden and Norway suggests that these drugs are more widely available in these countries. It is essential to consider the potential harms associated with opioid use and abuse, such as addiction and overdose. Thus, it is crucial to monitor and regulate the use of these drugs to ensure safe and effective pain management. Barriers to collecting and sharing data on opioid usage may hinder efforts to understand and regulate opioid prescribing practices. Addressing these barriers could help improve the safety and effectiveness of opioid use in these countries.
2. Lithuania showed a consistent increase in the use of opioids from 2014 to 2021, while Norway and Sweden demonstrated a decline in opioid use over the same period. It is essential to analyze the distribution of different opioid substances to gain insight into their usage patterns. In Sweden, codeine, paracetamol, and tramadol had the highest usage in 2014, with a subsequent decline in usage until 2021. The usage of oxycodone increased from 2014 to 2021. These patterns may reflect changes in prescribing practices and shifts in the availability and accessibility of different opioids. Moreover, the slight reduction in codeine and other non-analgesics and morphine over the years

might suggest a change in prescribing practices or a shift in patient needs. It is worth noting that the reduction in opioid use in Sweden is an encouraging sign and could indicate the effectiveness of public health initiatives aimed at reducing opioid abuse. Similarly, Norway reported a decline in the use of codeine, paracetamol, and tramadol from 2014 to 2021, with a slight increase in oxycodone usage over the same period. The slight reduction in fentanyl and morphine usage in Norway could indicate a shift in prescribing practices, but more research is needed to determine the cause of these trends. It is possible that public health initiatives aimed at reducing opioid use may have played a role in these trends, although further analysis is necessary to confirm this. In contrast to Sweden and Norway, Lithuania's usage of codeine and paracetamol remained relatively stable from 2014 to 2021, with a slight increase in usage in 2021. Tramadol usage remained almost constant throughout this period. The slight increase in fentanyl usage from 2014 to 2021 might reflect changes in prescribing practices or increased demand for this opioid. The slight reduction in morphine usage in Lithuania could suggest a shift in prescribing practices, although further analysis is necessary to confirm this.

3. The data presented highlights a rapid increase in the prescription of opioids in Lithuania during the two-month period of April and June 2017. The increase in prescription amounts, especially for female patients, shows that the prescription amount nearly doubled across the two months. The data provided shows a difference in opioid prescription amounts between males and females. The prescription amount for females was higher than that of males, with a significant increase observed from April to June 2017. The reasons for this difference are unclear and require further investigation. However, this finding highlights the importance of examining demographic factors when analyzing opioid usage patterns. One possible explanation for the increase in prescription amounts could be related to changes in the healthcare system or prescribing practices during this period. It is also possible that the rise could be due to an increase in the number of patients seeking medical care for chronic pain conditions. Regardless of the reasons behind this trend, it is essential to monitor the prescription of opioids to prevent misuse and abuse of these potent medications. Another trend identified in the data is the significant increase in the number of patients prescribed opioids across all age groups. This suggests a growing reliance on opioid medications for pain management in Lithuania, which may have significant consequences in terms of addiction and overdose. It is important to note that while opioids can be an effective pain management tool, they also carry the risk of addiction and dependence, especially

when used for extended periods. The prescription amount for some of the most common opioid medications, is also noteworthy. Tramadol Hydrochloride, a potent opioid medication, saw the most significant increase in prescription amounts, indicating that it is the drug of choice for pain management in Lithuania. This highlights the need for healthcare providers to evaluate their prescribing practices and consider alternative pain management strategies to avoid overreliance on opioids.

Healthcare providers must carefully assess patients' needs and risk factors before prescribing opioids and closely monitor their use. Non-pharmacological and patient-centred multidisciplinary pain management should be encouraged. Pain mechanisms and pain inequities need further study.

6.1. STUDY'S STRENGTHS:

This study focused on the comparative analysis of three countries to identify and study the trends across the period stating from 2014 to 2021. The study uses official wholesale data which provides highly accurate data collected through official channels, moreover Lithuanian prescription data was used, which provide insinght into opioid usage trends between different sex and age groups, comparing two months, selected randomly for a reference. This increases the use value of the study as the data is highly reliable. Moreover, the cross-sectional analysis provides suitable comparative assessment for the trends in all three countries. Moreover, relevant comparison with other studies helps in interpretation of the results much more easily and reliably.

The quantitative analysis helps eliminate any bias that may influence the analysis of the qualitative form. Moreover, use of graphs and figure help in the interpretation of the visual data more easily and verify the interpretations by the third parties as well.

6.2. LIMITATIONS:

It is important to note that the wholesale data on opioid use only reflects the usage of opioids prescribed by healthcare providers and does not account for opioid misuse, illegal sale, and other forms of opioid consumption. Therefore, it is essential to combine this data with other sources, such as data on opioid-related deaths, opioid-related hospitalisations, and opioid misuse surveys, to gain a comprehensive understanding of the opioid crisis in these countries.

There is a need for ongoing monitoring and evaluation of opioid prescribing practices, particularly for chronic non-cancer pain. The study highlights the importance of developing and

implementing evidence-based guidelines for managing chronic non-cancer pain, focusing on non-opioid pain management strategies.

Aggregate data tends to be less detailed than individual-level data, making it difficult to draw conclusions about specific subgroups or individuals within the population of interest. Moreover, aggregate data is typically reported in pre-defined categories, which may not align with the specific research questions being asked. This can limit the ability to analyze data in a nuanced way or to draw meaningful insights from the data.

The quality of aggregate data can vary widely depending on the source and how it was collected and reported. In some cases, the data may be incomplete, inaccurate, or biased, which can compromise the validity of any conclusions drawn from the data. Additionally, aggregate data is often presented without contextual information that could help to explain the trends or patterns observed. Without this context, it can be difficult to interpret the data accurately and draw meaningful insights from it. Lastly, official sources of aggregate data may not cover all aspects of the research question being investigated, which can limit the scope of the analysis and the conclusions that can be drawn from the data.

6.3. RECOMMENDATIONS:

Future research should focus on the following areas:

Problemtic Opioid Use: There is a need for the research on the problematic uses of drugs along with the illegal use of opioids and other drugs. Moreover, another factor that needs to be researched is the addiction development in patients that are taking opioids or opioids based drugs for pain management or through prescriptions for other purposes.

Long-term outcomes of opioid use: Many studies have focused on the short-term effects of opioid use, such as pain relief and the risk of overdose. However, there is a need for more research on the long-term effects of opioid use, including chronic pain management, OUD development, and opioid-related morbidity and mortality.

Factors contributing to opioid misuse: There is a need for more research into the social, psychological, and environmental factors that contribute to opioid misuse. This includes examining the impact of socioeconomic status, social support, trauma, and mental health on opioid use.

Developing effective interventions: There is a need for more research into effective interventions for opioid misuse, including both prevention and treatment. This includes examining the effectiveness of MAT, behavioural interventions, and harm reduction strategies such as safe injection sites and naloxone distribution programs.

Impact of policy and regulatory changes: The opioid crisis has led to policy and regulatory changes aimed at reducing opioid prescribing and improving treatment for OUD. There is a need for more research into the impact of these changes, including their effectiveness, unintended consequences, and potential for improvement.

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