REGULATORY STRATEGIES FOR PROMOTING THE SAFE USE OF PRESCRIPTION OPIOIDS AND THE POTENTIAL IMPACT OF OVERREGULATION

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Dr. Katja Bendrin

aus Torgau

Bonn 2020

Betreuer und Erster Referent: Dr. Birka Lehmann

Zweiter Referent: Dr. Jan Heun

Acknowledgment

I want to thank Dr. Birka Lehmann for her willingness to supervise this work and for her support. I further thank Dr. Jan Heun for assuming the role of the second reviewer.

A big thank you to the DGRA Team for the organization of the master's course and especially to Dr. Jasmin Fahnenstich for her support to find the thesis topic and supervisors.

Furthermore, thank you Harald for your patient support.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACDA	Act on Counteracting Drug Addiction
art	Article
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical
AWMF	Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel)
BMG	Federal Ministry of Health (Bundesministerium für Gesundheit)
BtM	Narcotics (Betäubungsmittel)
BtMG	German Narcotic Drugs Act (Betäubungsmittelgesetz)
BtMVV	Narcotic Drugs Prescription Ordinance (Betäubungsmittelverschreibungsverordnung)
CBD	Cannabidiol
CBN	Central Bureau of Narcotics
CDC	Centers for Disease Control and Prevention
CDSA	Controlled Drugs and Substances Act
CDSCO	Central Drugs Standard Control Organisation
CHM	Commission on Human Medicines
CIOMS	Council for International Organizations of Medical Sciences
CNCP	Chronic non-cancer pain
CND	Commission on Narcotic Drugs
CNS	Central nervous system
CP	Caudate putamen
DDD	Defined daily dose (The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults)
DOP	Delta (δ) OPiate receptor
e.g.	For example (lat. "exempli grazia")
EML	Essential Medicines List
EWG	Expert Working Group
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GPM	Good Pain Management
HIV	Human immunodeficiency virus
HPRG	Health Products Regulation Group

HRH	Human resources for health
IASP	Association for the Study of Pain
ID	Identification
INCB	International Narcotics Control Board
INT	International
JSPM	Japanese Society for Palliative Medicine
KOP	Kappa (κ) OPiate receptor
Kv	Voltage-gated potassium
Law N°03/201	Law N°03/201 governing narcotic drugs, psychotropic substances and precursors
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHLW	Ministry of Health, Labour, and Welfare
MHRA	Medicines and Healthcare product Regulatory Agency
MOP	Mu (μ) OPiate receptor
MRSA 101	Medicines and Related Substances Act 101
NAc	nucleus accumbens
NC	Narcotics Commissioner
NCR	Narcotic Control Regulations
NDA	Narcotic Drugs Act 1967
NDPS Act	Narcotic Drugs and Psychotropic Substances Act 1985
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMPA	National Medical Products Administration
NOP	Nociception
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NPCA	Narcotics and Psychotropics Control Act
ODC	Office of Drug Control
OIH	Opioid-Induced hyperalgesia
Order Nº 001	Ministerial Order Nº 001/MoH/2019 of 04/03/2019
OTC	Over the counter
p.	Page
PBS	Pharmaceutical Benefits Scheme
PMDA	Pharmaceutical and Medical Devices Agency
PPA	Prescription Pricing Authority

PSEHB	Pharmaceutical Safety and Environmental Health Bureau
reg	Regulation
RMP	Risk Management Plan
SAHPRA	South African Health Products Regulatory Authority
sc	Section
S-DDD	Defined daily doses for statistical purposes
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (Poisons Standard)
THC	Tetrahydrocannabinol
TGA	Therapeutic Goods Administration
UK	United Kingdom
UN	United Nations
UNODC	United Nations Office on Drugs and Crime
US	United States
WHO	World Health Organization

1. Scope

Access to pain management is internationally recognized as a fundamental human right and to date, opioids are the most potent class of pain relievers. However, the availability of opioids throughout the world is highly imbalanced. The regional discrepancy in opioid consumption results in a discrepancy in pain management and often physical suffering of patients from cancer as well as from non-cancer pain. In contrast, some regions, such as North America, are currently facing an opioid epidemic.

This work will provide a global overview concentrating on nine countries that are very diverse in terms of their average consumption of narcotic drugs, and that were selected to illustrate the factors and barriers influencing opioid accessibility in different global and cultural regions. The selection comprises countries from Europe (Germany, United Kingdom, Poland), North America (Canada), Oceania (Australia), Asia (India, Japan) and Africa (South Africa and Rwanda).

The focus will be on factors that influence the path of opioids to the patients, which are demonstrated in the respective national legislations for controlled substances, in comparison with the international control by the 1961 United Nations (UN) Single Convention on Narcotic Drugs. A special emphasis will be on the scheduling of opioids used for pain management and prescription requirements.

In addition, the availability of national clinical guidelines for pain management will be investigated to evaluate the acceptance of opioids for the pharmacotherapy of pain in general among health care professionals.

Furthermore, regulatory actions, if existing, against an opioid epidemic or against an undersupply with opioids, will be highlighted.

2. Introduction

2.1 Classification of Opioid Medicines

The term “opioid” comprises a group of substances having morphine-like properties with effects on the relief of pain (analgesia) and the feeling of wellbeing (euphoria). Opioids act at opioid receptors in the central nervous system (CNS) and their origin can be either exogenous such as natural, semisynthetic or synthetic opioids, or they are endogenous opioid peptides including endorphins and enkephalins [1].

Opioids can be classified in several ways. The classification based on the **origin** of the drug considers whether the drug is naturally occurring or manufactured (Table 1). Natural opioids are referred to as opiates and include morphine and codeine. Semisynthetic derivates are based on natural alkaloids for example hydrocodone, hydromorphone, oxycodone and buprenorphine. Synthetic opioids are classified according to chemical groupings and can be divided in:

- morphinan derivatives such as levorphanol, butorphanol
- diphenylheptane derivatives such as methadone and propoxyphene
- benzomorphan derivatives such as pentazocine and phenazocine
- and the phenylpiperidine derivatives such as pethidine, alfentanil, fentanyl, sufentanil and remifentanil [2, 3].

Regarding to their **source**, botanically opioids are defined as a class of natural alkaloids found in opium that are derived from the resin of the opium poppy, *Papaver somniferum*, and thus refer to natural opioids. Chemically opioids are defined having a similar structure as natural opioids, including natural, semi- and synthetic opioids. The pharmacological definition of opioids describes them as substances which have similar pharmacological activity independent of a similar structure such as morphine or codeine, and include natural, synthetic and endogenous opioids [4].

The classification considering the analgesic **potency** of the opioid distinguishes between strong, medium or weak. For example, Tramadol as a weak opioid, has a 10 times lesser analgesic potency than morphine, a strong opioid (Table 1).

The **functional classification** of opioids considers their action at the opioid receptor as pure agonist, partial agonist, agonists-antagonists or pure antagonists [5]. Opioids actioning as agonists, e.g. fentanyl and oxycodone, interact with a receptor (see 2.2) to produce a maximal response from that receptor. Antagonists such as naloxone and naltrexone bind to receptors without producing a functional response and have thus no intrinsic activity, but they prevent an agonist from binding to that receptor. Partial agonists such as buprenorphine bind to receptors but induce only a partial functional response from the receptor no matter the amount of drug administered (Table 1).

Table 1: Classification of Opioids

Adapted from [5].

Potency	Origin	Function
Strong	**Naturally occurring**	**Pure agonists**
• Morphine	• Morphine	• Morphine
• Pethidine	• Codeine	• Fentanyl
• Fentanyl	• Papavarine	• Alfentanil
• Alfentanil	• Thebaine	• Remifentanil
• Remifentanil	**Semisynthetic**	• Sufentanil
• Sufentanil	• Diamorphine (Heroin)	• Oxycodone
• Oxycodone	• Dihydrocodeine	• Piritramide
• Piritramide	• Buprenorphine	• Hydromorphone
• Hydromorphone	• Oxycodone	• Tapentadol
• Tapentadol	• Hydromorphone	• Tillidine
Intermediate	**Synthetic**	**Partial agonist**
• Buprenorphine	• Pethidine	• Buprenorphine
• Nalbuphine	• Fentanyl	**Agonists-antagonists**
• Tillidine	• Alfentanil	• Nalbuphine
Weak	• Sufentanil	**Pure Antagonists**
• Codeine	• Methadone	• Naloxone
• Tramadol	• Levorphanol	• Naltrexone
	• Piritramide	
	• Tapentadol	
	• Tillidine	

According to their **legal status** opioids can be divided in prescription and illicit opioids. Prescription opioids are utilized by medical doctors for medical purposes in the therapy of moderate to severe pain, for palliative care, during anesthesia or as treatment for an opioid dependence and include natural opioids such as morphine, semi-synthetic opioids such as oxycodone and synthetic opioids such as fentanyl. Over-prescription and misuse of those drugs can result in abuse or in developing an opioid dependence. Illicit opioids are produced, obtained and used illegally for non-medical consumption or to produce derivates as heroin, which is the most prevalent illicit opioid worldwide [6].

All opioids are classified as narcotics. The term **Narcotic Drugs**, however, includes several other substances besides opioids, such as products derived from coca bush or cannabis plant which all are internationally controlled under the UN Single Convention 1961 (see 3.1) [7].

2.2 Opioid Receptors and Mode of Action

Three main human opioid receptors are known, which are all G-protein-coupled receptors that are mainly distributed in the central nervous system, and also to a lesser extent in the gastrointestinal tract, skin and spinal cord.: DOP (delta (δ) OPiate receptor), KOP (kappa (κ)) and MOP (mu (μ)) and a fourth homologues, but non-opioid receptor NOP (nociceptin). In the brain all receptors are found to be highly abundant in the amygdala, the nucleus accumbens (NAc) as part of the reward system, and the caudate putamen (CP). Through binding to those opioid receptors, opioids alter neural signal transmission. Dopamine is a neurotransmitter which is responsible for feelings of euphoria and pleasure amongst other functions. In conjunction with the opioid

peptides and receptors it stimulates the dopaminergic pathway (mesolimbic pathway) for dopamine transmission. When opioid agonists bind to presynaptic mu-opioid receptors of GABAergic interneurons, the release of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) is decreased. This inhibition of the GABAergic neurons allows dopaminergic neurons to release more dopamine into the reward pathway, which creates a positive reinforcement of pleasurable feelings.

The Opioid receptors have different binding affinities to specific ligands which results in the varying degrees of analgesic effect and anti-nociception. All clinical opioids can bind at the MOP receptor, whereas only a subset has additional activity on other opioid receptors in addition. Morphine has higher affinity for MOP receptor that for other opioid receptors. Codeine has higher affinity to MOP, low affinity to DOP and no affinity to KOP receptor. However, binding of opioids to any of those receptors produces analgesia. Still, the possibility of physical dependence is higher for the activation of the MOP receptor than for the KOP receptor [2, 8].

A recent study found that opioids seem not only to bind in the same surface receptors as endogenous opioids, but also to receptors that are not a target for the naturally occurring opioids. The study hypotheses that current medically used opioids distort the normal time and spatial sequence of mu-opioid receptor activation and signaling, which could provide and explanation for the undesired side effects of medical opioids [9].

2.3 Need for Opioid Medicines

According to its origins, pain can be classified in multiple categories. Nociceptive pain is produced by tissue injury, neuropathic pain is induced by nerve injury and neuroplastic pain occurs due to musculoskeletal disease e.g. inflammatory pain. Acute pain usually occurs as a response to acute tissue injury. According to the International Association for the Study of Pain, chronic pain is defined as *"[…] pain that lasts or recurs for more than three months."* where *"Chronic primary pain represents chronic pain as a disease in itself"* while *"Chronic secondary pain is chronic pain where the pain is a symptom of an underlying condition" (p. 1)* [10]. Opioid analgesics are widely accepted and used for the treatment of severe acute pain and chronic pain. Especially for the treatment of cancer associated pain there is high medical and scientific evidence for the benefit of the use of opioids. About 30% to 50% of cancer patients will experience pain during the disease progress and there is a tendency that this pain increases with advancing cancer stages. Since the occurrence of cancer is associated with a higher age, an effective treatment of cancer associated pain is a problem especially in countries with an older population structure [11].

In the 1980s the WHO developed a pain treatment ladder (see 2.3.1) that recommends the use of opioids according to their strength in the treatment of moderate and severe cancer associated pain [12].

However, besides the use of opioids for treating cancer related pain they are used with increasing frequency also for the management of chronic non-cancer pain, in part controversially. Chronic non-cancer pain is a significant problem worldwide and its prevalence ranges from 10.1% to 55.2%

in the general population [13]. The most prominent prescription opioids used for management of acute or chronic pain are morphine, oxycodone, hydromorphone, fentanyl and codeine. Aside from cancer pain management opioids are used during anesthesia, or as treatment of heroin and other opioid dependencies with methadone and buprenorphine as the most commonly used opioids. For example morphine is used for chronic pain or post-operative pain management, codeine to treat cough and mild to moderate pain, methadone and buprenorphine are used for detoxification or opioid dependence therapy and fentanyl can be used for severe postoperative pain but also for patients with chronic pain, who developed a physical tolerance to other opioids [14]

2.3.1 WHO Analgesic Ladder

In 1986 the WHO developed a three-step ladder for cancer pain treatment. The goal was to avoid that patients suffer unnecessarily from pain, either due to acute or end of life pain, and to enable conditions that are as comfortable as possible during the progression of cancer. This three-step approach suggests using analgesics gradually starting with a slow introduction and titration of analgesics in accordance with the patient's reported pain intensity (Figure 1) [15, 16]. However, this scheme should be used as a general guide to pain management and careful assessment and individualized therapeutic planning is mandatory [17].

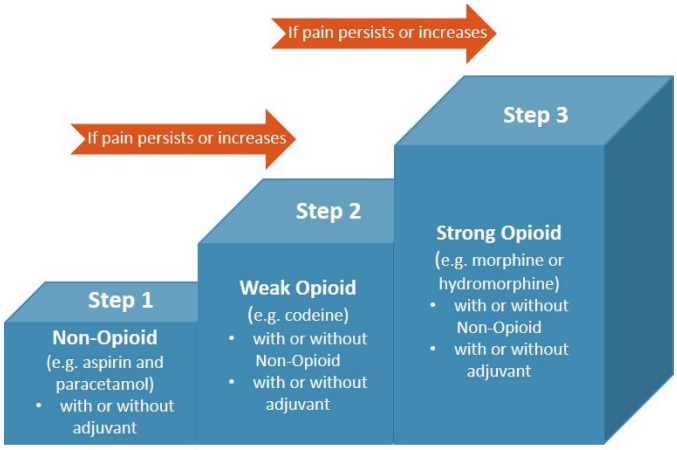


Figure 1: The WHO Cancer Pain Ladder for Adults
Adapted from [16]. If pain occurs, there should be rapid oral administration of drugs in the following order: non-opioids (e.g. paracetamol), followed, as necessary, by mild opioids (e.g. codeine). Then strong opioids (e.g. morphine), until the patient is free of pain. To calm fears and anxiety, additional drugs (adjuvants) should be used.

Level 1 drugs contain active substances from the group of non-opioid analgesics and non-steroidal anti-inflammatory drugs. These include derivatives of salicylic acid (e.g. aspirin), phenylacetic acids derivates (e.g. diclofenac and indomethacin), propionic acid derivates (e.g. ibuprofen, ketoprofen and naproxen), *para*-aminophenol derivatives (e.g. paracetamol) and others.

If non-opioid painkillers have an inadequate analgesic effect, they can be supplemented or replaced by Level 2 active ingredients. These comprise the low-potency opioid analgesics, possibly in combination with non-opioid analgesics and / or adjuvants. The low-potency opioid analgesics include tramadol, tilidin (plus naloxone) and dihydrocodeine.

If a satisfactory analgesia cannot be achieved even with active ingredients of levels 1 and 2, the drugs listed in level 3 are suggested for pain management. These comprise the highly potent opioid analgesics, again in possible combination with non-opioid analgesics and / or adjuvants. A combination of low and high potency opioid analgesics is not recommended due to the antagonistic mechanisms of action. In addition, the so-called ceiling effect could occur as saturation and despite increasing the dosage, an increase in potency could no longer be expected. Therapy-relevant, highly potent opioid analgesics are buprenorphine, fentanyl, hydromorphone, morphine and oxycodone [15, 16].

2.3.2 WHO Essential Medicines List

Since 1977 the World Health Organization (WHO) publishes semiannually the Essential Medicines List (EML), which serves as a model list of essential medicines that help to meet the primary health needs of patients in different countries. It also serves as a guide for the development of national and institutional essential medicine lists. With the EML the WHO presents *"[…] a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority condition."(explanatory notes)* [18]. To identify medicines that should be added or removed from the list, based on proposals from individuals, organizations or pharmaceutical companies, the WHO Expert Committee on Selection and Use of Essential Medicines reviews the latest scientific evidence for safety, efficacy and cost effectiveness of medicines and thus evaluates their real-world implications. The WHO Expert Advisory Panels selects the committee members for this review, considering equitable geographical representation, professional competencies and gender balance [19].

In the EML, six Opioid analgesics together with their respective dosage are listed as essential medicines for pain and palliative care (see Appendix 1): codeine, fentanyl, morphine with hydromorphone and oxycodone as its alternatives as well as methadone for the management of cancer pain [18]. The inclusion of opioids in this list underlines the essentiality of opioids in the treatment of moderate to severe pain. Thus, lack of access to those medicines can result in millions of people suffering from untreated severe pain due to infectious diseases, terminal cancer or chronic-non-cancer pain.

2.3.3 Adverse Events of Opioid Medicines

Opioid administration, like most pharmaceutical therapies, is associated with several side effects. Natural and synthetic opioids bind to μ opioid receptors and the respiratory centers in the brain. Despite, the areas of the stem, gut and chemo trigger zone also contain μ receptors and side effects often result from the activation of the receptors in these areas [20]. When used in accordance to prescription, **common side effects** are nausea, sedation, vomiting, constipation, drowsiness and confusion. When applying high doses, adverse consequences can be respiratory depression and circulatory failure [21]. 15 to 30% of cancer patients report nausea as a side effect of an opioid therapy but tolerance often develops. Sedation occurs in about 20-60% of patients, but tolerance also usually develops fast. A very common side effect is constipation which occurs in up to 70% of patients undergoing an opioid therapy, however tolerance only develops in rare

cases. In patients that do not develop tolerance, these side effects can lead to opioid discontinuation, under-dosing and inadequate analgesia. Due to the individual biological variations, the occurrence and intensity of side effects of the available opioids for treatment differ individually. Therefore, well-educated clinical staff is mandatory to initiate preventive treatment of potential side effects, to switch and rotate opioids or the route of administration to maximize the effectiveness of the opioid treatment while reducing the severity of side effects and adverse events [21, 22].

Further detrimental effects of opioid analgesics are tolerance, hyperalgesia as well as dependence and addiction. The latter probably constitute the currently most feared and most widely known complications associated with opioid use. The development of a **tolerance** to the analgesic effect, referring to a lower sensitivity to the prescribed opioid doses, most likely occurs because of a deceased receptor activation or because of a downregulation of the cellular expression of the targeted opioid receptor. The increasing lack of the response to the drug requires an increasing dose to maintain the analgesia [20].

Opioid-Induced hyperalgesia (OIH) is a phenomenon where patients become more sensitive to pain when receiving opioids for the treatment of pain. It is important to note, that the mechanism of OIH is not identical to developing a tolerance, where a lower sensitivity to opioids occurs. In contrast, in OIH the increase of the dose of the drug increases the pain. However, the distinction is often difficult in clinical practice. OIH, as a form of pain sensitization, occurs in the CNS and is induced by the drug. Conversely, reducing the opioid doses can reduce the pain and thus improve the treatment [20, 23].

Physical dependence is rarely serious. Ceasing opioid administration after a longer time may result in unpleasant physical symptoms. Such withdrawal symptoms can be avoided by slowly decreasing the opioid dose instead of an immediate stop [24].

Psychological dependence is a more complex problem and does usually not result from the treatment of the pain itself but rather from the treatment of the emotional response to the pain: suffering. These so called “chemical cope” patients are at risk to misuse and abuse the medication on the long run [24].

The development of an **addiction** is a disease in itself. An opioid addiction happens when patients are exposed to sufficiently high doses of an opioid for a sufficiently long period of time. Some patients seem to be more susceptible to opioid addiction than others, but since it is currently unknown what exactly determines the individually susceptibility, *per se* every patient under long term opioid treatment can be at risk and should be carefully monitored. However, in general over 90% chronic pain patients that are treated with opioids do not develop an addiction. Addiction to opioids as a chronic disease should not be mistaken with opioid abuse, where the drug is intentionally used to induce states of euphoria, or with opioid diversion, where the patient illicitly shares and sells their medication [24]. The concerns of developing physical or psychological dependence and addiction can also lead to an improper prescription and thus to inadequate pain management [21].

Opiophobia describes the fear of prescribing opiates to control pain, both in physicians as well as in patients. This fear can result from inadequate training of physicians regarding the dangers and risks when using opioids appropriately as well as from inadequate information of the patients and especially the fear of getting patients addicted or getting addicted as a patient. Cultural reasons can lead to opiophobia or the fear of legal actions of disciplinary sanctions since opioids are controlled substances that are generally known for their potential of being abused [25].

Pseudoaddiction is a concept introduced in the late 1980s and describes, that aberrant behavior of patients using opioids is caused by undertreatment with opioids for pain, while no addiction *per se* is present. This syndrome mimics the behavioral symptoms of addiction and can be relieved by improving the pain treatment. However, there is certain criticism targeting this concept since empiric verification and currently objective signs and specific treatment is missing to guide clinical decision-making [26] [27].

2.4 Consequences of Unmanaged Pain

Insufficiently treated or untreated severe and chronic pain can have substantial impact in patient's life and in the progression of their disease. Chronic pain influences the overall quality of life with a negative impact on daily activities, with negative effects on social life such as relationship disruption, employment loss and financial ruin, with sleep disturbances and a negative impact on mental health, resulting in depression, impaired cognitive function and suicide, making chronic pain the second common cause for suicide [28, 29]. If chronic pain is not controlled, this can have an influence on the peripheral and central nervous system (CNS) leading to neuroinflammation, tissue destruction, and loss of CNS tissue mass and receptors. These alterations result in a loss of an opioid and other analgesic response and consequently, when treated with opioids, patients require higher doses to reach an analgesic response [29]. Furthermore, substance use disorder from self-medication was observed in patients due to insufficient pain control, who then misused prescribed drugs or used illicit substances to alleviate pain [30]. Thus, chronic pain is increasingly being considered as a disease itself.

Consequences of unmanaged chronic pain do not only affect the patients physical, social and psychological well-being itself, but can result in an individual financial burden as well and generally can also have economic impact due to reduced and lost productivity and increased health care costs, as seen for arthritis, back, headache, and other musculoskeletal pain, as well as for cancer pain [31, 32].

3. International Control and Availability of Opioid Medicines for Pain Management

3.1 International Control by Drug Control Treaties

Narcotic drugs are classified and placed under international control by the **1961 United Nations (UN) Single Convention on Narcotic Drugs**, as amended in 1972 (hereafter referred to as UN Single Convention) [33, 34] as the principal international treaty regulating the control of opioids and supplemented by the Convention on Psychotropic Substances (1971) [35] and the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988) [36]. These conventions provide measures for drug control to prevent abuse and illicit transfer of narcotic drugs while ensuring the availability of controlled substances for medical and scientific use. All 186 countries that signed the UN Single Convention are expected to observe the provisions given by the UN Single Convention and to ensure the availability of these drugs in their countries. The UN Single Convention sets out minimum regulatory requirements for prescribing controlled drugs at national levels, while the respective countries are allowed to enforce stricter controls if necessary.

The Commission on Narcotic Drugs (CND) represents the states parties and is empowered, upon recommendation of the WHO, to add or remove substances scheduled as narcotic drug or psychotropic substance from the list of controlled substances. The role of the International Narcotics Control Board (INCB) is to monitor the compliance of the governments with the treaties regarding drug production, international trade, and dispensation and INCB prepares an annual report based on information provided by the governments to the board.

In the UN Single Convention drugs are classified in four Schedules where each Schedule provides a different level of control. The majority of opioids is listed in Schedule I which contains those substances that are considered as being essential for medical and scientific purposes but that have addictive properties and are harmful (see Appendix 2). Conversely, these substances, e.g. morphine, fentanyl or oxycodone, present the most serious risk of abuse and are therefore subject to the highest degree of control, and all measures of control under the UN Single Convention apply to them. Schedule II lists substances that are considered to be used for medical purposes and have a lower abuse liability (see Appendix 2). They include e.g. codeine and its derivates and are less strict controlled, compared to Schedule I substances. Schedule III contains preparations of drugs from Schedules I or II and those preparations are exempt from certain requirements. Heroine or several fentanyl analogues are listed in Schedule IV, which are particularly harmful and liable to abuse but without substantial therapeutic advances. For those substances *"the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research" (p. 16)* is completely banned (art. 2.5.b) [33, 34]. A current list of narcotic drugs under international control in accordance to the UN Single Convention can be found in the Yellow List of the INCB [37].

Psychotropic substances are classified in four schedules as well, where Schedule I implies high public health risk and low therapeutic utility and the control measures for those substances are

the strictest e.g. for LSD, whereas Schedule IV substances are considered to have lower public health risk and higher therapeutic utility e.g. certain tranquillizers [35].

The UN Single Convention limits *"[..] the production, manufacture, export, import, distribution of, trade in, use and possession of drugs." (p. 19))* exclusively to medical and scientific purposes (art. 4c). Furthermore, it contains obligations for e.g. record-keeping, requirement of prescriptions for supply and dispensation, licensure of manufacturers and distributors, as well as the control of drugs under legal authority, and it requires the governments to provide statistical reports to the INCB. The UN Single convention requires that every participant in the opioid supply chain, such as manufacturer and wholesalers, hospitals and pharmacies and health care personnel for dispersion to patients, needs to be authorized or licensed [33, 34].

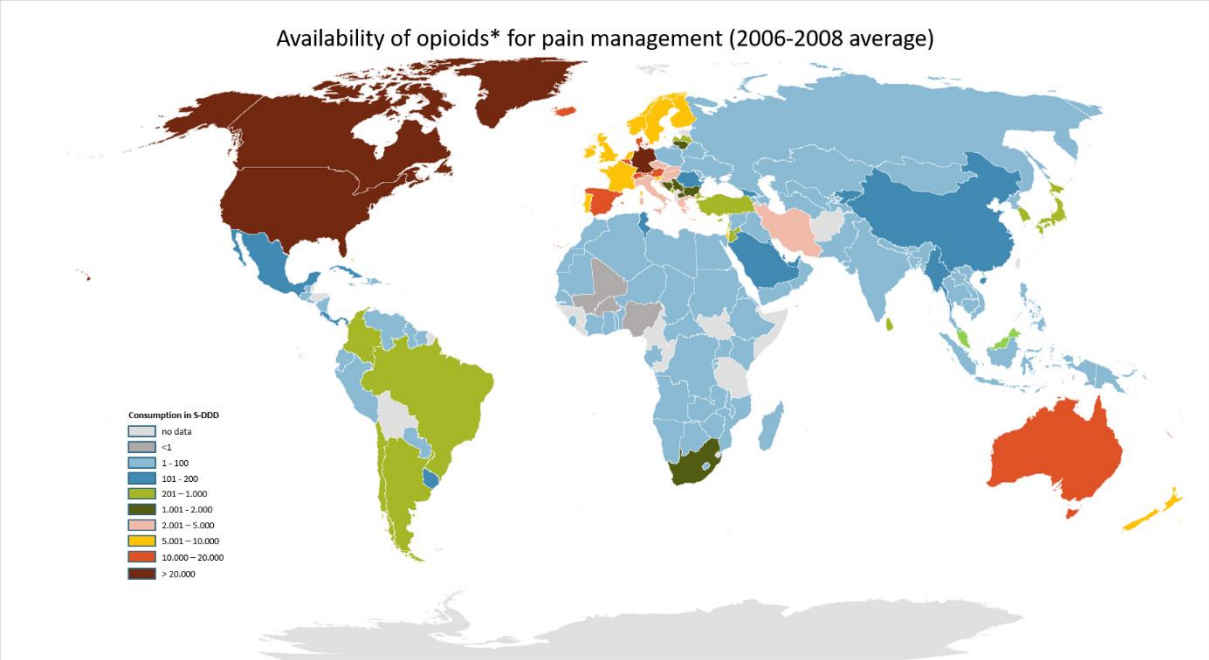
The UN Single Convention strongly supports the use of opioids for pain relief since *''[…] the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering, and adequate provision must be made to ensure the availability of narcotic drugs for such purposes.' (p. 13 preamble)* [33]. International drug regulatory bodies such as the INCB and UN bodies such as the United Nations Economic and Social Council, and the United Nations Office on Drugs and Crime (UNODC) presented several statements and initiatives to improve and ensure the availability of opioids for pain relief worldwide rather than only restricting opioid misuse and abuse [4, 38, 39]. As also the WHO recognizes in the EML, the International Association for the Study of Pain (IASP) clearly underlines the indispensability of opioids for the treatment of severe short-lived pain and that for opioids, when used for a short-term treatment of pain, the risk of addiction is rare [40]. The "Declaration of Montreal", that was endorsed by the IASP and the International Pain Summit Steering Committee, states, that the access to pain management is a fundamental human right. Thus, there is an international consensus that narcotic drugs need to be made available to everyone in need. However, current estimations suggest that 5 billion people worldwide do not have or have only limited access to controlled medicines in their country and thus will be left untreated or not sufficiently treated if they suffer from moderate or severe pain [41].

3.2 Availability of Opioids for Treatment

The general availability of drugs can be expressed by assessing the defined daily dose (DDD), which stands for the average maintenance dose (long term therapeutic dose) per day for drugs having an Anatomical Therapeutic Chemical (ATC) classification code. One DDD is assigned per ATC code and per route of administration. Although it will only give a rough estimate of consumption, the DDD is used as a fixed unit especially for comparisons between population groups [42]. Fentanyl (ATC code N02AB03) for example has a DDD of 0.6 per mg for nasal and sublingual/buccal/oromucosal route of administration, and an DDD of 1.2 per mg for transdermal administration [43]**.** The DDD controlled for population size differences (e.g. per million inhabitants) provides a measure for the therapeutic intensity in a certain population. The term S-DDD (defined daily doses for statistical purposes) is used by INCB as a technical unit of measurement to compare e.g. narcotic drugs with different levels of potency for statistical analysis

but it does not reflect the recommended prescription dose. According to INCD a consumption level between 100 S-DDD and 200 S-DDD per million inhabitants per day is considered to be inadequate and below 100 S-DDD is very inadequate [44].

Globally the availability of opioid analgesics increased from 602 S-DDD in the period 1994-1996 on average to 2,375 S-DDD on average in the period 2014-2016 [38]. Figure 2 provides a comparison of the global availability of opioids in the period of 2006-2008 and 2016-2018. While this figure demonstrates the general further increase in opioid availability in this period, it also underlines an imbalance in the availability of opioids throughout the world. Mainly high-income countries, for example Europe or North America, report morphine to be generally available in primary care facilities while in middle- and low-income countries, for example South America or Africa, morphine is not generally available. Between 2016 and 2018, the availability of opioid analgesics is highest in Canada, USA, Europe and Australia, followed by further highly developed countries such as New Zealand, Norway or the United Kingdom (UK). In contrast in low income countries that are predominantly located in Africa, Asia, Eastern Europe or South America, the availability of opioids for consumption remains inadequate or, in some cases like Namibia or South Africa, at least decreased [45, 46].



--- figure is continued on next page --

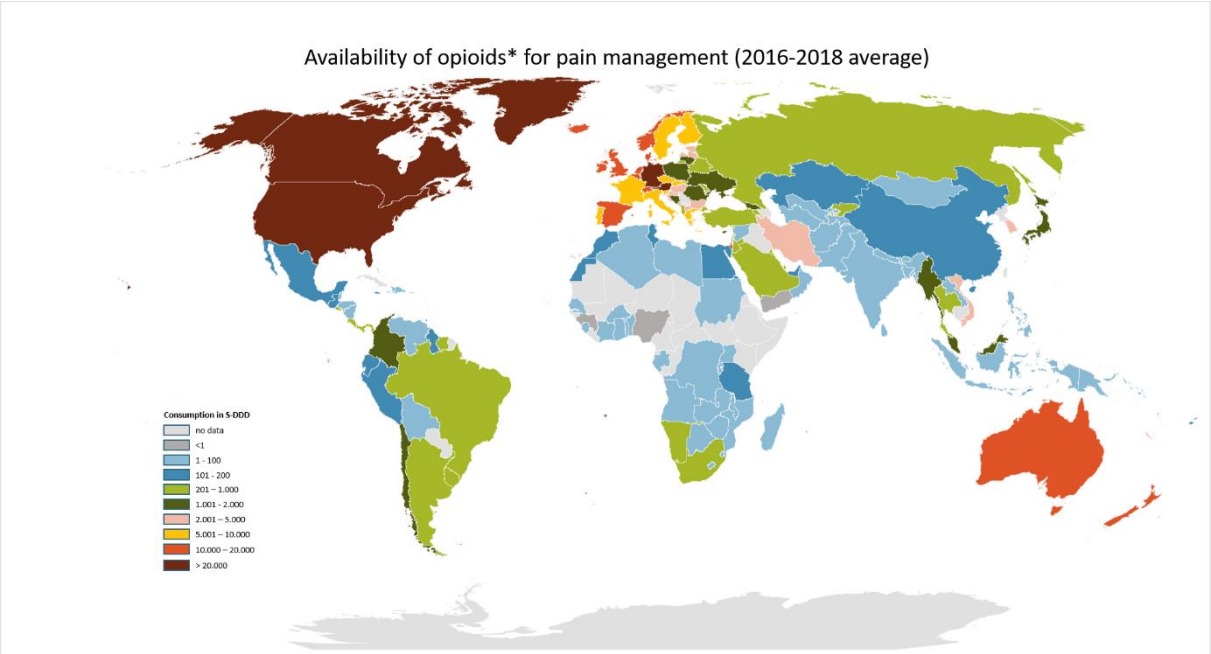


Figure 2: Availability of Opioids for Pain Management
Upper panel 2006-2008, lower panel 2016-2018 average: Levels of consumption in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day. Data for 2006-2008 from [45] Table XIV.1 and data for 2016-2018 from [46] Table XIV.1. The color code for the consumption is presented in defined daily doses for statistical purposes (S-DDD) per million inhabitants per day: Dark grey: < 1 S-DDD, bright blue: 1-100 S-DDD, dark blue: 101-200 S-DDD, bright green: 201-1,000 S-DDD, dark green: 1,001-2,000 S-DDD, rose: 2,001-5,000 S-DDD, yellow: 5,001-10,000 S-DDD, bright red: 10,001-20,000 S-DDD, dark red: > 20,000 S-DDD. Light grey indicates no data availability.
* The term "opioids" includes mainly the following: codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, pethidine, tilidine.

As already mentioned in 2.3 the main opioid analgesics used for pain management are morphine, oxycodone, hydromorphone, fentanyl and codeine. Among those, different trends in consumption level can be overserved as well. In general, the fentanyl consumption increased exponentially in the last 20 years. Consumption of oxycodone, one of the drugs associated with overdose deaths related to prescription drug abuse, has also markedly increased making it the second most consumed opioid. In contrast, morphine consumption increased only slightly since the late 1990s and remains rather stable. In 2018 only 13% of the morphine used for pain management was used by 79% of the world population while most of the morphine consumption was concentrated in Europe (39,5%), US (39,3%) and Canada (5,1%) [38].

3.3 The Prevalence of Opioid-Related Harms Increases Worldwide

In 2018 the global opioid market size was valued with 18.5 billion US dollar ($) with a global market value of $19,007.2 million in 2019. Forecasts prognose a steady growth with an expected gain of market size up to $22,387.2 million by 2026 due to the trend of increased usage of opioid drugs as analgesics and for pain management, especially concerning the oxycodone and fentanyl segments. Emerging markets are seen in the Asia-Pasic region, with a current growth rate of 3% in India, China, Australia and South Korea and an expected growth rate up to 5% in the coming years. However, the opioid crisis and increased mortality due to over consumption of opioids have been shown to negatively impact and slow down the growth rates [47].

In the past years, an increase of opioid-related harms up to opioid-related deaths were observed in several countries such as the USA and Canada, where it became an important public health concern. As shown in chapter 3.2, these countries displayed an increase in the availability and prescription of opioids, which in several media reports was communicated as being directly correlated to the opioid-related harms. However, other countries show an increase in opioid availability as well without recognizing signs of increasing opioid-related harms (see chapter 4).

The global illicit opioid market expanded in the past years with 19.4 million users in 2016 globally, predominantly comprising the heroin but also the morphine market. 58% of illicit opioid users are from Asia, 17% from Europe and 15% are from America. The highest prevalence of illicit opioid users in America is present in North America with 86%. In Europe the prevalence of illicit opioid use increased in the recent years, especially in Poland. Drug related deaths, mostly heroin- and morphine-related deaths, increased between 2012-2016 by 58% in England and Wales and by 70% in Germany. The market for non-medical use of pharmaceutical opioids is expanding as well. Data about seized illicit pharmaceutical opioids from 2016 indicates a rise of the illicit use of hydrocodone, oxycodone, codeine and tramadol in North America, buprenorphine and fentanyl in Europe and tramadol in Africa [48].

However, the differentiation between opioid-related harms caused by prescription opioid analgesic or illicit opioids is difficult. Opioid-involved deaths include prescription opioid analgesics, illicit opioids, or both. The availability of illicitly manufactured opioids which were originally prescription medication, such as fentanyl, makes the differentiation even more complicated. For example, the US Centers for Disease Control and Prevention (CDC) estimates the prescription opioid deaths by including the synthetic opioid-involved deaths from illicit manufactured opioids such as fentanyl, which could significantly influence the estimations [49].

4. Regulatory Barriers to Opioid Accessibility

The previous chapters provide an overview on the need and availability of opioids worldwide and highlighted, that the accessibility to opioids for pain management is below the required amount in some countries while other countries observe increasing amounts much higher than the global average. Naturally, older adults are more likely to have pain problems in general. In addition, also the occurrence of cancer is associated with a higher age [11]. Thus, pain management in older adults is of additional relevance in countries with an older population structure (see Appendix 3 for population pyramids of the countries studied in this thesis).

Several factors influence the availability of medicinal opioids in countries and the reasons for the unequal distribution of opioids for pain management globally are divers. The IASP identified some explanations why pain management is still inadequate in many regions of the world:

- Inadequate access to treatment for acute pain.
- Deficits in knowledge of health care professionals regarding the mechanisms and management of pain.

- Stigmatization of chronic pain.
- Lacking or inadequate national policies regarding the management of pain as a health problem.
- Severe restrictions on the availability of opioids and other essential medications. [41]

Besides cultural aspects such as the stigmatization of patients using opioids and the fear of prescribing opiates to control pain (Opiophobia, see 2.3.3), two major topics are the legal limits due to restrictive laws and policies and the acceptance and knowledge of health care professionals for the use of opioids for pain management.

The following chapters (4.1 - 4.5) will focus on 9 countries, that were selected to illustrate the factors and barriers influencing opioid accessibility in different global and cultural regions. These include countries from Europe (Germany, UK, Poland), North America (Canada), Oceania (Australia), Asia (India, Japan) and Africa (South Africa and Rwanda).

The selected countries are very divers in terms of their average consumption of narcotics (see 3.2). For each of the countries analyzed in this work the average consumption of narcotic drugs overall and for certain opioids mainly used for pain management such as codeine, fentanyl, morphine and oxycodone between 2008-2008 and 2016-2018 is compared in Table 2 including the ranking of each of the countries worldwide. Table 3 provides an overview on special aspects for the control of opioids taken from the UN Single Convention and from the laws and regulations on narcotic drugs for each of the countries assessed in this work.

For each country, firstly, the legal basis for the control of narcotic drugs will be highlighted. Secondly, the availability of national clinical guidelines for pain management will be investigated to evaluate the acceptance of opioids for the pharmacotherapy of pain in general among health care professionals. Lastly, the prescription behavior in the respective countries and, if available, regulatory actions against an opioid epidemic or against an undersupply with opioids, will be highlighted.

Table 2: Average Consumption of Narcotic Drugs in the Selected Countries, 2006-2008 and 2016-2018

Table 2: Average Consumption of Narcotic Drugs in the Selected Countries, 2006-2008 and 2016-2018

Numbers indicate defined daily doses for statistical purposes (S-DDD) per million inhabitants per day. Data for 2006-2008 from [45] Table XIV.1 and data for 2016-2018 from [46] 2016-2018 Table XIV.1. The symbol '<<' indicates an amount less than 1 defined daily dose for statistical purposes per million inhabitants per day, the symbol '-' indicates no availability, '↔' indicates no change in S-DDD from the period 2006-2008 to the period 2016-2018, '↓' indicates a decrease of S-DDD between the respective periods, '↑' indicates an increase of S-DDD between the respective periods.
The column 'Total' includes further opioids aside from codeine, fentanyl, morphine and oxycodone.

	Codeine			Fentanyl			Morphine			Oxycodone			Total			World Ranking	
	2006-08		2016-18	2006-08		2016-18	2006-08		2016-18	2006-08		2016-18	2006-08		2016-18	2006-08	2016-18
Europe																	
Germany	2	↔	2	14,050	↑	15,584	556	↑	582	707	↑	1,511	22,210	↑	27,419	2	2
United Kingdom	11	↓	-	1,845	↑	9,055	752	↑	1,119	314	↑	803	5,364	↑	15,859	22	9
Poland	211	↓	-	1697	↓	1,270	158	↓	129	1	↑	250	2,265	↓	1,940	37	50
Canada	373	↑	533	7,482	↓	6,938	1,930	↓	1,475	4,465	↓	3,443	20,990	↑	22,402	3	3
Australia	97	↑	113	2,907	↑	5,433	1,433	↓	668	2,058	↑	4,172	10,360	↑	15,454	10	11
Asia																	
Japan	27	↓	17	673	↑	909	83	↓	42	82	↑	168	885	↑	1,184	52	62
India	-	↔	-	3	↑	15	7	↓	6	<<	↔	<<	16	↑	37	143	145
Africa																	
South Africa	664	↓	-	75	↓	139	144	↑	233	-	↑	43	1,080	↓	511	47	78
Rwanda	-	↔	<<	<<	↑	3	1	↑	13	-	↔	-	1	↑	19	175	158

4.1 Europe

In Europe, a general increase of opioid consumption can be observed, especially of tramadol, fentanyl and oxycodone. For example, Spain recorded a 14-fold increase in opioid use between 1992 and 2006, mostly for fentanyl and tramadol prescriptions, Scotland a 5-fold increase between 1995 and 2010 with an increase mainly for tramadol, and Italy an increase of almost 3-fold for fentanyl and tramadol prescriptions. Germany recorded a 4-fold increase for fentanyl, oxycodone, hydromorphone and buprenorphine prescriptions and over 100% increase in tramadol prescriptions. Also Scandinavian countries, the UK and France recorded increases in opioid prescription [50]. However, it must be considered that these numbers only give an overview on trends in opioid consumption patterns in Europe which likely also reflect regulatory and clinical strategies for better pain management or an increase in opioid availability in general, and do not allow any direct conclusion about a risk of public health consequences such as over-prescription, misuse or an upcoming opioid epidemic as it was seen in the USA.

Although the consumption levels in Europe increased overall, there is a discrepancy among European countries. The following chapters will present a more detailed overview on three European countries: Germany as an example for a European country with the highest reported consumption levels for opioid analgesics (rank 1 in Europe and rank 2 globally between 2016 and 2018) but without indication for an opioid epidemic, the UK as a medium consumption country (rank 7 in Europe and rank 9 globally between 2016 and 2018) but with indications for an opioid epidemic, and Poland as an example for a country among the lowest reported consumption levels of opioid analgesics (rank 33 in Europe and rank 50 globally between 2016 and 2018) in Europe (Table 2) [44].

4.1.1 Germany

With a current population of over 83 million people, Germany is the second most populated country in Europe, following the European part of Russia. In the world it ranks number 19 by population, with 1.07% of the world population. 76.3% of the population lives in urban areas and the median age in Germany is 45.7 years [51]. The population pyramid of Germany shows the classical distribution of an aging population with few young to middle aged people and a large portion of people above 50 years (see Appendix 3). Germany is composed of 16 federal states referred to as “Bundesländer” having own state constitutions.

Estimates suggest that in 2020 around 510,000 new cancer cases will be diagnosed in Germany. Between 2015 and 2016 the 5- year survival rate was at over 90% for prostate and testis cancer as well as melanoma while the rate was much lower and partly below 20% for lung or pancreatic cancer. Several cancer types are in general diagnosed in an early or medium stage (stage I and II) in most patients. More than 60% of prostate cancer cases and approximately 80% of breast cancer cases are diagnosed early, with increased effectiveness of curative therapy approaches. In contrast many other cancer types are mostly diagnosed in late and very late stages (III and IV) in the

majority of cases, for example pancreatic cancer. In those late-stage cancer cases the limited curative therapy options crucially necessitate pharmacotherapy against cancer related pain [52].

In addition, 8 to 16 million people in Germany, corresponding to 10-20% of the population, are estimated to suffer under chronic pain, mostly from diseases of the musculoskeletal system or backpain. 19% of the chronic pain patients believe that their pain is not adequately treated [53].

4.1.1.1 Tight and Comprehensive Control of Opioid Prescription - BtMG and BtMVV

The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) is the medical regulatory body in Germany operating under the Federal Ministry of Health (Bundesministerium für Gesundheit, BMG). The BfArM is responsible for approval of medicinal products, the detection, evaluation and prevention of drug risks, improvement of the safety of medicines and assessment of medical devices. The Federal Opium Agency (Bundesopiumstelle) is a department of the BfArM and is responsible for monitoring the legal trade of narcotics and psychotropics based on the German Narcotics Act of 1981 and subsequent orders, including the preparation and distribution of special prescription forms for narcotic drugs and the trade of precursors [54]. Certain activities, such as import and export, are in the responsibility of competent health authorities of the respective federal states.

Opioid prescription is tightly regulated by the German Narcotic Drugs Act (Betäubungsmittelgesetz, **BtMG**) and by the Narcotic Drugs Prescription Ordinance (Betäubungsmittelverschreibungsverordnung, **BtMVV**) [55, 56]. The **BtMG** implements the treaty obligations set under the Single Convention on Narcotic Drugs 1961. It is structured in 8 parts: part 1 terminology (§1-2), part 2 permission and licensing procedure (§3-10a), part 3 obligations in the field of narcotics (§11-18), part 4 monitoring (§19-25), part 5 government regulations (§26-28), part 6 offenses and misdemeanors (§29-34), part 7 narcotics-dependent offenders (§35-38) and part 8 transitional and final regulations (§39-41) followed by annexes I-III, which list all preparations and substances that are considered as narcotics [55].

The assignment of a substance in the three annex sections is based on the scientific justification of its mode of action, potential to cause dependence, direct or indirect danger to health, potential of abuse and possibility of producing narcotics from it [57]. Substances listed in Annex I are considered as non-tradable and are available only by a special permission for scientific or other purposes of public interest by the Federal Opium Agency (§ 3 (2)). Substances from Annex II are often needed to produce other narcotics and can be traded upon special permission, but they are not prescribable (§ 1 (1)) and §3). Annex III substances are tradeable and prescribable as preparations only by using a special prescription form and if the purpose of use cannot be met by other means (§13) [55].

In general cultivation, manufacture, trade, import, export and marketing of narcotics require permission by the Federal Opium Agency of the BfArM (§3 Abs. 1). Exceptions from this permission are listed in §4. Schedule III drugs can be disposed by a pharmacy on the basis of a medical, dental or veterinary prescription (§12 (3)) [55].

The **BtMVV** provides detailed rules for prescription and supply, dispensing and proving the whereabouts of Annex III drugs [56]. It furthermore regulates the principles for prescription procedures on narcotic drugs (BtM)-prescriptions (Betäubungsmittelrezept) and BtM-certificates as well as documentation requirements. Prescription of Annex III drugs is allowed by physicians, dentists and veterinarians (Annex III and §1, §3, §7, §13). The maximum quantities of opioids that are allowed to be prescribed within a timeframe of 30 days are listed as well as the maximum amount of different opioids that are permitted to be prescribed at once (§2-4), e.g. a maximum of 500 mg of fentanyl in 30 days may be prescribed by a physician. Opioids require special narcotic prescriptions known as BtM-prescriptions for personal use. The numbered forms are handed out by the Federal Opium Agency of the BfArM to the respective physician, dentist or veterinarian, where one form remains at the prescribing doctor, one form remains at the pharmacy and the third form is required for the insurance company (§ 8). Dispensing of Annex III opioids requires to record details about the patients, including name and address, the date of dispense, designation and amount of the dispensed drug, instructions for use and details about the physician, dentist or veterinarian such as name, address and job title (§9). The prescription form is valid for 7 days from the date of issuance (§12(1)1.). BtM-certificates (BtM-Anforderungsscheine) are handed out by the Federal Opium Agency for requirements of hospitals, for ambulance services, emergency supplies in hospices and for ambulant palliative care (§10-11) [56].

4.1.1.2 Elaborate Clinical Guidelines for Opioid Prescription in Cancer and Non-Cancer Pain Management

Opioid therapy in Germany mainly follows the WHO analgesic ladder and the WHO guideline for cancer pain treatment [17]. Several societies and associations develop, implement and evaluate in close collaboration clinical practice guidelines for physicians but also to support patients with guidance. The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) includes over one hundred scientific societies from all fields of medicine and represents Germany in the Council for International Organizations of Medical Sciences (CIOMS) [58]. Guidelines are classified in S1 based only on recommendations by experts, S2 based on structured consensus process (S2k) or a systematic literature review (S2e) and S3 including both, consensus and evidence based [59].

The **S3 guideline of palliative care for patients with incurable cancer** represents the basic principles of palliative care with a main objective of improving symptom control and care for patients and their relatives. The use of opioids is recommended for symptomatic therapy and every recommendation is underlined with the current scientific and practical evidence. For respiratory distress as a symptom of cancer, oral or parenteral opioids are endorsed with a recommended dosage, e.g. for morphine with 2.5-5 mg every 4 hours for patients which have not been treated with opioids so far. Furthermore, the guideline lists recommendations whether to use morphine, hydromorphone, oxycodone, fentanyl and buprenorphine as opioids for patients under dialysis. Patients with mild to moderate pain should, in addition to non-opioid analgesics, be administered with recommended doses of oral stage II or low dose stage III opioids. For patients with moderate to strong tumor pain, stage III opioids are recommended with morphine,

oxycodone and hydromorphone as first choice opioid. However, all recommendations require a qualified assessment from the physicians to decide the individual modes of treatment. Examples include whether to use first choice opioids or other stage II opioids, if opioid titration is necessary, or if transdermal fentanyl is a valid treatment option [60].

The **S3 guideline on long-term opioid therapy for chronic non-cancer pain (CNCP)** was updated in 2020, also in part due to the current opioid epidemic in USA. This guideline provides guidance on benefits and risks of opioid-containing analgesics, indications and contraindications and gives recommendations on how the treatment should be conducted. These are based on criteria of evidence-based medicine, on scientific evidence and on experience in clinical practice. The guideline differentiates the use of opioids in short term (4-12 weeks), intermediate (13- weeks up to 12 weeks) and long-term use (≥ 3 months). The measures and decision-making processes for the indication, implementation and possible termination of a therapy with opioid-containing analgesics are summarized in an algorithm and special groups of patients are considered, such as elderly people, infants or pregnant woman. Treating patients solely with opioids is not recommended. Here, non-drug treatments should be considered first, and anamnesis regarding a general addiction, pain and the general physical and psychological status of the patient should be compiled. The guideline furthermore supports practitioners with several tools ("Praxiswerkzeuge") for further information or for direct use in anamnesis and during therapy [61].

Besides the mentioned guidelines, several further indication specialized guidelines from other associations exist. For example, the German Cancer Society has published guidelines that detail the recommendations of opioid therapy in different cancer types.

4.1.1.3 Frequent Prescription of Opioids for Pain Management but no Signs of an Opioid Epidemic in Germany

In Germany every opioid except oxymorphine can be prescribed, however only by physicians (4.1.1.1). Germany has the highest number of opioids that are authorized for pain treatment in Europe, and all of them are fully or partly reimbursed by health insurance companies depending on dosage and pack size of the medicinal product [62].

Currently only a few studies that analyze the prevalence of opioid treatment in Germany are available. However, due to the different study design, they are difficult to compare.

One study analyzed the opioid prescription in Germany between 2000 and 2010 with data from one statutory health insurance in one German state only. In this regional study the number of persons receiving at least one opioid prescription increased from 3.31% in 2000 to 4.53% in 2010. Taking the population structure into account this results in an increase of 22%, of which 15% can be explained by the aging population [63]. A systematic review from 2019 analyzed 12 published studies, including the previously described one, regarding the prevalence of opioid prescription in Germany. This review found that overall, similar to other developed countries, the number of opioid prescriptions increased from 1985 to 2006 for both, cancer and non-cancer pain treatment. Considering the diversity of the study settings, a general outcome was that the majority of opioid

prescriptions in Germany was used for con-cancer pain, with fentanyl being the most prescribed strong opioid. However, neither any sign of insufficient treatment of pain was recognized nor any sign of a current or expected opioid epidemic resulting from prescription opioids [64].

The authors of the S3 guideline on long-term opioid therapy for chronic non-cancer pain share the opinion that there is no evidence of an opioid epidemic in Germany [61].

4.1.2 United Kingdom

The current population of the UK is above 67 million people, ranking worldwide and third in Europe by population. 83.2% of the population lives in urban areas and the median age is 40.5 years [51]. The population of the UK also shows a distribution with increased numbers of people aged above 50 years (see Appendix 3). The UK consists of four countries, England, Wales, Scotland and Northern Ireland, with all but England having their own devolved governments.

In the UK every year about 367,000 new cancer cases are diagnosed, with highest incidence rates for breast, prostate, lung and bowel cancer, that together account for more than 53% of all cancer cases. The overall cancer incidence rate increased since the early 1990s up to 2017 by more than 12% and date for England and Northern Ireland indicate that almost half of all cancers are diagnosed at a late stage. Over 28% of all deaths in the UK result from cancer, around 165,000 cancer deaths every year. However, over the last decades, overall cancer mortally rates decreased. The 5-year relative survival rate for all cancers combined was between 46% and 54%. [65]

It is estimated that about 43% of adult people are affected by chronic pain in the UK with about 14% experiencing moderate to severe chronic pain. However, studies on the prevalence of pain in the UK population are limited [66].

4.1.2.1 Legislative Control of Opioid Prescription by law and regulation - MDA and MDR

In the UK the Medicines and Healthcare products Regulatory Agency (MHRA) under the Department of Health is responsible for e.g. assessment and authorization of medicinal products, regulating clinical trials and more. The Home Office, which is a ministerial department of the Government of the UK, is responsible for regulating controlled drugs, and, e.g. issues domestic licenses for manufacture, production and supply or controlled drugs.

The primary law for controlled drugs in the UK is the **Misuse of Drugs Act 1971** (**MDA**), as amended, which represents the implementation of the treaty commitments under the UN Single Convention [67]. In addition, the **Misuse of Drugs Regulations 2001** (**MDR**), as amended, is focused on the therapeutic use of drugs, on their potential for abuse and diversion as well as on their need for control [68].

The **MDA** is structured into six Schedules that follow the introduction: Schedule 1 constitution etc. of advisory council on the misuse of drugs (section (sc) 1), 2 controlled drugs (sc 2-15), 3 tribunals, advisory bodies and professional panels (sc 16-24), 4 prosecution and punishment of offences (sc 25-38), 5 savings and transitional provisions and 6 repeals (sc 39). In the MDA, the controlled

substances are classified in classes A, B and C under Schedule 2, based on their level of potential harm. The MDA furthermore recognizes specific governmental differences between the UK countries, such as different appropriate authorizes for certain purposes in Scotland, England, Wales or Northern Ireland [67].

Class A drugs are considered to represent the most dangerous drugs and include most of the opioids, e.g. morphine, oxycodone and fentanyl, while codeine is classified as class B drug. The MDA allows *"[…] doctor, dentist, veterinary practitioner or veterinary surgeon, […], to prescribe, administer, manufacture, compound or supply a controlled drug, […]* and *"[…] a pharmacist or a person lawfully conducting a retail pharmacy business, […], to manufacture, compound or supply a controlled drug […]" (p. 9)* (sc 7, (3) (a)) [67].

The **MDR** provides certain exemptions from the MDA concerning prescription, records and furnishing of information as well as prohibitions to production, importation, exportation, possession and supply of controlled substances. It denotes five drug schedules for regulatory purposes. Schedule 1 drugs are most strictly controlled and are not authorized for medical use, e.g. raw opium, since those drugs are considered to have little or no therapeutic value, being addictive and having a high potential for abuse [68].

Schedule 2 drugs, such as morphine, codeine, oxycodone or fentanyl, and schedule 3 drugs, such as buprenorphine, are drugs available for medical use and are considered to have a therapeutic value but are understood as highly addictive. Their use is strictly controlled. They need to be prescribed and without prescription, possession of these drugs is illegal. Prescriptions of the controlled drugs in Schedule 2 and 3 can be provided by a doctor, dentist or veterinary (regulation 7 (2)-(3) and originally needed to be written in ink and signed and dated by the prescriber. However, since 2005 all details on prescriptions for controlled drugs can be computer generated, except the signature. Details to be included are the name and the address of the patient, the dose as total uptake quantity, and the form as well as the strength of the preparation when appropriate (regulation 15). Since 2006 it is furthermore strongly recommended to limit the maximum quantity to 30 days. For prescription of a Schedule 2 or 3 drug, a special form must be used, which is different for England (FP10PCD), Wales (WP10PCD or WP10PCDSS) and Scotland (PPCD). Schedule 2 and 3 drugs cannot be prescribed on repeat dispensing prescriptions [68].

The predominant possibility to issue prescriptions for opioids, comprising 99% of all such descriptions, is via a National Health Service (NHS) prescription form, providing the six-digit prescriber identification number as well as the patients ten-digit National Health Service (NHS). NHS prescriptions are sent to the Prescription Pricing Authority (PPA) which has functions in pricing prescriptions, reimburse dispensers and collecting and analyzing information. Private prescriptions of Schedule 2 and 3 drugs are also possible, providing the same details as mentioned for NHS prescriptions. After dispensing, the private prescription forms need to be sent to the NHS prescription Services for processing and monitoring. A prescription is valid for 28 days from the date of issuance (regulation 16) [68-70]. When destroying or disposing Schedule 2 stock-controlled drugs, health professionals require to record the name, the strength, the form and the quantity of

the drug, the date of destruction and the signature of the authorized person witnessing the destruction (regulation 27) [68].

Although MDA and MDR are applicable to all countries in the UK, country specific additional regulations exist. Examples are the Controlled Drugs (Supervision of Management and Use) Regulations 2013, which are only applicable for England and Scotland and are mainly about the responsibility of an organization to appoint a Controlled Drugs Accountable Officer.

4.1.2.2 No Clinical Guidelines for Chronic or Cancer Pain Management from NICE

In the UK the National Institute for Clinical Excellence (NICE) is responsible for centrally generated guidelines. The evidence-based guideline on **Palliative care for adults: strong opioids for pain relief** addresses *"[…] first-line treatment with strong opioids for patients who have been assessed as requiring pain relief at the third level of the WHO pain ladder." (p. 1)*, considering buprenorphine, diamorphine, fentanyl, morphine and oxycodone. It states that treatment and care should always be patient-centered and thus adjusted according to patients needs and preferences. The guideline gives the recommendation to titrate the dose when starting with strong opioids, e.g. suggesting a starting dose of oral morphine of 20-30 mg and using transdermal patches if oral opioids are not suitable. Furthermore, guidance is given how to inform patients and how to manage side effects from strong opioids. All information is summarized in a care pathway to support practitioners in their decision. The guideline also provides tools to practitioners for education, research recommendations or guidance into practice [71].

It seems that no guideline specifically dedicated to cancer or chronic non-cancer pain exists. However, in 2018 the department of Health in England requested the NICE to develop such a guideline for chronic pain, which is currently under development. Despite, several pain specific guidelines also cover the treatment with opioid analgesics such as buprenorphine, fentanyl, morphine, oxycodone and tramadol. For example, **Neuropathic pain in adults: pharmacological management in non-specialist settings** states that, according to the health economic modeling carried out for this guideline, that assessed the costs and effects of all treatments, only morphine and tramadol met the required criteria of *"[…] at least 1 estimate of dichotomous pain relief (30% and/or 50% relief compared with baseline) and data on withdrawal due to adverse effects […]" (p. 49)*. Morphine and tramadol should not be used in non-specialist settings [72].

In addition to the centrally generated guidelines by NICE, additional support is given by specialized associations or faculties. Examples are the **Guidance on the management of pain in older people** [73] published by the British Geriatrics Society or several guidelines from The Faculty of Pain Medicine of The Royal College of Anaesthetists for various aspects of pain. In addition, they provide, in collaboration with NICE, NHS England and various other contributors, a resource called **Opioids aware** for patients and healthcare professional to support them with prescribing opioids for pain. This resource provides information to various aspects of opioids for pain therapy, including a best professional practice guidance, information about pain and medicines for pain, as well as the clinical use of opioids for acute pain management, for example in palliative care and for long term pain, and a structured approach to opioid prescribing [74].

4.1.2.3 High Prescription of Opioids for Pain Management and First Signs of an Opioid Epidemic in the UK

Between 1998 and 2017 the prescription of opioids in the UK rose consistently with an increase of 34% of opioids overall and 127% of oral morphine equivalent doses. Especially the prescription of high dose and long-acting opioids increased by 580%. Furthermore, it was recognized that from 2000 to 2014 the prescribing period duration for opioids increased from 64 days to 102 days [75]. This trend is visible for all countries in the UK. Between 2008 and 2013 the number of prescribed opioid analgesics increased by 1.5 million in England, with co-codamol prescriptions increasing by 5% in the years 2010-2014, morphine use increasing by 66%, buprenorphine by 53%, oxycodone by 44% and fentanyl by 22%. In Scotland, the fastest increases were seen for codeine with an increase of 64% in those four years and morphine, with over 50% increase in prescriptions. Wales recognized an increase in morphine prescription of 105%, followed by codeine with 63% and oxycodone with 23 % and also in Northern Island the overall use of opioids increased by 9.7% from 2010-2014 [76] (see also Table 2).

However, the number of opioid-related deaths did not sustainably increase in any of the UK jurisdictions between 2010 and 2015. Most deaths were caused by heroine, accounting for 51% of opioid deaths in England and Wales in 2013, followed by methadone (23%) and tramadol (15%) [77].

4.1.2.4 Regulatory Response on Opioid Misuse in the UK

To investigate the trend of over-prescription and misuse of opioid medicines in the UK, the MHRA set up an **Expert Working Group** (EWG) of the UK's Commission on Human Medicines (CHM) in 2019. The EWGs goal is to review all available evidence on the benefits and risks of opioid medicines, to examine whether further risk minimization measures for prescription opioids are required, to consider the current data on the consumption of opioid-containing medicines in the UK, and finally to establish recommendations for regulatory action to better support appropriate uses of prescription opioids. Depending on the outcome of this evaluation, changes will be implemented in the relevant fields and documents, such as affect the Summary of Product Characteristics and the Patient Information Leaflet, product labelling and packaging, and to any other risk minimization measures. However, to date no specific changes have been implemented [78].

To support the practitioner's understanding of the UK legislation for controlled drugs, the NICE issued a guideline on **Controlled drugs: safe use and management** in 2016. This guideline provides evidence-based recommendations on processes or interventions for the safe use and management of controlled drugs based on the MSA and MDR. It highlights that in addition to the legal framework, prescribers need to use their clinical and professional judgment when prescribing controlled drugs. It provides certain explanations to the MDR and gives further recommendations. For example, in addition to regulation 27 of the MDR regarding destruction and disposing of Schedule 2 stock-controlled drugs, the guideline recommends recording similar details also for Schedule 3 drugs, although this is no regulatory requirement. The same recording is also recommended for controlled drugs, which have been returned by patients [79].

4.1.3 Poland

Poland is located in Eastern Europe by most definitions, although it is sometimes also referred to as a Central European country, depending on the context. The current population is over 37.8 million people, which equivalents to 0.49% of the world population, ranking 38th in the world and 8th in Europe by population. 60.2% of the population in Poland is living in urban areas and the median age is 41.7 years [51]. The population pyramid of Poland shows a bimodal distribution with few very young people and two bulges with people aged 25-45 years and above 65 years (see Appendix 3). Poland is a representative democracy and is composed of 16 provinces (voivodeships).

In 2016, Poland had over 164,000 new cancer cases with prostate, breast, lung and colorectum cancer representing the most frequent ones. Over 38,000 deaths occurred due to cancer. The overall 5-year survival rate increased for all cancer types and was 56% for woman and 41% for men in 2016. However, the 5-year cancer survival rate in Poland is among the lowest in Europe. The highest 5-year survival rates in Poland were observed for breast cancer with 94.4% in women and 75.8% for prostate cancer in men [80].

In 2006 the prevalence of chronic non-cancer pain in Poland was 27%, and thus one of the highest in Europe. In comparison the prevalence for chronic pain defined as pain lasting more than 6 months was 13% in the UK and 17% in Germany in the same year [81].

4.1.3.1 Legal Control of Opioid Prescription - Act on Counteracting Drug Addiction

The national competent authority in Poland is the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products under the Ministry of Health, which is responsible for e.g. marketing authorization of medicinal products, biocidal products and medical devices, assessment of clinical trials and pharmacovigilance activities [82]. The responsible authority in Poland for the implementation and coordination of national policies regarding narcotic drug and psychotropic substances is the National Bureau for Drug Prevention under the Minster of Health and Welfare [83].

The main drug legislation is the **Act on Counteracting Drug Addiction (ACDA)**, as amended [84], which regulates drug possession and supply in Poland. The ACDA is structured in 8 chapters: chapter 1 general provisions (article (art) 1-4), chapter 2 entities to perform tasks of counteracting drug addiction (art 5-15), chapter 3 upbringing, education, information and prevention (art 19-24), chapter 4 conduct with addicted persons (art 25-30), chapter 5 precursors, narcotic drugs and psychotropic substances (art 31-44), 6 chapter cultivation of poppy and hemp (art 45-52), chapter 7 penal provisions (art 57-74) and chapter 8 amendments to binding provisions, transitional and final provisions (art 75-91).

Narcotic Substances are listed as annex to the Act under Schedule 1, and psychotropic substances under Schedule 2. Schedule 1 narcotic drugs are further classified in groups I-N, II-N, III-N and IV-N. Morphine, fentanyl, hydromorphone and oxycodone are listed under group I-N, that is the most strictly controlled group. Buprenorphine is considered as a group III-P psychotropic substance and

is as such less strictly governed. Groups I-N and II-N are legally allowed to be used for medical, industrial and research purposes only (art 33). Production of I-N, II-N and IV-N drugs is only allowed for companies who have already a license to manufacture medicinal products and upon receiving a license by the main pharmaceutical inspector *"[…] specifying drugs or substances that may be the object of manufacturing, processing or conversion." (p. 24)* (art 35.1-4). The license to manufacture narcotic drugs needs to specify the legal limit, the purpose and the use of the narcotic drug (art 35.8). Wholesaling requires a license from the main pharmaceutical inspector as well. Every wholesaler needs to keep record about the narcotic drugs in their possession and they need to be stored safe from theft and destruction (art 40.4). Retail trade of group I-N drugs is allowed for pharmacies, but only with special prescriptions or demand orders.

Further aspects regarding narcotic drugs are regulated under Poland's main law for medicinal products, the **Pharmaceutical Law** [85], as amended, which also applies *"[…] to the medicinal products which are narcotic agents, psychotropic substances and their precursors within the meaning of the drug addiction counteracting regulations, to the extent unregulated by those regulations." (p. 1)* (art 1). Medicinal products containing narcotics can only be dispensed when prescribed by physicians, dentists and veterinarians (art 23a). With the ordinance of the Minister of Health of March 8th, 2012 on medical prescriptions, these prescriptions forms are white with a unique number issued by the Provincial Department of the National Health Fund or by the Provincial Pharmaceutical Inspector. The prescription needs to contain the name of the drug, the dose, the cause of the drug release, personal data of the patient, the date of the prescription and the signature and stamp of the pharmacist authorized to issue the document. Every prescription for a narcotic drug contains the symbol 'RpW' (medicines dispensed with physician's prescription and containing certain narcotic or psychotropic substances) (art 23a. [85])[86]. Advertising products containing narcotic substances is forbidden (art 54.5) [85].

4.1.3.2 Clinical Guidelines for Pain Management from Expert Groups

A group of 21 experts from different polish health associations and societies developed the **Guideline for the pharmacotherapy of pain in cancer patients**. The guideline is based on medical literature and on randomized studies to the pharmacotherapy of cancer pain. In general, the pharmacotherapy is based on the WHO analgesic ladder (see 2.3.1). Opioids used for patients with moderate pain, included in the second step of the WHO analgesic ladder, that are available in Poland are tramadol, codeine and dihydrocodeine. For each of those drugs special recommendations are given. For example, *"Tramadol is not recommended in patients with the history of epilepsy due to the increased risk of seizures." (p. 60)* [87]. For the treatment of moderate to severe pain WHO analgesic ladder step III medications are recommended, with morphine and oxycodone being the first choice of opioids (as opposed to fentanyl, buprenorphine, tapentadol, and methadone), while hydromorphone is not available in Poland. For all recommended opioids the administration route, formulation and recommended starting dose is given. For oral morphine and oral oxycodone, the analgesic treatment is specifically highlighted in an algorithm. Furthermore, the guideline gives guidance on the rotation of opioids and provides equianalgesic

doses to 10 mg oral morphine. It also gives recommendations on the therapeutic management of adverse events [87].

The Polish Association for the Study of Pain together with the Polish Neurological Society issued recommendations for the **Diagnosis and Management of Neuropathic Pain** part I and part II. Part I provides an overview on definition, epidemiology, pathomechanism, assessment and diagnosis of neuropathic pain [88]. Part II covers certain types of neuropathic pain and provides recommendations on the pharmacologic management for each type involving antidepressants, anticonvulsants, opioid analgesics and tramadol, topical drugs and NMDA receptor antagonists. For post-herpetic neuralgia it recommends opioids, e.g. morphine or oxycodone, as fist-line therapy, depending on the type and intensity of pain. For complex regional pain syndromes affecting the distal part of an upper or lower limb there is no clear therapy recommendation due to limitations of available data. However, aside from the general use of opioids. For painful diabetic polyneuropathy tramadol and strong opioids are recommended as second-line medicines. Besides five other types of neuropathic pain in addition to those mentioned, also neuropathic pain in cancer patients is considered and it is recommended to start the analgesic treatment with tramadol. For severe pain, strong opioids are recommended [89].

4.1.3.3 Rising Opioid Prescription but Decreasing Opioid Consumption

Although the drug induced deaths due to illicit drugs are decreasing since 2014, the countries' drug report 2019 of the European Monitoring Centre for Drugs and Drug Addiction highlights that some deaths among females could be related to long-term opioid prescription for cancer and non-cancer pain. However, the contribution of opioids to the drug induced deaths cannot be fully assessed due to limitations in the recording of the cases in general [90].

Between 2000 and 2015 the prescription of opioid analgesics has been consistently growing. While in 2000 morphine was the main opioid used, tramadol was the most commonly used opioid in Poland in 2015. Buprenorphine transdermal formulations have been increasingly used since 2007, when full reimbursement for pain treatment was established. Furthermore, buprenorphine is the only strong opioid which can be prescribed with a regular prescription form, while for all other strong opioids a special prescription form needs to be requested. Oxycodone has been available in pharmacies only since 2009 [91].

However, the average consumption opioid levels decreased by 15% in the period 2016-2018, especially for codeine, fentanyl and morphine while it increased for oxycodone (Table 2).

4.2 North America

North America is currently experiencing a major public health crisis due to an increase of accidental opioid-related mortality both in the United States (US) and in Canada. Since the opioid epidemic in the US was already discussed in a previous DGRA Master Thesis, the focus will be on Canada in the following chapters. However, for both Canada and the US, the reasons for the opioid crisis are discussed in detail in chapter 6.3.

4.2.1 Canada

Canada ranks number 39 in the list of countries by population with currently 37,653,998 inhabitants, which is equivalent to 0.48% of the total world population. 81.3% of the population is urban and the median age is 41.1 years [51]. The population distribution of Canada is very similar to that of the UK with comparably large numbers of people aged above 50 years (see Appendix 3). Canada consists of ten provinces and three territories. The provinces in principal have a great legal power with certain jurisdictions in areas such as health care. Between 2016 and 2018 Canada was among the countries with the highest level of consumption of narcotic drugs with rank 2 in North America after the US and rank 3 globally (Table 2) [44].

For 2020 it is estimated that over 220,000 new cancer cases will be diagnosed in Canada, with lung, breast, colorectal and prostate cancer being the most common types of cancer that together account for 48% of all new cancer cases. The mortality is estimated with over 83,000 deaths from cancer, responsible for 30% of all deaths and making it the leading cause of death in Canada. The 5-year survival rate for all cancers is 63% in Canada. Thyroid, testis and prostate cancer have the highest 5-year survival with over 97% and pancreas cancer represents the lowest 5-year survival rate with 8% [92].

Recent estimates suggest that about 6 million people and thus 19% of the population experience chronic pain. Over 65% of those chronic pain patients report that their pain is moderate (52%) to severe (14%). The highest prevalence of chronic pain was reported for patients with neurological conditions, especially by patients with traumatic spinal cord damage [93, 94].

4.2.1.1 Non-harmonized National Control of Opioid Prescription in Jurisdictions

Health Canada is a federal department under the Government of Canada and is, as the regulatory authority, responsible for assessment of the safety, efficacy and quality of drugs and medical devices and for granting marketing authorization. In Canada all drugs are regulated under the Food and Drugs Act and the Food and Drug Regulation. In addition, opioid pain medications are subject to the **Controlled Drugs and Substances Act (CDSA)** [95], and the **Narcotic Control Regulations (NCR)** [96], as amended, where the CDSA serves as the implementation of the UN Single Convention.

The **CDSA** is structured in general information followed by seven parts that provide regulations, with part I offences and punishment (sc 4-10), part II enforcement (sc 11-12.1), part III disposition (sc 13-29), part IV administration and compliance (sc 30-32), part V administrative orders for contraventions of designated regulations (sc 33-43), part VI general (sc 44-60.1) and part VII transitional provisions, consequential and conditional amendments, repeal and coming into force (sc 61-95). Furthermore, it establishes six Schedules (I to VI, two additional Schedules VII and VIII were repealed in 2018), where Schedule I to V comprise the controlled substances, while precursors for the synthesis of controlled substances are listed in Schedule VI.

The drug classification from Schedule I to Schedule V classifies drugs according to their risk of abuse and harm. Schedule I drugs, substances or chemicals, including most opioids such as

codeine, morphine, fentanyl, hydromorphone and oxycodone, are drugs with a high potential for abuse and are therefore subject to the strictest control measures. Substances under the CDSA are only allowed for use in medical and scientific purposes or otherwise in the public interest (sc 56). However, the CDSA mainly focuses on offenses and penalties when possessing, trafficking, importing and exporting substances included in the schedules.

In contrast, the **NCR** outlines the circumstances and requirements under which activities with controlled substances are permitted for licensed dealers (sc 8-29), pharmacists (sc 30-52), practitioners (sc 53-62) and hospitals (sc 63-65). Possession of narcotics is legal for persons who are exempted according to sc 56 CDSA and require the narcotic drug for their profession or business, are licensed dealers, pharmacists or registered practitioners (medicine, dentistry or veterinary medicine) or have obtained the narcotic drug for own use from a practitioner in accordance with a prescription or from a pharmacist (sc 3 (1)). Production, assembly, sale, provision, transport, delivery, import or export of narcotics are allowed for licensed dealers (sc 9) and the license is issued by the Minister of Health for each site at which any of these activities are conducted (sc 10). Sales from a licensed dealer to another licensed dealer as well as to a pharmacist, practitioner or hospital employee are allowed, but only upon receipt of prescription within 5 working days after the order, covering the name and quantity of the narcotic drug, the date, and the signature of pharmacist or practitioner (sc 25 to 25.7)). For the destruction of narcotics at site or elsewhere, a licensed dealer requires the prior approval of the Minister of Health (sc 27.5 to 27.8).

A pharmacist needs to record the receipt of narcotic drugs from a licensed dealer, including the name and quantity of the narcotic drug, receipt date and name and address of the licensed dealer (sc 30). The pharmacist is only allowed to sell narcotics upon a written or a verbal order or prescription for provision to a practitioner. A verbal order is possible for a narcotic drug that e.g. contains two or more medicinal ingredients that are not narcotics (sc 2). For all orders the pharmacist must record the drug name or initial, the practitioners name or initial, and address, name and address of the patient, details of the narcotic as well as date and number assigned to the prescription order (sc 31-39). A practitioner may only administer a narcotic drug to a person when this patient is under their professional treatment and the narcotic is required for the treatment. If the maximum daily dosage exceeds the dosage which is recommended by the manufacturer or the generally recognized maximum daily therapeutic dosage by three times, the practitioner needs to keep records including the name and the quantity of the narcotic drug, the name and the address of the person to whom it was provided and the date (sc 53-55).

However, Canada has thirteen provinces and territories and those partially have additional laws and regulations in place. In Ontario, Canadas most populated province, the **Narcotics Safety and Awareness Act, 2010** came into force in order to monitor the prescription and dispensing of certain controlled substances and to address the health and safety concerns related to their use [97]. The act defines, that for dispensing of narcotic drugs it is required to record details about the patient (e.g. name and address, patient identification number), the drug (e.g. name, strength, quantity and form of drug), the prescriber (e.g. name and address of prescriber, prescriber's registration number) and the pharmacist with the signature (authorization) of the pharmacist and

the pharmacy technician (if applicable), among other details [97]. Refills and transfers are not permitted and purchase and prescription sales must be recorded in the Narcotic and Controlled Drug Register or in other records for that purpose that are readily available for audits which take place at least every two years [95] [98]. In addition, the Ontario Regulation 381/11 under the Narcotics Safety and Awareness Act, 2010, provides additional requirements of information which need to be recorded by a dispenser, e.g. on prescriber identification number, and that all opioids including those which are not yet listed in CDSA are considered as monitored drugs in Ontario [99].

4.2.1.2 No Central Canadian guideline on cancer pain management

The evidence based Canadian **Guideline for opioid therapy and chronic non-cancer pain** aims to provide guidance on the use of opioids for non-cancer pain management in adults. It recommends strongly to optimize first non-opioid pharmacotherapy and non-pharmacologic therapy before considering a therapy with opioids. In general, it is recommended to acquire informed consent prior to initiating opioid use, and clinicians should monitor the patients under opioid therapy and adjust treatment if needed. A discussion about potential benefits, adverse effects, and complications will facilitate shared-care decision making regarding whether to proceed with opioid therapy. Clinicians should monitor chronic non-cancer pain patients receiving opioid therapy for their response to the treatment and adjust the treatment accordingly. For patients with an active substance use disorder, clinicians should facilitate treatment of the underlying substance use disorders and should not use opioids. For all other patients who still have pain despite optimized non-opioid therapy, a trial of opioids is recommended. When starting an opioid therapy, the prescribed dose should be restricted to less than 90 mg morphine equivalents daily. However, it is suggested to restrict the maximum prescribed dose further, to less than 50 mg morphine equivalents daily. If patients are currently using opioids and still suffer from persistent problematic pain but also from problematic adverse effects, a rotation to other opioids is recommended. The guideline furthermore lists opioid options for initiating a therapy trial and provides additional comments for use. For example, morphine should be avoided in renal insufficiency, and buprenorphine oral formulations are preferred over transdermal formulations [100].

There seems to be no general Canadian guideline on cancer pain management available. Instead, Canadian provinces each have own guidelines addressing this indication. An example is the clinical practice guidelines on cancer pain from the Alberta Health Services, which follows the principals of the WHO analgesic ladder for the pharmacological management of pain [101]. Also, there are no general Canadian guidelines available addressing pain or cancer pain in children. However, a project to develop a comprehensive clinical practice guideline regarding pain in children was recently initiated and is under development [102].

4.2.1.3 Second Highest Prescription of Opioids for Pain Management Worldwide - the Opioid Epidemic in Canada

Canada is the second largest consumer of prescription-opioids after the USA, with over 20 million prescriptions for opioids issued in 2016. In 2018 40.5% of adult Canadians reported to use

prescription opioids for pain relief, among those 2.9% for non-medical purposes. However, although the number of opioid prescriptions increases, in the past years the overall doses of prescription opioids decreased slightly, most likely because physicians prescribed smaller amounts more frequently. In 2019, almost 4,000 apparent opioid related deaths occurred from both prescription drug use and illicit drug use, and over 19,000 individuals were hospitalized due to opioid-related poisoning. Substantial differences exist between provinces. While in Ontario opioid-related deaths increased about 17% between 2017 to 2018, the number remains stable in Alberta. However, those two provinces together accounted for the majority of opioid-related deaths in Canada. Fentanyl-related opioids account for most opioid-related deaths, with 55% in 2016. This number increased in the first nine months of 2019 to even 78% [103, 104]. Since 2016, the Government of Canada has implemented several actions to address the opioid crisis.

4.2.1.4 Canadas Regulatory Response on Opioid Misuse

In response to the opioid crisis, the Government of Canada initiated **legislative changes** to the CDSA and other Acts with the Royal Assent of Bill C-37 [105], adopted in 2017. One change is that the application requirements for supervised consumption sites will be streamlined. This already led to an increase of approved supervised consumption sites from initially two to now over 40 sites. Furthermore, a registration is now required to import pill presses. It is now illegal to import unregistered pill presses to Canada, which is thought to help the government to identify illegal drug production in an early stage and take early action against. Another change is that the Minister of Health can quickly control new dangerous substances which are not yet subject of the CDSA, and which enter the illegal market, by temporary accelerated scheduling. This empowers the Minister of Health to temporarily add a substance which poses a significant risk to public health or safety to a schedule of the CDSA. Furthermore, border officials are allowed to open mail weighing 30g or less if there are reasonable grounds to suspect that those packages contain unauthorized controlled substances [106].

In addition, several **regulatory actions** under the CDSA and the Food and Drugs Act were addressed.

- **Naloxone** will be available without a prescription.
- Naloxone temporarily reverses the effects of an opioid overdose. By enabling health care providers and individuals to access naloxone without prescription and provide easy and fast availability in emergency situations, more deaths from an opioid overdose could be prevented [106].
- A **nasal spray version of naloxone** was approved.
- An easier-to-use nasal spray version of naloxone available would further help to prevent opioid overdose deaths. In June 2017 Health Canada authorized naloxone Nasal Spray (NARCAN) [107].
- Physicians are now able to apply to Health Canada to request access to **medical grade heroin** for their patients.

Access to medical grade heroin can be requested by physicians for patients with chronic relapsing opioid dependence via a special access program [108].

- The **import** of medications approved elsewhere **for urgent public health** needs is allowed.
- Health Canada permits to import certain medications for urgent public health need which are not yet authorized in Canada but are authorized in the US, EU or Switzerland and are listed in the List of Drugs for an Urgent Public Health Need. These include e.g. suboxine, that contains buprenorphine hydrochloride and naloxone hydrochloride, for the treatment of an opioid dependence [109].
- The access to **six fentanyl precursor chemicals** will be **restricted**.
- Since most of the deaths from opioid-related overdoses involved fentanyl, which is considered to be highly potent and addictive, Health Canada restricts the access to six precursor chemicals by adding those to Schedule IV in the Precursor Control Regulations, since they are used especially to manufacture illicit fentanyl [110].

In addition to the legislative changes and regulatory actions, the Government of Canada supports several programs in the areas of prevention, treatment, harm reduction and improving clinical evidence. The Government of Canada committed $5 billion to provinces and territories over ten years to improve access to mental health and addiction services for Canadians. Supported are efforts to promote harm reduction initiatives and the provision of educational materials for offenders. Further attempts aim to reduce the lack of information at a national, provincial and regional levels by increasing efforts on collecting data and a quarterly reporting on opioid-related deaths, by deploying epidemiologists in 8 provinces and territories to assist with data collection, by providing online information toolkits, and more. With these and planned future actions, e.g. the support of innovative educational approaches or improved reporting of overdoses, the Canadian government, in close collaboration with non-government organizations, health and public safety professionals, as well as single individuals, are trying to address the different routes that lead to the Canadian opioid crisis [106].

4.3 Oceania

The following chapters will focus on Australia that is also currently experiencing an opioid epidemic. While there are indications that also in New-Zealand the non-medical use of fentanyl is increasing, the additional inclusion of New Zealand would go beyond the capacity of this work.

4.3.1 Australia

Although Australia is one of the largest countries of the world by area, the Australian population equivalents only to 0.33% of the total world population with a current population of 25,420,578 people ranking 55th in the list of countries by population. 85.9% of the Australian population is urban and the median age is 37.9 years [51]. The population in Australia shows a mushroom-like age distribution with a notable decrease of younger people aged 0-20 years and a large number of people aged 20-50 years, but also a comparably large number of people above 50 years (see

Appendix 3). Australia has six states, which have plenary legislate power, as well as two territories. Between 2016 and 2018 Australia was among the countries with the highest levels of consumption of narcotic drugs with rank 1 in Oceania and rank 11 globally (Table 2) [44].

It is estimated that in 2020 about 145,000 new cancer cases will be diagnosed and 48,000 deaths from cancer will occur in Australia. As in most countries with a highly developed health system, a large proportion of cases is already diagnosed in an early cancer stage (stage I and II), with at least 77% of breast, prostate cancer and melanoma cases being diagnosed at an early stage. The 5-year relative survival rate for all cancers combined was 69% between 2012 and 2016, depending on the type of cancer, with the lowest survival rates (10,4%) for pancreatic cancer and the highest survival rates (95,5%) for prostate cancer [111-113].

In 2016 almost 19% of Australians reported to suffer from chronic pain. This fraction increases with increasing age, and 24% of Australians aged 85 years and above report chronic pain. Over the last 10 years, the number of patients with pain that seek help from medical practitioners increased by 67% [114].

4.3.1.1 No Central Body for Schedule 8 Drugs

In Australia, the Office of Drug Control (ODC) is responsible for regulating and advising activities related to import, export and manufacture of controlled drugs, including the reporting activities to the INCB. The ODC belongs to the Department of Health under the Australian Government and is part of the Health Products Regulation Group (HPRG) of the Department of Health together with the Therapeutic Goods Administration (TGA) [115] [116].

Australia signed and acknowledged the three International Conventions which classify narcotic drugs, and which place them under international control (see 3.1), including the UN Single Convention. To meet the obligations under the UN Single Convention and to regulate narcotic drugs on a national level, Australia implemented the Narcotic Drugs Act 1967 (NDA 1967) [117] as latest amended by the Narcotic Drugs Legislation Amendment Act 2016. The NDA 1967 is structured in five chapters with chapter 1 general provisions (sc 1-8), chapter 2 licensing the cultivation of cannabis plants and the production of cannabis etc. (sc 8A-11E), chapter 3 licensing the manufacturing of drugs (sc 11F-13D), chapter 4 monitoring and enforcement (sc 13G-14G) and chapter 5 general (sc 14H-28).

The Narcotic Drugs Act 1967 classifies substances under control in Schedules I, II, III and IV where substances under Schedule I are subject to the strictest measures and substances under Schedule III are controlled less strict. Most opioid analgesics used for pain management are classified under Schedule I, such as morphine, oxycodone, and hydromorphone while codeine is listed under Schedule II, following the classification of the UN Single Convention [117].

The Narcotic Drug Act 1967 provides requirements for authorizing manufacture of controlled drugs and related activities such as packaging, transport, storage, possession or destruction of the

drug. A manufacture license requires an application to the Secretary[1] and the license can be refused, if the applicant is not a *".[…] fit and proper person to hold the license [...]"*, the location or facilities are not satisfying, the measures to ensure the physical security of the drug are not satisfying, and other reasons (sc 11J). The requirements whether a person is considered as fit and proper to apply for a manufacturing license are listed as well and include the financial background, the history of compliance with the Narcotic Drugs Act and the previous business experience, amongst others (sc 8A-8C).

However, another legislation in place is the **Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP))** from 2020 created under subsection 52D(2) of the Therapeutic Goods Act 1989. The Therapeutic Goods Act 1989 is the legislation in Australia which provides requirements for the establishment and maintenance of controls relating to the quality, safety and efficacy of therapeutic goods and the SUSMP provides information and decisions concerning the classification of medicines and chemicals, which are set out in Schedules 1 to 10 [118] [119]. In the SUSMP the opioids listed in the Narcotic Drugs Act 1967, such as morphine, oxycodone, hydromorphone and buprenorphine are classified as Schedule 8 drugs. That means they are considered as controlled drugs or substances which should be made available for use but only under restrictions of manufacture, supply, distribution, possession, and use. Since they have a potential of causing harm, these restrictions shall reduce abuse, misuse and physical or psychological dependence. Although also fentanyl is listed as a Schedule 8 drug, it seems not to be implemented in the Narcotic Drugs Act to date. Since February 2018 codeine is scheduled as Schedule 4 drug which is considered as prescription only medicine together with e.g. tramadol [117] [119].

Information about which parties are eligible to prescribe opioids can be retrieved from SUSMP Section 2, which states that Schedule 4 and Schedule 8 poisons, to which opioids belong, can only be prescribed by a medical, dental or veterinary practitioner. Such a drug can be sold by a pharmacist dispensing a legal prescription.

However, Australia has no central body to regulate the handling of Schedule 8 drugs and each state and territory self-regulates these under the general principles established by the TGA. While Schedule 4 requirements are standardized in Australia, legislative requirements for Schedule 8 medicines e.g. how they need to be prescribed, dispensed, documented, and destroyed, differ across states and territories and are highly specific. The prescription information must include prescriber name and address in all states and territories. The phone number is most often required as well, except for Queensland and Western Australia where it is necessary only for computer generated prescriptions. Information on the qualification of the prescriber is not required for South Australia, Tasmania, Victoria and Western Australia, but in the other regions. All regions, except South Australia, require a hand-written signature by the prescribing doctor. The same diversity exists concerning the requirements for patient information and information on the medicine. In the Northern Territory, Queensland, South Australian and Western Australia, the

[1] *"Secretary means the Secretary of the Department administered by the Minister administering the National Health Act 1953." (p. 7)* (sc 4 [121])

patient's date of birth is necessary, but this is not required in the other regions. In some regions, information on the prescribed medicine needs to be provided handwritten, in others not [120].

4.3.1.2 Clinical Guidelines for Pain Management considering Opioid Therapy

The guideline on **Acute Pain Management: Scientific Evidence issued by the Australian and New Zealand College of Anaesthetists** [121] aims to support medical practitioners and clinicians for their work with patients that suffer from acute pain and is based on evidence from published literature. It considers adult as well as paediatric patients and comprises several specific clinical situations, e.g. postoperative pain or acute cancer pain. The guideline ranks the levels of evidence and provides also a summary of key points that include this ranking as well as points to consider for clinical practice, e.g. *"No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil" (p xxviii)* in the context of epidural morphine. The guideline provides information and current evidence to analgesic medicines such as opioids. It addresses determinants of opioid dosing, including age, gender or genetic variability of patients. However, no specific dosing for opioids is suggested and dose recommendations are only provided in the context of current literature evidence e.g. *"Oral tramadol is an effective analgesic agent for postoperative pain with NNTs of 7.1 for 50 mg, 4.8 for 100 mg and 2.4 for 150 mg […]" (p 183).*

For acute pain in children opioids have been also evaluated and practice points are given, for example *"Because of its unpredictable effect, codeine should not be used in children, […], due to an increased risk of opioid-induced ventilatory impairment and death" (p 437)*. However, no concrete suggested dosing for opioids is provided and dose and efficacy is only mentioned for tramadol in the context of current evidence. An example for the systemic administration of tramadol intravenous dosing in children *"[…]is the same as in adults (1–2 mg/kg every 6 h), with an initial 2 mg/kg intravenous loading dose being recommended, followed by infusion rates of 0.25–0.41 mg/kg/h (6–10 mg/kg/24 h) […]" (p435)* [121].

4.3.1.3 Rise of Overdoses and Death as a Result of Problematic Opioid Use in Australia

From 2016 to 2017 15.6 million prescriptions for opioids covered by the Pharmaceutical Benefits Scheme (PBS), a list of medicines that includes Government-subsidized prescription drugs, were issued in Australia, with oxycodone being the most prescribed opioid, followed by codeine and tramadol. From 2012 to 2017 the number of opioid prescriptions increased by 9%, where oxycodone accounted for 30% of the total prescriptions. However, the rate of prescriptions for codeine, fentanyl and morphine decreased in this period. Interestingly, until 2018 codeine was available as over the counter (OTC) drug at pharmacies and no prescription was needed. In 2013 the OTC codeine accounted for about 37% of all opioid purchases. From 2007 to 2017 the rate of opioid related deaths increased by 62%, and 49% of this increase was accounted for by pharmaceutical opioids. The rate of hospitalizations of opioid poisoning increased by 25% in the same timeframe, with the majority due to pharmaceutical opioids [122].

To tackle the problem of over-prescription, deaths and hospitalization from opioids, the Australian Government and the TGA initiated several activities.

4.3.1.4 Australia's Regulatory Response on Opioid Misuse

In 2018 the TGA released a document for consultation which addresses options for a regulatory response in regards to the prescription of strong (Schedule 8) opioids and their use and misuse in Australia [123]. The TGA acknowledges that regulatory responses can only be one part to address the problem of inappropriate use of opioids and other areas such as changes in prescriber behaviors need to be considered as well. However, the TGA identified eight options to tackle the misuse of prescription opioids from a regulatory point of view, and some of those considerations already went into force, while others are planned to come into force during 2020.

- **Pack sizes** for Schedule 8 opioids for treatment of patients with acute pain should be smaller and suitable pack sizes should be made available for treatment of people with chronic pain due to malignancy.

  This regulatory change was implemented, and sponsors need to register smaller pack sizes for immediate-release opioids. Those will provide a more appropriate option for short-term pain relief and reduce the risk of harm from unused opioids. Larger pack sizes will remain to be available for those who need them.

- **Revision of the indications** for strong opioids (Schedule 8) in order to align them to the current clinical guidelines. For several strong opioids, the currently approved indications from the Australian Register of Therapeutic Goods (ARTG) entries are inconsistent between products as well as between members of the same substance class. Revision of these indications would therefore allow more appropriate prescription.

  This consideration was also recently implemented, and the sponsors need to update the prescribing indication for opioids in the future to ensure that an opioid is prescribed only when the benefit outweighs the risk.

- Considerations to **remove high dose products from the market** or restrict high dose products to specialist-only / authority-only prescribing.

- Encourage sponsors to establish or update **Risk Management Plans** (RMPs) for opioid products to minimize risks and reflect best practices in opioid prescribing.

- Revision of **label warnings** and **consumer medicines information** to identify and provide greater emphasis on the risk of dependence and overdose and the lack of efficiency for long term treatment of chronic non- cancer pain.

  At first, the sponsors need to improve the information available to prescribers and consumers. This should include information about the potential risk using opioids and statements how to minimizes those risks. Furthermore, the indication for fentanyl patches, immediate release products and modified release products were tightened. The overall goal is to encourage best practices in opioid prescription, and to better inform patients and medical practitioners. Secondly, additional warning statements need to be incorporated in the approved product information for all opioids, to raise awareness of

medical practitioners concerning appropriate circumstances to prescribe opioids as well as concerning potential adverse effects.

- Encourage the development of **alternatives to opioids** for pain relief by considering incentives, e.g. priority reviews for new therapeutic alternatives, smaller pack sizes, abuse-deterrent formulations or new formulations or antidotes.
- Changes in the appendices in the **SUSMP** to include controls for the prescription of opioids for particular patient populations or classes of medical practitioners, as well as additional safety directions, dispensing labels or label warning statements to provide additional control for strong opioids from a regulatory point of view.
- **Increasing awareness of health practitioners** on alternatives to opioids in pain management by e.g. development of a comprehensive repository about the appropriate use of Schedule 4 and Schedule 8 opioids. [123, 124]

In support of these regulatory changes, also changes in the PBS were made for opioid medicines for the treatment of pain on 1 June 2020. These changes include reduced pack sizes and exclusion of repeats for the treatment of non-chronic pain. Patients furthermore need to fulfil certain criteria to be eligible for treatment with opioids. They need to be unresponsive or intolerant towards non-opioid treatments, or their acute pain was only inadequately relieved by using maximum tolerated doses of non-opioid treatments. [125].

4.4 Asia

Asia is the most populated region worldwide, with a current population of over 4,6 billion inhabitants, which accounts for 59.76% of the total world population. 50.9% of the inhabitants live in urban regions and the median age is 32.0 years [51]. In this often densely populated region occur almost half of cancer cases worldwide, with estimated 8.2 million new cancer cases and 5.2 million cancer deaths in 2018. Lung cancer is the most common reported cancer in Asia followed by stomach and liver cancer. The cancer incidence rates among the Asian regions differ significantly, with the highest incidence in the Republic of Korea and the lowest in India, with 314 and 61 cases per 100,000 population, respectively [126]. However, Asia is a diverse region with strong ethnical, socio-cultural, socio-economical and dietary differences, and these differences are also reflected in the cancer burden among the individual countries. In low-income countries such as Cambodia, the healthcare infrastructure is poorly developed, and the majority of cancer patients do not receive adequate care and thus have poor survival prospects. In lower-to-middle-income countries such as India, the healthcare infrastructure is mostly centered in urban areas. Due to limitation on the availability of essential consumables, diagnostics and drugs, especially rural and socio-economically disadvantaged populations only have limited access to cancer care. High income countries such as China and Japan have a mostly well-organized healthcare infrastructure with highly accessible cancer care resources. Still, lack of availability or underuse of opioids as part of palliative care is common in many also highly developed Asian countries [127].

In general, also Asia recorded an increase in the opioid consumption levels from 2007-2009. With an average consumption below 200 S-DDD it is still significantly lower than compared to North America, Oceania or Europe with consumption levels ranging from over 5000 S-DDD to nearly 15,000 S-DDD in the same period. The following chapter will give a more detailed overview on the legal and clinical regulations for opioids in two Asian countries: Japan, which had the ninth highest opioid consumption in Asia with over 1,000 S-DDD between 2016 and 2018 and is on rank 62 globally, as well as India, which was with 37 S-DDD among the Asian countries with the lowest opioid consumption between 2016 and 2018 and ranks 37th in Asia and 145th globally (Table 2) [44].

4.4.1 Japan

With a population of over 126 million inhabitants, Japan counts for 1.62% of the total world population and ranks 11th by country population. Furthermore, 91.8% of Japans population live in urbanized areas, which is the largest fraction among the countries selected for this thesis. The median age is 48,4 years [51], and the Japanese population shows the largest numbers of old and elderly people with comparably few people aged below 40 years (see Appendix 3). Japan is a unitary state composed of 47 prefectures.

Also, in Japan, cancer is the leading cause for death since several decades. Epidemiological studies indicate that civilizational risk factors such as smoking, infection, alcohol and overweight, are responsible for about 50% of all cancer cases. Between 1965 and 2013, cancer deaths in young individuals (<40 years) have been decreasing while it increased in older people due to an increase in the lifespan in Japan. However, the mortalities of certain cancer types such as pancreatic or breast cancer are increasing at all ages [128]. With the increasing cancer mortality rate in general in Japan, also the overall prevalence rate of cancer pain is high and is reported to be between 53% to 71%. Nonetheless, the number of studies investigating cancer pain in Japan is limited [129].

Studies in the prevalence of chronic pain in the Japanese population revealed, that between 26% and 39 % of the adult population experience chronic pain. Among those people, more older people reported chronic pain, with a mean age of 60.9 ± 16.2 years [130].

4.4.1.1 Unidirectional from Manufacturing to Prescription - NPCA

In Japan, the Ministry of Health, Labour, and Welfare (MHLW) is in charge of pharmaceutical regulatory affairs, of which the Pharmaceutical Safety and Environmental Health Bureau (PSEHB) and the Pharmaceutical and Medical Devices Agency (PMDA) are subunits. The PMDA is responsible for authorization of clinical trials, medical devices, approval reviews and surveys of the reliability of application data among other functions. The role of the PSEHB is to undertake main duties of the MHLW and it is responsible for approvals and licensing, distribution policies and drug pricing. The Compliance and Narcotics Division is part of the PSEHB and is responsible for the control of narcotics and stimulants [131].

In Japan, opioids are tightly regulated by the **Narcotics and Psychotropics Control Act (NPCA)** which regulates the relevant processes such as the formulation, manufacturing, export, transfer,

licensing, disposal and more [132]. The NPCA is structured in 7 chapters with chapter 1 general provisions (art 1-2), chapter 2 control of narcotics (art 3-49), chapter 3 control of psychotropics (art 50-50.37), chapter 4 supervision (art 50.38-58), chapter 5 measures for narcotics addicts (art 58.2-58.19), chapter 6 miscellaneous provisions (art 59-63) and chapter 7 penal provisions (art 64-76). It furthermore regulates opium and powdered opium when formulated as a drug. A separate opium law exists for natural opium itself. Narcotic drugs are listed in table I of the act, plants containing a narcotic raw material are listed in table II and psychotropic substances are listed in table III. Morphine, codeine, oxycodone, and hydromorphone are classified as narcotic drugs in table I in the NPCA.

Every participant in the narcotic drug chain from manufacturer to prescriber requires a license which is issued by the Minister of Health, Labour and Welfare for each site of operations involving narcotic drugs. Everyone who wholesales, retails or administers narcotic drugs needs to be licensed by the prefectural governor. For getting licensed, persons functioning as narcotic drug wholesalers or narcotic drug retailer must be either a pharmacist or need to employ a pharmacist. Furthermore, only physicians, dentists or veterinarians are allowed to prescribe opioids. The way of an opioid from manufacturing to prescription is highly regulated and unidirectional since "*A Narcotics Manufacturer must not transfer a Narcotic to a person other than a Narcotics Exporter […] or Narcotics Wholesaler […] A Narcotics Wholesaler must not transfer a Narcotic to a person other than a […] Narcotics Retailer […] A Narcotics Retailer must not transfer a Narcotic other than to a person in possession of a Narcotics Prescription*." and notifications to the Minister of Health, Labour and Welfare or the prefectural governor are required for every part of the manufacturing, distribution and administration chain (art 24 (5) to (11)). When a prescription is issued, it is required to record details about the patient's name, product name, quantity, usage and dosage. A person licensed to administer the narcotic needs to record their name and license number which all must be documented on a prescription sheet with name and seal of the licensed person (art 27 (6)). For administering a narcotic drug, the licensed physician needs to record patient information (name, address), the reason for the administration (name of illness including primary symptoms), information to the drug (name and quantity) and the date of administration [132]. The medical record is additionally covered in specialized acts for physicians (Medical Practitioners' Act), dentists (Dental Practitioners' Act) and veterinarians (Veterinarians Act) [132].

4.4.1.2 Pain Specific Clinical Guidelines addressing Opioids for Therapy

The first Guideline for the Management of Cancer Pain was published in Japan in 2000 by the Japanese Society for Palliative Medicine (JSPM), which was the start of several clinical studies on cancer pain management in Japan, the introduction of several new drugs, and the further development of clinical guidelines in general.

The most current **Guideline for Pharmacotherapy for Cancer Pain** from 2010 based on evidence-based methodology provides 65 recommendations for the management of cancer pain, for the specific management of opioid-induced adverse effects, for patient education and for the management of pain from specific etiologies, that always start with a comprehensive assessment of the patient's pain symptoms. The use of opioids is not recommended for patients with mild

pain but should be used in cancer patients with moderate-to-severe pain, previously inadequately controlled pain, and breakthrough pain. This guideline provides also guidance on type of opioid to be used, how to deal with side effects, and how to deal with inadequately controlled pain although opioids are given, In addition, it gives recommendations for the management of pain arising from specific etiologies [129] [133].

Opioid prescription is also recommended for non-cancer pain in Japan and a multitude of clinical guidelines concerning opioid prescription in different healthcare settings is available. The **Clinical Guidelines of Pharmacotherapy for Neuropathic Pain** recommends weak opioid analgesics such as tramadol as second-line drugs and stronger opioid analgesics such as buprenorphine, fentanyl, oxycodone and morphine as third-line drugs, and includes recommendations on dosage form, specific use, treatment period, indications and adverse reactions. It must be noted that oxycodone should only be prescribed for neuropathic pain in the context of cancer pain [134, 135]. The **Clinical Practice Guideline for Chronic Pain** covers the pharmacotherapy with opioids. It provides information by answering questions such as *"CQ20: Are opioid analgesics [strong] effective in managing chronic pain?" (p232).* The answer on this is, according to the guideline, that for musculoskeletal pain, neuropathic pain, headache/orofacial pain and fibromyalgia the use of strong opioids is only weakly or not at all recommended. The opioids buprenorphine and tramadol are strongly recommended for e.g. musculoskeletal pain. All recommendations are summarized in a table covering the methods of administration, dosages, applicable diseases ad adverse events or precautions for usage. For example, for morphine it is recommended to administer the oral formula (quick-release formula) with an initial dose of 10−30 mg/day and a maintenance dose of 30-90 mg/day for chronic pain but also for cancer pain, although the guideline in general excluded cancer and acute pain [136].

In summary, these general and specialized guidelines show that opioids are in general accepted by the community of pain clinicians in Japan as effective treatment for multiple diseases and careful assessment it always recommended. For example, when considering a long-term administration of opioid analgesics including tramadol, it is endorsed to receive a collaborative consultation from a pain management specialist

4.4.1.3 Low Prescription in Japan Partially due to Cultural Aspects

The national insurance system in Japan covers the use of opioids but has strict obligations. Oxycodone is covered for cancer pain only, a tramadol-acetaminophen combination is covered only for non-cancer pain as well as tooth extraction, while codeine, morphine, fentanyl patches, and buprenorphine are covered for both cancer and non-cancer pain. Furthermore, a physician must fulfil several criteria to receive the license to prescribe opioids. For each specific opioid, the physician must complete an extensive E-learning module, and the physician and the patient need to sign an agreement prior the start of the treatment. Before opioids are given, the patient must have been treated with non-opioid analgesics, and prior to the planned opioid treatment the patient must undergo a trial use [137].

A survey conducted between 2014 and 2015 among members of the Japan Primary Care Association showed that of all physicians that possess a license to prescribe opioids, 24.1% do never prescribe opioids for acute pain. Only 27.3% of the Japanese physicians rated opioids as a standard of care for chronic pain therapy. However, 73.9% realize that opioids are indicated for chronic pain [137]. A recent survey among Japanese surgeons supports those numbers. Only 2.7% of Japanese surgeons believed that opioids are necessary for post-surgical pain control and would contribute to patient satisfaction, and only 66.6% of the surgeons prescribed opioids for postoperative pain control [138].

The low prescription rate of opioids for pain management in Japan can also be influenced from patient expectations and satisfaction. Chronic opioid use is often seen as a criminal act. Another cultural aspect is that Japanese patients do less likely complain about pain [137].

In 2015 only 6 deaths resulting from prescription opioids have been reported in Japan [139]. Between 2004 and 2017 the total number of opioid-related deaths was 335, where the number of fentanyl-related adverse events resulting in death was higher than that reported for morphine and oxycodone [140].

4.4.2 India

With a current population of over 1 billion inhabitants, India is the second most populated country in the world. 35.0% of the population is urban and the median age is 28.4 years. India still shows an expansive population pyramid with high numbers of young people and considerably fewer people aged 50 years and above (see Appendix 3). It is a federal state comprised of 28 states and 8 union territories [51].

Every year, over 1.16 million new cancer cases are registered in India, and over 780,000 people die from cancer. The most common types of cancer are breast, oral, cervical, gastric and lung cancer, which together account for over 47% of all cancers. Interestingly, the average age for breast cancer in India is much lower than compared to the Western Countries with an incidence rate that starts to rise in the early thirties and peaks at ages 50-64 years [141]. The 5-year survival rate for breast and prostate cancer is approximately 60%, while the 5-year survival rate for lung cancer is only 8.6% [142].

A recent study conducted in Indian adults revealed that the prevalence rate of chronic pain in the Indian population is 19.3%, corresponding to almost 200,000,000 adults in absolute numbers. The rural population was identified to suffer more from unrelieved and untreated pain. Although the study revealed that most patients used analgesics, mostly OTC drugs, 16% of the patients were not aware about the existence of analgesics at all and 15% did not use any medications [143].

4.4.2.1 Narcotic Drugs under Central Government Control

In India the Central Drugs Standard Control Organisation (CDSCO) under the Ministry of Health & Family Welfare is the national regulatory authority responsible for drug and medical device approval, authorization of clinical trials, import and registration issuance, among others. Those

activities are based on the Drugs & Cosmetics Act, 1940. The regulation of manufacture, sale and distribution of drugs is largely in the responsibility of the state authorities [144]. The Central Bureau of Narcotics (CBN) under the Central Government is headed by the Narcotics Commissioner (NC). The duties of the CBN are the supervision over licit cultivation of opium poppy in India, the issuance of licenses for manufacture of synthetic narcotic drugs and the issuance of export and import licenses for narcotic drugs. It furthermore has preventive and enforcement functions and the CBN interacts with the INCB to verify the authenticity of shipments before authorization [145].

India signed the UN drug conventions (3.1) and passed its national **Narcotic Drugs and Psychotropic Substances Act, 1985 (NDPS Act)**, latest amended 2014, which replaced the former Opium Acts and the Dangerous Drugs Act [146]. The NDPS Act is structured in seven chapters with chapter I preliminary (sc 1-3), chapter II authorities and officers (sc4-7) including national fund for control of drug abuse (sc7A-7B), chapter III prohibition, control and regulation (sc 8-14), chapter IV offences and penalties (sc 15-40), chapter V procedure (sc 41-68) including forfeiture of illegally acquired property (sc 68A-68Z) and chapter VI miscellaneous (sc 69-83). It mainly provides penalties for drug trafficking, enforcement powers and enforcement controls over controlled substances. A controlled substance is defined as *"[…] any substance which the Central Government may, having regard to the available information as to its possible use in the production or manufacture of narcotic drugs or psychotropic substances or to the provisions of any International Convention, by notification in the Official Gazette, declare to be a controlled substance."* (sc 2 (viid)). A narcotic drug is not defined, but in amendment 2014 the NDPS Act was edited by *"[…] "essential narcotic drug" means a narcotic drug notified by the Central Government for medical and scientific use."* (sc 2(viiia)). However, the Schedule in the NDPS Act only lists psychotropic substances.

In general, the Central Government is responsible to take measures for preventing and combating the abuse of narcotic drugs and its illicit traffic. It furthermore needs to ensure the availability of narcotic drugs for medical and scientific use by implementing relevant measures (sc 4 (1), (2)(d), sc 9)). State Governments have also the power to permit, control and regulate narcotic drugs through rules (sc 10) and are responsible for enforcement of the NDPS Act. The NDPS Act created several statutory authorities that possess specific functions, such as the Narcotics Commissioner (sc 5), the Competent Authority (sc 68D) and the Administrator (sc 68G), which are all part of the CBN.

Production, possession, purchase, trade, sale and consumption of narcotic drugs is strictly prohibited, except for medical or scientific purposes (sc 8 (c)). To legally conduct those activities in the context of essential narcotic drugs, a license or permit needs to be granted by the Central Government, in detail by the CBN (sc 9). However, requirements for such licenses are not mentioned. Sale, transport, use and consumption of narcotic drugs are regulated by the State Governments under the State NDPS Rules (sc 10 (a)). The NDPS Act does neither state who is legally allowed to prescribe narcotic drugs, nor which narcotic drugs are regulated. Furthermore, no details for legal distribution, disposal or acquisition are mentioned [146].

With the amendment 2014 a new category of Essential Narcotic Drugs (sc 2) was introduced. These drugs were placed under the ambit of the Central Government only and are no longer under the responsibility of the single state governments. With this, the CBN published several rules and notifications regarding narcotics and psychotropic substances, which are considered to amend the NDPS Act and to provide more details on legal activities. The **Gazette Notification G.S.R**. **359(E) (G.S.R, 359(E))** from 2015 lists the requirements to apply for a license for production, trade etc. (sc 38). It furthermore defines that a *"[…] "registered medical practitioner" means any person registered as a medical practitioner under the Indian Medical Council Act, 1956 […] or registered as a dentist under the Dentists Act, 1948 […]"* is allowed to prescribe essential narcotics drugs, once a training in pain relief and palliative care was conducted (sc 2(iv) [147]. According to the NDPS Act for addition or deletion of substances from the list of narcotic drugs, no formal bill or amendment is required and the government can implement changes through notification in the official gazette (sc 3) [146]. Thus, with the notifications 2015 and 2019, morphine, codeine, oxycodone, hydrocodone and fentanyl and its salts and preparations were added to the list of essential narcotic drugs while tramadol was added to the list of psychotropic substances [147-149].

Prescriptions need to be in writing, dated and signed by the practitioner, and details about the practitioner (name, address and registration number) as well as about the patient (name and address) and the total quantity of the essential narcotic drug (sc 52G) need to be stated. A registered medical practitioner can possess essential narcotic drugs listed for direct administration to the patient under care up to the quantity mentioned in the G.S.R, 359(E), which is e.g. for morphine up to 500 mg (sc 52A (1)-(3)). For possession of a narcotic drug an authorization from the Controller of Drugs is required. Medicinal practitioners need to maintain day to day accounts for all transactions of essential drugs and for each patient, which need to be preserved for two years (sc 52H). Forms for authorization (form 3B) and record keeping (form 3C-3E) are depicted, and an explanation on the use and retention period are given. For medical institutions, such as hospitals, special provisions are given (sc 52N-52Z) that include the inspections of stocks by authorized officers (sc 52Y) or estimates of requirements (sc 52T) which need to be submitted to the Controller of Drugs annually [147].

4.4.2.2 Opioids for Pain Management in Standard Treatment Guidelines and Clinical Guidelines

With the aim to improve the management of cancer pain and to provide the patients with at least a minimal acceptable quality of life, the Indian Society for Study of Pain issued the **Guidelines on Pharmacological Management of Cancer Pain** based on literature evidence. The pharmacological management guidelines are distributed into parts I, II and III of guidelines concerning cancer pain [150-152]. Special populations such as elderly people or children are not specifically addressed in any of those guidelines.

The part I guideline provides general information on the management of mild to severe cancer pain and about the utilization of non-opioid analgesics, opioid analgesics and adjuvant analgesics. This guideline recommends to follow the WHO three-step analgesic ladder for cancer pain

management using weak opioids, such as tramadol and codeine, for mild-to-moderate pain, and morphine as the first choice opioid for moderate-to-severe cancer pain [150].

The part II guideline advises on how to prescribe and titrate opioids. It provides recommendations on the treatment maintenance, on opioid drug rotation or switching, and on the management of side effects. A dose conversion table is included, which the guideline emphasizes to use as a rough guide to determine the dose of a newly administered opioid drug, since no universally accepted guidelines for equianalgesic conversion are available. It also provides a summary of recommendations, e.g. *"Morphine should be started at the dose of 5-10 mg 4 hourly using the oral IR formulation" (p S23)* [151].

The part III guideline provides further information on the metabolism of morphine, fentanyl, tramadol, methadone, codeine and buprenorphine when used in cancer patients with renal and liver impairment, which is a common issue for patients in advanced cancer stages. It furthermore provides information to adjuvant analgesics [152].

In addition, the Ministry of Health & Family Welfare provides several guidelines for different medical indications, which are considered as standard treatment guidelines. For example, the standard treatment guideline for major trauma recommends using opioids as first line analgesic for pain management, where the dose should be adjusted to achieve adequate pain relief. For this, intravenous morphine is recommended with 2.5-5 mg/hour every 4 hours, but also buprenorphine as slow intravenous with an initial dose of 0.3 mg every 6 to 8 hours as needed can be considered [153].

However, there seems to be no general guideline available in India addressing non-cancer pain or pain in special population groups.

4.4.2.3 Low Prescription of Opioids in India due to Unaffordability

India is among the largest producers for legal opium, and opium cultivation is permitted in the states Madhya Pradesh, Rajasthan and Uttar Pradesh. Furthermore, India is the only country in which it is legally allowed to produce opium gum. However, India is among the lowest opioid consumer countries worldwide (3.2, Table 2). A single-center study from 2016 about drugs used in palliative care revealed, that for 64.14% of the patients, opioids were prescribed, mostly when experiencing moderate and severe pain. 63.5% of patients with severe pain received morphine, while 54.5% received tramadol. Tramadol was more frequently prescribed than morphine for mild (3.2%) and moderate pain (42.1%) [154]. In further single-center studies from 2016 and 2019 is was shown that tramadol was also used for non-cancer pain. The most frequently prescribed opioid in an outpatient department for orthopedics was tramadol for 6.1% of the patients, and in perioperative periods for 2.8% of the patients, respectively. In a general surgery department, the prescription rate of tramadol was 1.6%, while about 20% of the patients did not receive any analgesic. During the intraoperative period fentanyl was mostly used (59.6%-93%) [155, 156].

However, in general, in the whole country for palliative care only 4% of the needed morphine doses are made available to patients. Although fentanyl and morphine are easily available in

private health facilities, they are rather expensive and not affordable for many people in public facilities. In addition, their availability is limited in general hospitals, and patients often need to travel large distances and even to other states to receive treatment. This causes additional costs which are difficult or impossible to afford for many people, especially considering that 22% of India's population live below the poverty line [157].

4.5 Africa

With a population of over 1.3 billion inhabitants in 2020, Africa is the 2nd most populated region on earth, with > 16.5% of the total world population [51]. Although the median age in Africa is 19.7 years and thus the demographic profile of the population of Africa is relatively young in general, cancer is an emerging public health problem. Ageing, growth of the population and civilizational risk factors such as smoking, obesity, physical inactivity as well as infections, such as HPV or HIV, are fundamental factors for the increase of cancer patients [126, 158]. In 2018 about 752,000 new cancer cases and 506,000 cancer deaths occurred in sub-Saharan Africa, corresponding to 4% of all global cancer deaths [126]. Due to the wide-spread limitations in early detection and curative treatment, about 80% of cancer patients in Africa are diagnosed only at advanced stages. Thus, palliative pain relief is often the only possible way of treatment. However, in 2008 only 10% of the for morphine and equivalent opioids quantity needed for the treatment of late stage cancer and HIV patients was available, indicating that the majority of patients suffering from severe pain cannot be adequately treated [158].

The following chapters will highlight two African countries. South Africa showed the 4th highest average consumption of narcotic drugs in Africa and ranks 78th globally, while Rwanda, with only 19 S-DDDs per million inhabitants, ranks 22nd of African countries and number 148 globally (Table 2) [44].

4.5.1 South Africa

With a population of approximately 59 million people, South Africa is the fifth most populated country in Africa and ranks 25th in the worldwide list of countries by population, contributing about 0.76% of the total world population. 66.7% of the population is urban and the median age in South Africa is 27.6 years [51]. The population in South Africa is mostly young to middle aged (see Appendix 3). South Africa is a parliamentary republic and composed of nine provinces.

In 2018, 107,467 new cancer cases were recognized in South Africa and 57,373 people died because of cancer. The most frequent types of cancer were prostate, breast, cervix and lung cancer, together accounting for over 40% of all cancer cases [159]. The 5-year survival rate for breast cancer patients was only 53,4% between 1995 and 2009 [160].

The prevalence of chronic pain in the South African adult population is 18%, with the majority of patients reporting chronic pain in limps and back. Woman and elderly people were more affected. As the current median age of the South African population is below 30 years, but life expectancy is currently rising, the prevalence of chronic pain is expected to increase [161].

4.5.1.1 Legal Control of Opioid Prescription – MRSA 101

In South Africa the South African Health Products Regulatory Authority (SAHPRA) is responsible for registration, monitoring, regulation and control of pharmaceutical health products for human and animal use, which also includes scheduled substances. SAHPRA is an independent entity of the National Department of Health under the South African Government and reports to the National Minister of Health [162].

To fulfill the obligations of the UN Single Conventions, South Africa implemented the **Medicines and Related Substances Act 101 of 1965 (MRSA 101)**, as amended [163]. This Act is structured into 40 sections (sec) including definitions (sec 1), information on the drugs control council (sec 2-9), information on the drugs control board (sec 10-11), information on the registrar of drugs and the drugs register (sec 12-13), prohibition on the sale of drugs which are not registered (sec 14), information to registration and certificates (sec 15-17) and also control of medicines and schedules substances (sec 22A.) or penalties (sec 30), and other sections.

This Medicines Act classifies medicines and substances into Schedule 1 to Schedule 8 substances. These Schedules also define the eligibility on prescribing such medicines. The opioids usually used in pain management, such as morphine, hydromorphone, codeine, oxycodone and fentanyl, are all classified as Schedule 6 substances. These Schedule 6 drugs can be sold by a pharmacist, pharmacist intern or a pharmacist's assistant, and by a manufacturer or wholesale dealer in pharmaceutical products, being holder of a respective license (sc 22A. (5) (a-c)). Prescription and supply are allowed by a medical practitioner or a dentist but also by a nurse or a person registered under the Health Professions Act,1974 but only for the indication for use of those medicines and to patients under their care and within their scope of practice (sc 22A. (5) (s-f)). The prescribed medicine needs to be recorded in a prescription book or other permanent record (sc 22A. (6) (a)) and it shall only be sold if the treatment periods does not exceed 30 consecutive days. It is not clarified which information needs to be recorded when prescribing a schedule 6 drug [162].

4.5.1.2 Clinical Guidelines addressing Paediatric Pain

The South African Cancer Pain Working Group published the **Guide to the Treatment of Cancer Pain in South Africa** [164] to provide a reference guide on the management of pain for all healthcare providers. The guideline provides recommendations for the management of cancer pain in adults and in children. It is mainly based on four guidelines for pain management in adults from the Scottish Intercollegiate Guidelines Network, the European Society for Medical Oncology, the European Association for Palliative Care and the National Institute for Health and Clinical Excellence, and on one guideline for pain management in children from the WHO.

The guideline provides a stepwise healthcare intervention plan for pain, including an analgesic ladder for nociceptive pain and a pharmacotherapeutic approach to neuropathic pain. For the prescription of strong opioids, guidance from a specialist is recommended for adult patients with advanced and progressive disease and which have moderate to severe renal or hepatic impairment. For patients with no such impairment, dose titration is recommended, with a starting dose of 20-30 mg of oral sustained-release or 5 mg of immediate-release morphine for rescue

doses during titration. Usual starting and maintenance oral doses of opioid analgesics in adults are listed for codeine, dihydrocodeine, tramadol, morphine, hydromorphone and oxycodone, and recommendations to alternative systemic routes of opioid administration, including dose conversation ratios, are provided. For children, age-appropriate pain assessment tools are presented in the guideline. The stepwise treatment of paediatric pain with analgesic medication differs from the approach for adults, for example codeine and tramadol are not recommended for use in children with step 2 pain. Furthermore, the starting doses for opioid analgesics differ depending on the patient's age. For example, for oral morphine (immediate-release) they range from 80-200 µg/kg every 4 hours for children aged 1 month to 1 year, to 200-400 µg/kg every 4 hours for children up to 2 years and to 200-500 µg/kg every 4 hours for children up to 12 years, with a maximum daily dose of 5 mg [164].

The **South African guideline for the use of chronic opioid therapy for chronic non-cancer** pain was developed to assist practitioners by providing recommendations for the use of opioids for chronic non-cancer pain [165]. The basis of this guideline are four international guidelines from the British Pain Society, the American Pain Society, the Canadian National Opioid Use Guideline Group and the American Society of Interventional Pain Physicians. Opioids should not be the first line choice but can be included in the pain management for moderate to severe chronic pain. Non-injectable opioids available in South Africa are buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, codeine, dihydrocodeine and tramadol. For those oral opioids, the guideline suggests initial doses and titration. Equianalgesic doses for conversion from one oral opioid to another opioid are given, as well as approximate equipotent doses for conversion from oral morphine to transdermal opioids. Overall the guideline emphasizes that prior to initiating a chronic opioid therapy as well as during the therapy, appropriate evaluation, including biopsychosocial screening and risk screening, is essential [165].

In addition, South Africa has several **Standard Treatment Guidelines** available for hospital level paediatrics as well as hospital adult and primary health care levels, in order to ensure that all those levels provide essential services for a wide range of chronic and acute pain conditions.

All three mentioned standard treatment guidelines contain a list of essential medicines from the Essential Drugs Programme from the Department of Health. All essential medicines stated on that list, including opioids such as tramadol and morphine, should be available in care clinics, community health centers and at hospitals. The availability must be ensured by the respective (provincial) Pharmaceutical and Therapeutics Committees [166-168].

4.5.1.3 General Availability of Opioids but Indications for Misuse of OTC Opioids

The average consumption of opioids in South Africa decreased between 2006 and 2018 (see 3.2, Table 2). However, the data on prescription of opioids in South Africa is very limited. A survey from 2010 in palliative care facilities in Sub-Saharan Africa, in which South Africa represented 43.5% of the participating facilities, displayed that 58.1% of all participating facilities dispensed opioids for palliative care. A major part of the prescribed weak opioids was accounted for by codeine, with 45% of prescriptions, followed by dihydrocodeine and tramadol. Morphine was the most frequent

prescribed strong opioid accounting with over 82% of prescriptions. The survey mentions that the availability of weak and strong opioids was not always 100% in all facilities. However, the survey does not indicate for which of the Sub-Saharan countries this was the case [169]. Since opioids are listed on the South African Essential Medicines List (see 4.5.1.2), they would be expected to be generally available in public health care facilities in South Africa.

In South Africa, codeine containing medicines are available as OTC-drugs or as prescribed formulations. Especially the OTC products are subject of misuse. A study from 2014 on misuse of codeine-containing medication revealed that 2.6% of all treatment admissions at specialist drug treatment centers involved codeine misuse or codeine dependence as a primary or secondary substance of abuse [170]. However, general studies on the prevalence of opioid misuse are missing. Due to the growing misuse of codeine-containing medicines, SAHPRA is currently reviewing the scheduling status of codeine [171].

4.5.2 Rwanda

The current population of Rwanda is approximately 13 million, which equivalents to 0.17% of the total world population. With this, Rwanda ranks number 76 in the list of countries by population in the world and rank 28 in the list of African countries. 17.6% of the Rwandan population is urban and the median age in Rwanda is 20.0 years [51]. Rwanda shows a classical expansive population pyramid with a high birth rate and a low life expectancy (see Appendix 3).

In 2018 Rwanda reported 10,704 new cancer cases, with the majority cases contributed by prostate, liver, breast and cervix cancer. Over 7,000 people died due to cancer [172].

For Rwanda no studies on chronic pain prevalence in general are available. However, lower back pain is the second highest cause of disability in Rwanda, with an increase of 41.8% from 2007 to 2017 [173].

4.5.2.1 Legal Control of Opioid Prescription - Law N°03/201 and Order Nº 001

The Rwandan Food and Drugs Authority was established in 2018 as affiliated institution of the Ministry of Health, and is the regulatory board for ensuring the quality, safety and efficacy of food and pharmaceutical products. The division of Drugs and Health Technologies Assessment and Registration of the Rwandan FDA is responsible for regulating clinical trials, licensing, as well as for inspection and approval of human and veterinary medicines, vaccines and medical devices, amongst others [174]. All activities related to narcotics and other controlled substances are under the responsibility of the Ministry of Health itself.

In Rwanda, opioids are regulated in **Law N°03/201 governing narcotic drugs, psychotropic substances and precursors (Law N°03/201)**, which implements the treaties of the UN Single Convention on narcotic drugs 1961 ratified by the Rwandan Presidential Order n° 172/14 of 16/04/198. The law is structured in three chapters: Chapter I General Provision (art 1-5), Chapter II Licit Narcotic Drugs and Psychotropic Substances (art 6-22) and Chapter III Miscellaneous, Translational and Final Provisions (art 23-31) [175].

In Law N°03/201, narcotic drugs and psychotropic substances are classified in three categories: category I includes four tables that further categorize narcotic drugs, category II includes four tables for psychotropic substances and category III contains information on drug precursors. Category I Table I includes chemicals that are considered to result in a heavy addiction and lead to abuse. Category I Table II includes chemicals that are considered to cause less severe addiction and result in less abuse than those of table I and includes most of the medicinal opioid drugs such as codeine, morphine, fentanyl, oxycodone and hydromorphone. Category I Table III includes preparations that contain narcotic drugs that are legitimate for medical purposes. Those preparations are composed in such a manner that they are less likely to be abused and that they cannot be easily used produce a strong narcotic drug. Table IV includes certain narcotic drugs already listed in in Table I that are considered as particularly harmful due to their properties and their potential of abuse [175].

Narcotic drugs are restricted to medical and research purposes only (art 7). Private or public enterprises, when authorized, can produce narcotic substances, but only up to the maximum quantity as annually determined by the Minister of Health (art 8). Record keeping for 10 years is required for *"[…] the quantities of the narcotic drugs […] that he/she has imported, acquired, made, used, he/she retains or has destroyed. [..] the dates of the transactions and the names of his / her suppliers."* (art 7). Furthermore, the quantities of drugs that were used, destroyed, or that are in storage, must be submitted to the Minister of health in an annual report. Pharmacists, business or hospital institutions, medical doctors and veterinary personnel, qualified dentists and midwives as well as nurses are legally allowed to acquire and store narcotic drugs, if they are being qualified and licensed or authorized for their profession (art 16). Opioids can be prescribed by medical practitioners, dentists, veterinaries, qualified midwifes and nurses (art 17). Pharmacists, nurses and midwifes are furthermore authorized to prepare and distribute narcotic drugs, and any delivery needs to be recorded in a prescription book with prescriber information (name, address, title), patient information (name, address), date of delivery, quantity and description of the drug (art 18) [175].

In addition to Law N°03/201, a current categorization list of narcotic drugs is available in the **Ministerial Order Nº 001/MoH/2019 of 04/03/2019** (Order Nº 001) that establishes a List of Narcotic Drugs and their categorization. Law N°03/201 Table I narcotics are categorized in Schedule I as very severe narcotic drugs, Law N°03/201 Table II drugs are listed in Schedule II as severe narcotic drugs and Law N°03/201 Table III drugs are listed in Schedule III as simple narcotic drugs. Codeine, fentanyl, morphine and oxycodone are categorized as Schedule II drugs, while buprenorphine is categorized as Schedule III psychotropic substance [176].

4.5.2.2 One Clinical Guideline for Acute, Chronic Non-Cancer and Cancer Pain

The Ministry of Health under the Republic of Rwanda published **Pain management guidelines** to provide a resource for health care professionals in order to improve diagnosis, management and treatment. The guidelines document is based on clinical and high-risk conditions from facility reports and on current evidence-based knowledge. It combines recommendations for acute pain, chronic non-cancer pain and cancer pain and has a special section dedicated to pain related to

cancer treatments. Goals of a pain assessment are defined, and recommendations and tools for pain assessment are provided.

The treatment approaches are adapted from the WHO analgesic ladder but do in contrast to all other countries considered in this thesis provide a four stepped approach to medication. Opioids should be considered for step 2 and 3, similar to the WHO recommendation. For each of the stated pain classifications (acute, chronic non-cancer and cancer), management goals and strategies as well as al and pharmacological interventions are given, respectively. Opioids are recommended for acute pain, for example high doses of intravenous opioids, but also non-opioids such as paracetamol and NSAIDs are recommended for pain from burns during the rehabilitative phase. For non-chronic cancer pain, the recommendations mention short- to long term opioids, depending on the type of pain. However, no definition on short- or long-term opioids is given. For cancer pain, opioids are recommended as mainstay of cancer pain management, but no recommendations concerning the opioids of choice are provided. In addition, the guideline contains a comparative table with equianalgesic doses of morphine, hydromorphone, fentanyl, codeine, oxycodone and tramadol, and includes recommendations on starting doses for patients without previous opioid treatment and with and further without risk factors [177].

4.5.2.3 Morphine Production and Distribution under Government Control

Still in 2001, morphine was not readily available in Rwanda, and palliative care was almost not existent. In 2012, Rwanda launched the HRH (human resources for health) partnership between the Rwandan Ministry of Health and US consortia of academic medical centers, with the aim to increase the quality of health care and health professional education in Rwanda. In this collaboration Rwanda made great progress in the implementation of palliative care and was the first African country with a national palliative care policy [178]. Morphine was used prior to the national palliative care program only by anesthetists for post-operative pain. Due to further education and training of physicians, morphine is currently also prescribed for moderate and severe pain of cancer patients and other patients in end-of-life care. However, the import of morphine is expensive, and on average it is nearly six times more expensive in many poor counties than it is in wealthy ones. To date, Rwanda produces its own morphine, with production and distribution under government control. Every district pharmacy can request the necessary quantities of morphine from the Rwanda Biomedical Center. For patients the medication is free of costs [179].

Table 3: Comparison of the National Control Acts for the Regulation of Opioids in Germany, UK, Poland, Canada, Australia, India, Japan, South Africa and Rwanda

	INT [a]	Germany	UK	Poland	Canada	Australia	Japan	India	South Africa	Rwanda
	UN Single Convention [34]	**BtMG [180], BtMVV [56]**	**MDA [67], MDR [68]**	**ACDA [84]**	**CDSA [95], NCR [96]**	**NDA [117], SUSMP [119]**	**NPCA [132]**	**NDPS Act [146], G.S.R, 359(E) [148]**	**MRSA 101 [163]**	**Law N°03/201 [175], Order Nº 001 [176]**
Schedules classifying controlled substances	Schedule I to IV	Schedule I to III	Class A-C (MDA) Schedule 1-5 (MDR)	Group I-N to IV-N	Schedule I to VI	Schedule I to IV (CDSA) Schedule 1-10 (SUSMNP)	Table I-III	List of essential drugs (G.S.R. 359(E))	Schedule 1-8	Table I to IV (Annex Order Nº 001)
Classifi-cation for drugs commonly used for pain manage-ment [b]	Schedule I, codeine in schedule II, buprenor-phine in schedule III of the Convention on Psychotropic Substances (1971)	Schedule III	Schedule 2 (MDR), buprenor-phine in schedule 3	Group I-N	Schedule I	Schedule 8 (SUSMP)	Table I (except buprenor-phine) (Appendix)	All essential drugs except buprenorphine (G.S.R. 359(E), sc 52A)	Schedule 6	Schedule II, buprenor-phine Schedule III psychotropic substance (Annex Order Nº 001)
Definition of narcotic drugs	"drug" (art 1 1.(j))	"Betäu-bungsmittel" (BtMG, § 1)	No	"narcotic drug" (ACDA, art 4.26)	"narcotic" (NCR, reg 2 (1))	"drug" and "narcotic preparation"	"narcotic" (NPCA, art 1)	"essential narcotic drug" (NDPS Act, sc 2)	No	"narcotic drug" (Law N°03/201, art 2(5))

	INT [a] UN Single Convention [34]	Germany BtMG [180], BtMVV [56]	UK MDA [67], MDR [68]	Poland ACDA [84]	Canada CDSA [95], NCR [96]	Australia NDA [117], SUSMP [119]	Japan NPCA [132]	India NDPS Act [146], G.S.R, 359(E) [148]	South Africa MRSA 101 [163]	Rwanda Law N°03/201 [175], Order Nº 001 [176]
Definition of controlled substance	No	"Stoff" (BtMG, § 2)	No	No	No	No	No	"controlled substance" (NDPS Act, sc 2)	"scheduled substance" (sc 1)	"controlled substance" (Law N°03/201, art 2(5))
Indispensa-bility of narcotic drugs for pain relief stated	Yes (Preamble p. 13)	No	No	No	No	Yes, in Annex - UN Single Convention 1961	No	No	No	No
Prescribing restricted to	Not mentioned but medical prescriptions required (art 30 2. (b)(i))	Physician, dentist, veterinary for Schedule III drugs (BtMG, § 13, BtMVV §2-§4)	Physician, dentist, veterinary (MDA art 7 (3), MDR reg 7)	No, content of Pharmaceuti cal Law: physician, dentist, veterinary	Practitioner (physician, dentist, veterinary) (NCR reg 53 (2)). Exemptions for midwives and nurses (NCR reg 11)	Physician, dentist, veterinary	Physician, dentist, veterinary (art 3(2)(vii))	Medical practitioner, dentist (G.S.R 359(E), sc 52G)	Physician, dentist, veterinary, qualified practitioner or nurse (sc 14(4))	Physician, dentist, veterinary, qualified midwife or nurse (Law N°03/201, art 17)
Prescriptible drugs separately listed	No	Yes (BtMVV §2-§4)	No	No	No	No	No	Yes (G.S.R 359(E), sc 52A)	No	No

	INT [a] UN Single Convention [34]	Germany BtMG [180], BtMVV [56]	UK MDA [67], MDR [68]	Poland ACDA [84]	Canada CDSA [95], NCR [96]	Australia NDA [117], SUSMP [119]	Japan NPCA [132]	India NDPS Act [146], G.S.R, 359(E) [148]	South Africa MRSA 101 [163]	Rwanda Law N°03/201 [175], Order Nº 001 [176]
Max. quantity to prescribe stated	No	Yes (BtMVV §2-§4)	No	No	No	No	No	Yes, (G.S.R 359(E), sc 52A	No	No
Max. quantity within days stated	No	30 days (BtMVV §2-§4)	No, 30 days recom-mended	No	No	No	No	No	30 days (sec 22A (6))	No
Form required for prescription stated	For Schedule I drugs, written in official form (art 30 2. (b)(ii))	Numbered three-part official form "BtM"-prescriptions (BtMVV §8)	For Schedule 1-3 (MDR, reg 15)	No, content of ordinance of the Minister of Health of 8 March 2012 on medical prescriptions	No	No	Yes, prescription sheet (art 27(6))	No	No	No
Details on prescription form stated	No	Yes, details on patient, prescriber, product and date etc. (BtMVV §9)	Yes, details on patient, prescriber, product and date etc. (MDR reg 15)	No (see above)	No, different for provinces and territories	No, different for states and territories	Yes, details on patient, prescriber, product and date etc. (art 27(6))	Yes, details on patient, prescriber, product, date etc. (G.S.R 359(E), sc 52G)	No	No

	INT [a] UN Single Convention [34]	Germany BtMG [180], BtMVV [56]	UK MDA [67], MDR [68]	Poland ACDA [84]	Canada CDSA [95], NCR [96]	Australia NDA [117], SUSMP [119]	Japan NPCA [132]	India NDPS Act [146], G.S.R, 359(E) [148]	South Africa MRSA 101 [163]	Rwanda Law N°03/201 [175], Order Nº 001 [176]
Validity prescription form stated	No	7 days (BtMVV §12 (1) 1. c))	28 days (MDR, reg 16)	No	30 days	No, depending on state and territory	No	No	No	No
record of stock and disposition	Yes, (art 34 (b))	Yes (BtMVV §13-15	Yes (MDR reg 27)	Yes (art 44)	Yes (NCR reg 28.1. (d), reg 44 (2), reg 27.5 (d))	Yes, (SUSMP part 2 sc 4)	Yes (art 25)	Yes (G.S.R 359(E), sc 52M,X-Y)	Yes (sec 22A (6), sec 35(xxiii))	Yes (Law N°03/201, art 7, Art 22)
Adver-tisement	No statement whether allowed or forbidden	Not allowed for Schedule I drugs. For Schedule II and III only in circle of experts in industry or for physicians, dentists and veterinaries (BtMG §14 (3) and (4))	Not stated	Allowed (art 20.2, 68.)	Prohibited (NCR reg 70)	Prohibited (SUSMP part 3 sc 1)	Prohibited except for medical and pharmaceuti cal specialists/ researchers (art 29-2)	Not stated	Prohibited (sc 18(2))	Prohibited (Law N°03/201, art 21)
Statement on Pack Size	No	Yes (§2-5 BtMVV)	No	No	No	No	No	No	No	No

[a] INT stands for International

[b] considers codeine, fentanyl, morphine, oxycodone and buprenorphine

5. Alternatives to Opioids, Novel Approaches, and their Regulatory Status

Opioids are the most potent class of pain relievers available to date. Patients with acute or chronic cancer and non-cancer pain should have the right that their pain is effectively treated and that they receive medications prescribed by qualified practitioners to get relieved from their pain (see 3). Currently, opioids are indispensable for the relief of high degrees of pain and suffering, and their availability must be ensured for everyone in need (see 2.3, 3.2). However, opioids bear certain risks. They have a plethora of side effects (see 2.3.3) and they are frequently misused (see 3.3). Thus, there is a need to have alternatives to the current 'classic' prescription opioids and some of the recently discussed alternatives are highlighted in the following sections.

5.1 Cannabis as Opioid Substitute

Cannabis mainly contains cannabidiol (CBD) and tetrahydrocannabinol (THC) as pharmaceutically relevant substances. THC has analgesic, muscle relaxing, antiemetic and psychotropic effects. CBD is psycho-inactive and known to counterweight the psychoactive effects of THC, while also showing effects within the inflammatory system e.g. to decrease proinflammatory cytokines. In 2018, the use of medicinal cannabis was already legalized in 33 states in the US and in several other countries worldwide such as Australia, Canada, Germany, the UK, Poland and South Africa. In other countries medicinal cannabis is still considered as illegal, e.g. in India, Japan and Rwanda. In most countries, cannabis is also regulated according to the three described UN Conventions (see 3.1) but its use is not harmonized in terms of the relevant medical conditions or whether they are legal for any use or only as authorized by a physician. Furthermore, there is a high variability in cannabis products concerning the concentration of THC and/or CBD, and no established effective dose, nor an appropriate risk-benefit analysis based on this dose, are available for medicinal cannabis. However, a large amount of evidence already exists that cannabis or oral cannabinoids can be effective therapeutic agents for chronic pain, chemotherapy-induced nausea and vomiting, and for some symptoms of multiple sclerosis. In addition, studies showed that cannabis has an opioid-sparing effect. That means, when cannabis is administered together with opioids, a lower opioid dose is necessary to maintain the analgesia than without cannabis. However, cannabis is not effective for some pain conditions and multiple studies are sometimes contradictive. More studies are needed to clarify the efficiency of medicinal cannabis for different pain and other medical conditions, as well as to elucidate the current safety concerns, since cannabis was also shown to increase the risk of developing additional psychiatric conditions [181].

5.2 Novel Non-opioids

The development of new drug combinations and medications resulting in an effective analgesia without having an increased abuse potential is a very interesting outlook for pain management,

and several new drug candidates are under development. The fixed-dose combination of **dexketoprofen**, an NSAID, and **tramadol**, in an effective synergistic dose ratio 1:3, promises better pain relief than both drugs alone. Furthermore, lower doses of each of the drugs are necessary in their combination. Efficacy of the combination was shown for several moderate to severe pain indications such as soft tissue surgery or low back pain. In addition, the known adverse events rates are low. The orally administered fixed-dose combination of dexketoprofen 25 mg and tramadol 75 mg (DKP/TRAM FDC) was approved e.g. in Europe in 2016 [182].

Opioid Agonists such as **CR845 (difelikefalin)**, a kappa opioid receptor agonist that acts by selectively targeting peripheral kappa opioid receptors, or **NKTR-181 (oxycodegol)**, a long-acting, selective mu opioid receptor agonist, are also promising new drug candidates. CR845 showed a reduction in mean joint pain scores in a Phase IIB trial in patients with osteoarthritis of the hip or knee experiencing moderate-to-severe pain. Opioid-related side effects are reduced. Currently Phase II and Phase III trials are conducted for CR845 for acute and chronic pain but also for moderate to severe pruritus, e.g. for patients with chronic kidney disease or atopic dermatitis. The originator received a FDA “breakthrough therapy” designation for the treatment of pruritis associated with chronic kidney disease [183]. NKTR-181 is the first full mu opioid receptor agonist molecule for the relief of chronic pain, but without the high levels of euphoria. This also means that it has a lower abuse potential than standard opioids. However, the US Food and Drug Administration (FDA) Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee did not recommend the approval for oxycodegol (NKTR-181) during a meeting with the originator for discussing the New Drug Application. As a result, the New Drug Application was withdrawn [182, 184].

A large number of further opioid alternatives are currently under consideration or development. **TrkA** (Tropomyosin receptor kinase A) Inhibitors, were shown to significantly attenuate tumor-induced pain. Oliceridine (TRV130), which is a novel mu-receptor G-protein path-way selective modulator, was tested in patients with moderate-to-severe pain following abdominoplasty and the NDA for the medicinal product, Oliceridine, is currently evaluated by the FDA. **Antibodies** are a promising field of pain relieve research as well. Pharmacotherapy with anti-NGF (nerve growth factor) antibodies, that promote the sequestration of free NGF, has demonstrated promising experimental and clinical evidence for pain management and the FDA accepted the Biologics License Application (BLA) for Tanezumab for patients with chronic pain due to moderate-to-severe osteoarthritis [182, 185].

5.3 Gene Therapy

It is thought that the downregulation of voltage-gated potassium (Kv) channels, e.g. by direct nerve injury, contributes to neuropathic pain. Downregulation of Kv genes with the use of viral vectors showed a significant pain relief in animal model. **NP2** Enkephalin for the treatment of intractable cancer pain reached Phase II of clinical studies. NP2 is a herpes simplex-based vector that expresses pre-proenkephalin, an endogenous opioid polypeptide hormone. Results from the

Phase II study are still missing. However, in Phase I NP2 was well tolerated in all subjects and pain relief was reported when patients received middle and high doses of NP2 [182].

6. Discussion and Conclusion

6.1 Implementation of the UN Single Convention 1961 into National Legislations

The current thesis outlined the international control of narcotic drugs by the **1961 United Nations (UN) Single Convention on Narcotic Drugs** (see 3.1) and evaluated the implementation of certain aspects, mostly regarding the path of opioids from manufacturer to patient, in the national legislations of countries, from different continents, of which national laws and guidelines for controlled substances in English and German language were available. The selected countries are Germany (4.1.1.1), UK (4.1.2.1), Poland (4.1.3.1), Canada (4.2.1.1), Australia (4.3.1.1), India (4.4.2.1), Japan (4.4.1.1), South Africa (4.5.1.1) and Rwanda (4.5.2.1).

The UN Single Convention sets out the minimum regulatory requirements for prescribing controlled drugs at national levels, but the states are allowed to enforce stricter controls if necessary. However, the drug schedules of the UN Single Convention do not necessarily correspond to those in the national laws (see Table 3).

The criterion of the **indispensability of narcotic drugs** for pain relief was not incorporated in any of the national laws and regulations except in Australia, where the UN Single Convention is annexed to the NDA and thus, the criterion can be found there. This statement was included to underline the importance of keeping a balance between **provision and punishment**. To strengthen the medicinal importance of narcotic drugs and especially opioids, and implementation of this statement into national laws and regulations would be a benefit. Studies indicate that also the further measures proposed by the UN Single Convention are not always incorporated completely in the national laws of each country that ratified it, and thus not all national laws fulfil the recommended criteria on drug availability. In 2014 statutory drug control legislations of 15 countries were reviewed against the provisions of the UN Single Convention. It was found that only 13% of the countries incorporated the criterion of the indispensability of narcotic drugs for pain relief in their national law, 20% established the government's responsibility for ensuring adequate provision to ensure the availability of narcotic drugs and only 33% implemented a special administrative body that is responsible for international drug control conventions in their country [186].

In most countries, the major goal of the legislations for the control of narcotic substances is to avoid the misuse of narcotic drugs by restricting their availability. Mostly the drugs are classified according to their abuse potential, and offences against the law and resulting punishment cover a large part of the of the main laws for controlled substances. However, many of the countries have additional regulations for legal use and related activities, such as production, possession and

prescription. Only Poland, Japan and South Africa seem to have no additional regulations available (Table 3). However, regarding the selected aspects which have been compared in Table 3, the Japanese NPCA law covers the same amount of information and topics as other countries that have both laws and additional regulations. Therefore, having only one law or one additional regulation is equally practicable in principle, if all relevant information is included in those.

Almost every country has a different **scheduling systematic** for the classification of narcotic drugs. Canada is the only country which has four schedules, as recommended in the UN Single Convention. The UN Single Convention classified fentanyl, morphine and oxycodone under Schedule I, which requires most strict control, while codeine is listed under Schedule II and buprenorphine is considered as a psychotropic substance. Only India and Japan also did not classify buprenorphine as narcotic substance. The other countries capture all six medicinally relevant opioids for pain management under the strictest schedule for narcotic substances, in line with the UN Single convention (see 3.1).

All states mention, either in their law or in the regulations, which professions are legally **allowed to prescribe** opioids. In all countries these comprises at least physicians, dentists and veterinarian. South Africa and Rwanda also include midwives and nurses. Canada includes those professions in their regulation as well, however with certain exceptions. These additional permissions for nurses and midwives most likely have their origin in respective health systems. In South Africa authorized nurses have already been allowed for decades to prescribe medicines, and play important additional roles in healthcare, e.g. in the context of nurse-managed services for HIV-positive patients in antiretroviral therapy programmes [187]. In South Africa, those authorizations are regulated in the Nursing Act, 1978 (Act 50 of 1878) and additional regulations. Also, in Rwanda registered nurses can prescribe medications, e.g. in palliative care and as such can also prescribe narcotics [179] (Table 3).

Missing in most of the national legislations are provisions concerning the **maximum quantity** of opioids that may be prescribed, and within which period, the duration of the prescription validity, and what form the prescription needs to have. This information was only included in Germany and in part in the UK (Table 3), probably since it is no requirement according to the UN Single convention. For the other countries, those aspects are often covered by separate regulations, for example the ordinance of the Minister of Health of 8 March 2012 on medical prescriptions in Poland (see 4.1.3.1). However, since narcotic drugs are under special control, it could be beneficial if this kind of information would be stated in the respective laws or guidances for narcotic drugs. This would provide a greater transparency about all circumstances and requirements under which activities with controlled substances, such as possessing, prescribing and administering opioids, are prohibited and permitted. Furthermore, medical practitioners could be more confident about the legal framework within which they need to work. In case it would not be practicable to include all those details in one law or regulation, it would be at least beneficial to include such aspects into the main legislation for narcotic drugs and indicate the separate laws and regulations under which these aspects are captured.

Another observation is the **non-alignment of the narcotic drug legislation** in the devolved governments and legal jurisdictions in the constituent states (provinces, territories and countries) of the Commonwealth nations Australia and Canada, and partly UK, although the main law and guidance in the UK is applicable to all constituent states (see 4.1.2, 4.2, 4.3). Firstly, this complexity makes it difficult for prescribers relocating to a different constituent state. Secondly, patients traveling with opioid prescriptions might be faced with having a prescription which is not legal in some other constituent states. Although the devolved self-government of constituent states in the three countries is historically rooted, a higher level of alignment on the narcotic drugs legislations would be beneficial, especially considering the currently ongoing or arising opioid epidemics in these three countries.

In contrast, the Commonwealth nation India already **streamlined the control of opioids** among its states and territories. Opioids, such as morphine, fentanyl, methadone, oxycodone, codeine, and hydrocodone, were previously regulated under the state governments. Since 2014 they fall under the ambit of the Central Government (see 4.4.2.1). Prior to this change, the states differed in their regulations, comparably to Australia and Canada, in terms of prescription forms, the maximum number of allowed days for the supply of opioids, special authorization to prescribe opioids, amongst others. [188]. The implementation of the category of Essential Narcotic Drugs under the Central Government in India thus enables a harmonized approach for opioids prescription throughout the country.

In general, the **laws and guidelines** of all countries considered in this thesis **comply with the UN Single Convention** at least concerning the special aspects considered here (Table 3). The German BtMG and BtMVV provide the most comprehensive and detailed information, producing a comparably clear and transparent understanding of the permissions and restrictions for the parties that are involved in the handling of narcotic drugs for medical purposes. This might also result in a more confident and secure handling of opioids by health care providers, since the range of permissions is very clear. In contrast in many further countries there seems to be still the need to adjust their laws to fully embrace the UN Single Conventions goal in providing a balance between opioid drug availability and control and beyond to be more precise. Missing statements about a government's responsibility for ensuring the availability of medicines in national legislations, likely hinders health professionals and associations to convince government agencies that certain medical compounds should be made available for medical purposes. If the respective national regulations are not detailed or clear enough, this can result in over- or under-prescribing of opioids simply due to legal uncertainty.

Interestingly, South Africa is the only country considered here that has a separate rule in their law for *"Measures to ensure supply of more affordable medicines" (sc 15C)*. Here, the Minister has the right to define conditions to import more affordable medicines, when they are identical in composition and quality as medicines which are already registered in the country. To have such a statement incorporated in the law signalizes the awareness and the willingness of the government to ensure not only the availability but also the affordability of important medicines for patients.

6.2 Availability of Clinical Guidelines for the Use of Opioids in Pain Management

The availability of clinical guidelines addressing cancer, acute and/or chronic pain and including opioid therapy was evaluated as an indication for the acceptance of opioids for pain management in the respective country. For this, exemplary national guidelines available in English or German language have been selected for cancer, chronic and/or acute pain.

All countries in the present work had **national clinical guidelines in place** which address cancer pain, acute or chronic non-cancer pain, or all three (see 4.1.1.2, 4.1.2.2, 4.1.3.2, 4.2.1.2, 4.3.1.2, 4.4.1.2, 4.4.2.2, 4.5.1.2, 4.5.2.2). Opioids were an element of the pharmacotherapy in each of the chosen guidelines in every country considered. This implicates that the authors of the guidelines, and thus specialty societies and experts, consider opioids as standard practice in pain management. Although clinical guidelines alone do not establish the standard of care for individual patients, they nevertheless act as a source of guidance and assist the physician in taking decisions. Thus, the absence of clinical guidelines is likely not a factor that may lead to the low opioid consumption in some of the selected countries.

However, there are great differences between the guidelines. Firstly, major discrepancies exist in the **basis of the recommendations**. In some countries, the selected guidelines provide their recommendations weighted for the evidence. For example, Germany provides the recommendations in their S3 guidelines based on the Scottish Intercollegiate Guidelines Network (SIGN) system (weights 1++ to 4) and Australia rates the levels of evidence from I to IV, in each case, based on whether the evidence originates from randomised-controlled trials or from case series (see 4.1.1.2, 4.3.2). The selected NICE guidelines in the UK do not have such a rating system but express the certainty of their recommendations via their wording e.g. ‘must’ or ‘must not’ or ‘offer, ‘refer, ‘advice’ etc. (see 4.1.2.2). The guidelines in Germany, Poland and India are evidence based, for example on outcomes of randomised-controlled trials or current published studies. In contrast, the guidelines in South Africa are based on guidelines from Scotland, European Societies and the WHO (see 4.5.1.2). A special case are the Rwandan guidelines, which are based on clinical conditions selected from facility reports as well as by health experts and clinicians from different specialties (see 4.5.2.2). Nevertheless, the Rwandan guidelines cover acute pain, chronic non-cancer pain and cancer pain management. The UK, Canada, Australia and India seem not to have special guidelines for all three aspects of pain. Furthermore, patients with special needs, such as children, are considered as well in the Rwanda clinical guidelines, a feature that is also present in South African and Australian guidelines, but largely lacking in the guidelines from all other countries included in this thesis.

Also, the **kind of recommendations** for treatment schemes and options which are given in the respective guidelines vary. All guidelines, except the Australian one, provide such recommendations, which are mostly included as separate chapters. The Australian guideline provides the results from reviews, trials and studies, followed by rather general key messages, but no special recommendations (see 4.3.2) as consequences of these. In contrast, as the other extreme of the spectrum, Rwanda provides a cumulative guideline with a very detailed guidance

which has a handbook-like character (see 4.5.2.2). It must be noted that the health care system in Rwanda differs a lot from the Western Countries and politics as well as general economic issues also greatly influence the health care sector. Thus, the development of guidelines started much later in Rwanda than in other countries. In the light that healthcare professionals probably need increased amounts of guidance compared to Western Countries, this detailed and easy to understand guideline is a very valuable approach. Another interesting approach can be seen in the Japanese Clinical Practice Guideline for Chronic Pain. This guideline provides information and recommendations by answering questions that were envisioned to be asked by healthcare personnel (see 4.4.3.2), thus, taking the point of view of those professions to which the guideline is addressed.

Interestingly, most of the guidelines from the selected countries are generally based on the **three step WHO analgesic ladder** and its recommendations, at least for the treatment of cancer pain. However, the utility of the existing three step WHO analgesic ladder is currently under scientific debate since it was introduced over 30 years ago and was intended for cancer pain only. However, especially opioid analgesics are now widely used for acute and chronic non-cancer pain as well. Again, Rwanda has a different approach and provides a modified four step ladder, that also includes neurosurgical procedures such as the use of brain stimulators for the treatment of crises with chronic pain. In contrast, the Rwandan four-step ladder is bidirectional. For chronic pain and cancer pain a slow upward pathway from one step to the next can be considered, while for intense acute pain, uncontrolled chronic pain, and breakthrough pain, a faster downward direction can be used [189]. Since the Rwandan clinical guideline combines recommendations for acute pain, chronic non-cancer pain and cancer pain, this four-step ladder, unexpectedly, seems to be a more advanced approach compared to the widely used WHO three-step analgesic ladder that still serves as the basis for countries with, compared to Rwanda, very high healthcare standards and funding.

Overall it must be noted that the quality of each of the guidelines is **predominantly influenced by the data** it is based on. The British Medical Association recognized that, especially for opioids, there is not sufficient data and only limited evidence available, that opioids are efficient for treating long-term pain. With their briefing paper from 2017 they aimed to set out a range of recommendations for governments, policy makers and healthcare professionals, to support the safer prescribing of analgesic medicines. They suggest developing an evidence base by expanding research efforts, in order to better inform clinical practice. Furthermore, consideration should be given to the available range of support for doctors and patients, including sufficient investments and resources in primary care, and to ensure that multidisciplinary pain management services are available for all patients as required. Medical pain treatment competencies should be more trained and educated in all medical schools [76]. Naturally, these detailed recommendations are applicable to all countries, and especially but not exclusively to less developed countries. However, a worldwide effort for conducting well-designed, controlled trials seems to be a desirable essential effort for improving clinical guidelines in general and thus for improving the management of pain.

6.3 Are Prescription Opioids the Drivers of Opioid Crises?

From the countries analyzed in this work, **Australia** and **Canada** both have problems due to licit use of prescribed opioid medications and from illicit use. In Australia the use of legal or pharmaceutical opioids, mostly oxycodone, codeine and morphine, results in more deaths and hospitalization that the use of heroin (see 4.3.1.3). However, heroin use is higher in Australia that in Canada. In Canada in 2019 almost 4,000 apparent opioid related deaths occurred from both, prescription drug use and illicit drugs and the majority accounted for fentanyl (see 4.2.1.3). Here the illicit use of fentanyl is higher in Canada than in Australia. Overall, both countries experienced a downward trend in the total average opioid dosage prescribed in the 5 years to 2016–17 [122]. However, in the 10 years trend the overall S-DDD between 2006-2008 and 2016-2018 still increased by 6.3% for Canada and 33% for Australia (Table 2). The numbers also show, that the differentiation between illicit and licit opioids and adverse events resulting in hospitalization and overdose death, is difficult. Thus, a conclusion whether prescription opioids are the root of an opioid epidemic cannot be drawn when the data availability is not clearly distinguishable. Especially when having other countries in comparison, which have a liberalized opioid analgesic prescribing mentality which is not leading to an increase of addiction or overdose rates. For example in Germany in 2012 the one year prevalence of prescribed opioid analgesic problems in 870,000 health insures persons was 0.008% only [190].

The **United States (US)** was one of the first countries affected by an opioid epidemic. Although they are beyond the scope of this work, a brief insight into the impact of prescription opioids in their crisis might help to evaluate the impact of prescription opioids as drivers of opioid crisis. In the US, the opioid analgesic prescribing rates and drug overdoses increased in the past decade and led to an epidemic of drug overdose deaths. The CDC reported that since 2000, deaths from drug overdoses increased by 137%, and the rate of overdose deaths involving opioids, such as opioid pain relievers and heroin, rose by 200%. However, the substances tested in toxicological laboratory tests during autopsy vary by jurisdiction. This might result in an incomplete picture of substances involved in the overdose deaths. Secondly, in 2013, 22% of drug overdose deaths did not had any information about the specific types of drugs involved on the death certificate. And thirdly, because morphine and heroin are metabolized similarly, some deaths due to heroin might have been misclassified as morphine [191]. However, while data from CDC indicates continued increases in prescription opioid analgesic overdoses, other sources show that overall opioid prescribing and in special prescribing of hydrocodone and oxycodone, decline since 2012. While opioid analgesic prescribing rates and related overdoses decline, illicit fentanyl and heroin fuel the current epidemic in the US and not opioid prescribing. One explanation for this discrepancy is the CDC classification of opioids. As mentioned in 3.3, CDC includes fentanyl overdoses as prescription opioid analgesic overdoses and since 2014, illicit fentanyl and fentanyl analogs are the primary reasons for opioid analgesic overdoses. Thus, since 2016 fentanyl is de-aggregated from other prescription opioids. Furthermore, opioid analgesics are rather infrequently the cause of fatal drug overdoses, and opioid overdoses result primary from methadone or combinations of opioids with other drugs. Prescription opioid analgesics are often mentioned as the start or gateway to heroin. However, movement from prescription opioid abuse to heroin is infrequent. In a study with over

2.500 chronic pain patients only 0.27% developed an opioid use disorder and the prevalence is low in other studies as well (see also 2.3.3). Thus, the roots and the degree of the opioid epidemic in the US is rather based on other factors beside the pure opioid exposure. Those factors include preferential insurance coverage for drug over non-drug chronic pain therapies and aggressive marketing of extended release opioids. And after all, the current increase in opioid-related deaths accounts mainly for illicit opioids, such as fentanyl and heroin, and this process cannot be addressed by regulating the access to medical prescribed opioids [29]. Thus, the overall impact of prescription opioids on the US crisis seems to be lower than indicated by media.

In both countries, Canada and Australia, advertisement of narcotic drugs and thus of prescription opioids is prohibited (Table 3). Nevertheless, the opioid epidemic in Canada appears very similar to that in the US. Illicit and licit fentanyl and other fentanyl-related substances are a major driver of the crisis with over 70% off all opioid-related death accounting for those substances (see 4.2.1.3). The epidemic in Australia seems to have its roots indeed in prescription opioids. In 2016, 49% of all opioid deaths were caused by pharmaceutical opioids such as oxycodone, codeine and morphine. In addition, until 2018 codeine was available as over the counter (OTC) drug at pharmacies and the OTC codeine accounted for about 37% of all opioid purchases in 2013 (34). Although the UK is not officially facing an opioid epidemic and the opioid-related deaths remain rather stable considering yearly fluctuation, still the increasing prescribing rates of opioids are under observation. Especially the increase of the prescription of high dose and long-acting opioids and the increase in the prescribing period from opioid durations of 64 days to 102 days should be carefully watched (see 4.1.2.3) since the likelihood of long-term opioid use and misuse is associated with longer-duration and higher-dose initial opioid prescriptions [192].

Thus, as mentioned previously, reasons for an opioid epidemic are divers and they differ among the countries. For Australia the regulations such as making opioids available as OTC-drugs might have promoted the epidemic, while Canadas' epidemic was more influenced by the illicit market. If the UK really faces an opioid problem, the reasons need to be evaluated but probably the increase in opioid duration and high dose opioid prescription is one facet. Thus, the high prescription of opioid medications does not necessarily lead to an epidemic, since other factors, such as advertisement and insurance system as seen in the US, can trigger irresponsible overuse. While countries surely can learn and benefit from earlier experiences in other countries, the analysis and the resulting actions need to be taken individually.

6.4 Addressing the Problematic Availability and Use of Opioids through Regulatory Measures

In the last decade, the opioid availability increased globally, although certain countries faced a decrease and some still are below an adequate consumption level (see 3.2). Most of the countries discussed in the present work, Germany, the UK, Canada, Australia, Japan, India and Rwanda, increased their opioid consumption level between 2006 and 2018. However, India and Rwanda are still at or below a consumption level of 200 S-DDD per million inhabitants per day, which is considered to be inadequate. In South Africa and Poland, the opioid consumption level even

decreased in this period by 52% and 14%, respectively (see Table 2). For both countries, the reasons of this decrease could not be identified, and probably lie in aspects which were not part of this work.

Surveys on the formulary availability and regulatory barriers to the accessibility of opioids for cancer pain in various regions worldwide showed, that access to opioids is often impaired by regulatory barriers. In India, regulatory restrictions that limit the accessibility of opioids identified in such surveys included additional requirements, e.g. for physicians to receive a special license to prescribe opioids, for duplicate prescriptions, for special prescription forms, as well as prescription limits [188]. Similar restrictions have been identified in European, African and Asian countries [193-195]. While Germany has some of those restrictions implemented as well, they do however not result in an indication for limited accessibility to opioids.

Special prescription forms are required for Germany, the UK and Japan according to their laws and regulations for narcotic drugs. Poland has an additional ordinance which sets out the requirement for special prescription forms (see Table 3). Although it might be seen as additional effort for physicians to obtain special prescription forms for opioids, as this was evaluated for Poland [91], this should not be a burden. The use of specialized prescription forms for opioids allows the accurate monitoring of the number of single prescriptions, the quantity and type of prescribed drugs and allows early detection of opioid misuse in general or for certain opioid medications. For example, in some states of the US, special prescription drug monitoring programs were initiated as a result of the opioid epidemic in order to track dispensing of controlled substances and to detect diversion, abuse and misuse for prescription medications [196]. The only burden seen with special prescription forms is, that physicians might not be able to easily request them from the respective agency due to administrative hurdles, which need to be addressed and removed.

Whether the necessity for physicians to receive a **special license to prescribe opioids** is useful or a burden, depends on the clinical education system in the respective country. Persons need to proof their qualification for prescribing and dispensing opioids, which are under special control due to their abusive potential. This might be already implemented in the general education of physicians or an additional qualification is necessary. In each model, physicians need to be aware of the characteristics of pain and the risks and benefits of opioids, to minimize the risk of over prescription. For example, one aspect of tackling the opioid epidemics in US, Canada and Australia is the improvement of education and training of physicians on opioids, which was identified to be necessary in those countries [123].

Overall, probably **other barriers are more relevant** for the unequal availability of opioids for pain management. Not all countries have at least those opioids available that are listed under the WHO essential medicines list (see 2.3.2). For example, hydromorphone is not available in Poland and oxycodone has only been available since 2009 (see 4.1.3.2, 4.1.3.3). Thus, the administrative authorities should primarily ensure the **availability of all essential medicines** in their country as a first step.

Even if all essential opioids are available, they might not be prescribed sufficiently. One contributing factor can be the affordability of opioids. While opioids for pain management are

reimbursed by health insurance companies in some countries such as Germany (4.1.1.3), the reimbursement is limited to certain conditions and to certain opioids in other countries such as Japan (4.1.3.3) and in some countries, such as India, it is not affordable for the major population (4.4.2.3). As such, the **affordability** is a major aspect for the usage of opioids for pain management and this must be addressed in the health system of the respective countries.

Furthermore, cultural aspects lead to under- or over-prescription of opioids and involve prejudices, expectations and behavior of both, doctors and patients. Although Japan has a high amount of old and elderly population, the prescription of opioids is very low compared to other countries, and reasons for this are mostly the stigmatization of opioids and other cultural aspects (see 4.4.1.3). The education of patients and the general public is therefore another aspect which is addressed in countries already facing an opioid epidemic, such as US, Canada and Australia [123]. **Patients** should be **aware** of the availability and benefits of opioids for pain management, to not unnecessarily suffer from pain due to opiophobia. But they should also be aware of the risks when taking opioids over extended periods of time.

However, **regulatory measures are important** to not only ensure the availability of opioids for pain management, but also to regulate and adjust measures against an opioid misuse that could result in opioid epidemics. Canada and Australia responded differently to their opioid epidemics, which have different origins (6.3). Regulatory actions from Canada mainly focused on the treatment of opioid dependences, opioid overdoses and the regulation of illicit opioid production (4.2.1.4). In contrast, Australia implemented regulatory measures focusing on prescription and use of pharmaceutical opioids, such as reducing pack sizes for Schedule 8 opioids, revising their indications, introducing label warnings, and more (4.3.1.4).

Overall, the reasons for both, overuse and underuse of opioids for pain management, are divers and cannot be addressed only focusing on one aspect. But regulatory measures provide an important tool to react on certain developments that are often associated to local conditions, regarding the use of opioids.

7. Summary

Opioids constitute the to date most potent known class of pain relievers. However, great differences concerning the access of the general population to opioid drugs exist between countries. Although access to adequate pain management is a fundamental human right, these discrepancies often result in inappropriate treatment of cancer pain as well as non-cancer pain. On the other hand, an inadequacy of barriers to the general availability of opioids bears the risk of an epidemic opioid dependency, as currently evident in several countries worldwide.

This thesis provides a global overview on the availability and the regulation of controlled drugs, focusing on nine countries that were selected to illustrate the factors and barriers influencing opioid accessibility. The comparison of the national legislations in these countries is based on the respective legislation(s) for narcotic drugs. Aside from the main national laws and regulations on narcotic drugs, further specialized acts, e.g. for physicians, might exist in the respective countries,

which include additional information in a particular context. These are, however, beyond the scope of this work.

All countries considered in this thesis ratified the UN Single convention on narcotic drugs that dates from 1965. Still, the availability of narcotic drugs is highly imbalanced between the countries, as it was shown in a comparison of the average consumption overall and of certain opioids mainly used for pain management such as codeine, fentanyl, morphine and oxycodone between 2008-2008 and 2016-2018. While the national legislations implement the evaluated aspects of the UN Single Convention in general, they are highly divers in their level of detail. The outcome of this thesis considers a higher level of detail in the main legislations for narcotic drugs as beneficial, that in turn provides a greater transparency about all circumstances and requirements under which activities with controlled substances are prohibited and permitted and thus, about the legal framework within medical practitioners need to work. Furthermore, a higher level of alignment on the narcotic drugs legislations between the respective constituent states of the Commonwealth nations Australia and Canada is recommended, especially considering the currently ongoing opioid epidemics in these two countries.

To evaluate the acceptance of opioids for the pharmacotherapy of pain in general among health care professionals, exemplary national guidelines available in English or German language were selected that encompass the therapy of cancer, chronic and/or acute pain. All selected guidelines considered opioids as an element of the pharmacotherapy. However, the level of detail and the data basis of the recommendations is very divers. Furthermore, guidelines for all three types of pain, cancer, chronic or acute pain, are available in only a few of the selected countries, and special patient populations, such as children, were often not considered separately. Surprisingly, Rwanda, as a less developed country with a low opioid consumption, provides a comparatively more advanced approach by using a four-step analgesic ladder in their guidelines, while most of the guidelines from the other selected countries are generally based on the three step WHO analgesic ladder and its recommendations, at least for the treatment of cancer pain. As such, a worldwide effort for conducting well-designed, controlled trials seems to be a desirable essential effort to improve the clinical guidelines for pharmacotherapy with opioids, and thus for improving the management of pain in general.

Existing regulatory actions against an opioid epidemic or against an undersupply with opioids were highlighted as well. Regulatory measures provide an important tool to react on certain developments regarding the use of opioids. However, reasons and mechanisms for overuse and underuse of opioids for pain management are divers and often specific for the respective country. Thus, measures to reduce misuse or to increase the opioid availability cannot be addressed equally to all countries.

In conclusion, robust scientific data availability is crucial for legislative and regulatory frameworks, as well as for clinical guidelines. Only based on this principle, a safe and appropriate use of opioids and a balance between restrictions against abuse and permissions for pharmaceutical treatment can be achieved.

8. References

1. WHO. *Lexicon of alcohol and drug terms*. 2020 [cited 2020-10-03; Available from: https://www.who.int/substance_abuse/terminology/who_lexicon/en/.
2. Pathan, H. and J. Williams, *Basic opioid pharmacology: an update.* Br J Pain, 2012. **6**(1): p. 11-6.
3. *Opioids*, in *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. 2012, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD).
4. WHO, *Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines*. 2011, World Health Organization: Geneva.
5. Trivedi, M., S. Shaikh, and C. Gwinnut, *Pharmacology of opioids.* Anaesthesia Tutorial of the Week - Update in Anaesthesia, 2007: p. 118-127.
6. OECD, *Addressing Problematic Opioid Use in OECD Countries*. 2019, OECD Publishing, Paris: OECD Health Policy Studies.
7. INCB. *Narcotic Drugs*. 2020 [cited 2020-06-26; Available from: https://www.incb.org/incb/en/narcotic-drugs/index.html.
8. Mistry, C.J., et al., *Genetics of Opioid Dependence: A Review of the Genetic Contribution to Opioid Dependence.* Curr Psychiatry Rev, 2014. **10**(2): p. 156-167.
9. Stoeber, M., et al., *A Genetically Encoded Biosensor Reveals Location Bias of Opioid Drug Action.* Neuron, 2018. **98**(5): p. 963-976 e5.
10. *Chronic Pain has arrived in the ICD-11*. 2019 [cited 2020-06-07; Available from: https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=8340.
11. Schofield, P., *Pain in Older Adults: Epidemiology, Impact and Barriers to Management.* Rev Pain, 2007. **1**(1): p. 12-4.
12. Wiffen, P.J., et al., *Opioids for cancer pain - an overview of Cochrane reviews.* Cochrane Database Syst Rev, 2017. **7**: p. CD012592.
13. Harstall, C. and M. Ospina, *How Prevalent Is Chronic Pain?* Pain: Clinical Updates, International Association for the Study of Pain, 2003. **XI**(No. 2).
14. *Terminology and Information on Drugs*. 2016, United Nations Office on Drugs and Crime: New York.
15. Ballantyne, J.C., E. Kalso, and C. Stannard, *WHO analgesic ladder: a good concept gone astray.* BMJ, 2016. **352**: p. i20.
16. *WHO's cancer pain ladder for adults*. 2020 [cited 2020-03-10; Available from: https://www.who.int/cancer/palliative/painladder/en/.
17. *WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents*. 2018, World Health Organization: Geneva.
18. *World Health Organization Model List of Essential Medicines*. 2019, World Health Organization: Geneva.
19. WHO. *WHO Expert Committees*. 2020 [cited 2020-03-10; Available from: https://www.who.int/selection_medicines/committees/en/.

20. Colvin, L.A., F. Bull, and T.G. Hales, *Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia.* Lancet, 2019. **393**(10180): p. 1558-1568.

21. Benyamin, R., et al., *Opioid complications and side effects.* Pain Physician, 2008. **11**(2 Suppl): p. S105-20.

22. Consult, P., *Opioid-induced adverse effects and their management*, in *HemOnc Today*. 2009.

23. Lee, M., et al., *A comprehensive review of opioid-induced hyperalgesia.* Pain Physician, 2011. **14**(2): p. 145-61.

24. Taylor, D.R., *Managing Patients with Chronic Pain and Opioid Addiction*. 2015: Springer Cham Heidelberg New York Dordrecht London.

25. Moldovan, B.R., *'Opiophobia' Past and Present.* PPM Practical Pain Management, 2012. **5**(1).

26. Passik, S.D., K.L. Kirsh, and L. Webster, *Pseudoaddiction revisited: a commentary on clinical and historical considerations.* Pain Manag, 2011. **1**(3): p. 239-48.

27. Greene, M.S. and R.A. Chambers, *Pseudoaddiction: Fact or Fiction? An Investigation of the Medical Literature.* Curr Addict Rep, 2015. **2**(4): p. 310-317.

28. McCarberg, B.H., et al., *The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey.* Am J Ther, 2008. **15**(4): p. 312-20.

29. Rose, M.E., *Are Prescription Opioids Driving the Opioid Crisis? Assumptions vs Facts.* Pain Med, 2018. **19**(4): p. 793-807.

30. Alford, D.P., et al., *Primary Care Patients with Drug Use Report Chronic Pain and Self-Medicate with Alcohol and Other Drugs.* J Gen Intern Med, 2016. **31**(5): p. 486-91.

31. Stewart, W.F., et al., *Lost productive time and cost due to common pain conditions in the US workforce.* JAMA, 2003. **290**(18): p. 2443-54.

32. Perez-Hernandez, C., et al., *Observational Study Evaluating the Economic Impact of Breakthrough Pain in Cancer Patients in Clinical Practice in Spain: The IMDI Study.* Pain Ther, 2018. **7**(2): p. 227-240.

33. *The International Drug Control Conventions, Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol*. 2013, United Nations: Vienna.

34. *The International Drug Control Conventions, Schedules of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, as at 7 May 2020*. 1961, United Nations: Vienna.

35. *Convention on Psychotropic Substances of 1971*. 1971, United Nations: New York.

36. *United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988*. 1988, United Nations: New York.

37. INCB, *List of Narcotic Drugs under International Control*, in *edition 58*. 2019, International Narcotics Control Board: https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/58th_Edition/Yellow_List_-ENG.pdf.

38. *Progress in ensuring adequate access to internationally controlled substances for medical and scientific purposes - Report of the International Narcotics Control Board for 2018*. 2019, International Narcotics Control Board, United Nations.

39. *Demand for and supply of opiates used to meet medical and scientific needs*. 2005, UN. Economic and Social Council: New York.

40. *IASP Statement on Opioids*. 2018 [cited 2020-03-10; Available from: https://www.iasp-pain.org/Advocacy/Content.aspx?ItemNumber=7194.

41. *Declaration of Montreal*. 2010, International Association for the Study of Pain.

42. WHO, *Guidelines for ATC classification and DDD assignment 2020*, in *Oslo, Norway*. 2019, WHO Collaborating Centre for Drug Statistics Methodology: https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/.

43. WHO. *ATC/DDD Index 2020*. 2019 [cited 2020-06-26; Available from: https://www.whocc.no/atc_ddd_index/?code=N02AB03].

44. *Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes*. 2016, International Narcotics Control Board, United Nations.

45. INCB, *Narcotic Drugs - Estimated World Requirements for 2010 - Statistics for 2008*. 2009, International Narcotics Control Board, United Nations, New York 2010.

46. INCB, *Narcotic Drugs - Estimated World Requirements for 2020 - Statistics for 2018*. 2019, International Narcotics Control Board, United Nations, New York 2020.

47. Sumant, O. and K. Joshi. *Opioids Market by Product (Codeine, Fentanyl, Methadone, Oxycodone, Morphine, Hydrocodone and Others) and Application (Pain Management, Cough Treatment, and Diarrhea): Global Opportunity Analysis and Industry Forecast, 2019-2026*. 2019 [cited 2020-07-19; Available from: https://www.alliedmarketresearch.com/opioids-market.

48. UNODC, *Analysis of Drug Markets*, in *World Drug Report 2018*. 2018, United Nations: Sales No. E.18.XI.9. p. 1-72.

49. Seth, P., et al., *Quantifying the Epidemic of Prescription Opioid Overdose Deaths.* Am J Public Health, 2018. **108**(4): p. 500-502.

50. Hider-Mlynarz, K., P. Cavalie, and P. Maison, *Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe.* Br J Clin Pharmacol, 2018. **84**(6): p. 1324-1334.

51. Worldometer. *Countries in the world by population (2020)*. 2020 [cited 2020-03-01; Available from: https://www.worldometers.info/world-population/population-by-country/.

52. *Krebs in Deutschland für 2015/2016*. 2016, Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg): Berlin.

53. *Schmerz – Zahlen und Fakten*. 2012, Deutsche Schmerzgesellschaft e.V.

54. *Federal Opium Agency*. 2013 [cited 2020-06-26; Available from: https://www.bfarm.de/EN/FederalOpiumAgency/_node.html;jsessionid=B8C933094776A43F873E52562EC2695E.1_cid319.

55. *Gesetz über den Verkehr mit Betäubungsmitteln (Betäubungsmittelgesetz - BtMG)*. 1981, Bundesministerium für Justiz und Verbraucherschutz, Bundesamt für Justiz: http://www.gesetze-im-internet.de/btmg_1981/BJNR106810981.html.

56. *Verordnung über das Verschreiben, die Abgabe und den Nachweis des Verbleibs von Betäubungsmitteln (Betäubungsmittel-Verschreibungsverordnung - BtMVV)*. 1998, 2018, Bundesministerium für Justiz und Verbraucherschutz, Bundesamt für Justiz: http://www.gesetze-im-internet.de/btmvv_1998/BJNR008000998.html.

57. *Betäubungsmittel*. 2020 [cited 2020-03-10; Available from: https://www.bfarm.de/DE/Bundesopiumstelle/Betaeubungsmittel/_node.html.

58. *AWMF is a network of Scientific Medical Societies in Germany*. 2020 [cited 2020-07-21; Available from: https://www.awmf.org/en/awmf-online-portal-for-scientific-medicine/awmf-news.html.

59. *AWMF-Regelwerk Leitlinien: Stufenklassifikatio*. 2020 [cited 2020-07-21; Available from: https://www.awmf.org/leitlinien/awmf-regelwerk/ll-entwicklung/awmf-regelwerk-01-planung-und-organisation/po-stufenklassifikation.html.

60. *Erweiterte S3-Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung*, in *Leitlinienprogramm Onkologie*, D.K. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, AWMF), Editor. 2020, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.

61. Häuser, W., *2. Aktualisierung der S3 Leitlinie „Langzeitanwendungen von Opioiden bei chronischen nicht-tumorbedingten Schmerzen „LONTS“*, in *Der Schmerz 2020*. 2020.

62. *Zuzahlungsbefreite Arzneimittel nach § 31 Abs. 3 Satz 4 SGB V*. 2020, GKV Spitzenverband.

63. Schubert, I., P. Ihle, and R. Sabatowski, *Increase in Opiate Prescription in Germany Between 2000 and 2010.* Dtsch Arztebl Int, 2013. **110**(4): p. 45-51.

64. Rosner, B., et al., *Opioid prescription patterns in Germany and the global opioid epidemic: Systematic review of available evidence.* PLoS One, 2019. **14**(8): p. e0221153.

65. *Cancer Statistics for the UK*. 2020 [cited 2020-07-25; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk.

66. *Almost half of all UK adults may be living with chronic pain*. 2016 [cited 2020-08-12; Available from: https://www.nhs.uk/news/medical-practice/almost-half-of-all-uk-adults-may-be-living-with-chronic-pain/.

67. *Misuse of Drugs Act 1971*, in *c. 38*. 1971, UK Public General Acts, Parliament of the United Kingdom: http://www.legislation.gov.uk/ukpga/1971/38/contents.

68. *The Misuse of Drugs Regulations 2001*, in *No. 3998*. 2001, Statutory Instruments, Parliament of the United Kingdom: http://www.legislation.gov.uk/uksi/2001/3998/contents/made.

69. NHS, *Background for the safer management of controlled drugs*. 2007, NHS Business Services Authority.

70. *Controlled drug prescribing*. 2014, NHS Business Services Authority.

71. *Palliative care for adults: strong opioids for pain relief*. 2012, National Institute for Health and Care Excellence (NICE).

72. *Neuropathic pain in adults: pharmacological management in non-specialist settings*. 2013, National Institute for Health and Care Excellence (NICE).

73. Abdulla, A., et al., *Guidance on the management of pain in older people.* Age Ageing, 2013. **42 Suppl 1**: p. i1-57.

74. *Clinical guidelines*. 2020 [cited 2020-07-21; Available from: https://fpm.ac.uk/standards-publications-workforce-guidelines-publications/clinical-guidelines.

75. Quinlan, J., et al., *Perioperative opioid use and misuse.* Clin Med (Lond), 2019. **19**(6): p. 441-445.

76. *Chronic pain: supporting safer prescribing of analgesics*. 2017, British Medical Association: BMA House, Tavistock Square, London WC1H 9JP.

77. *Reducing Opioid-Related Deaths in the UK*. 2016, Advisory Council on the Misuse of Drugs: SW1P 4D. p. 1-59.

78. *Opioid Expert Working Group meets at MHRA* 2019, Medicines and Healthcare products Regulatory Agency, News centre MHRA: 10 South Colonnade, London, E14 4PU.

79. *Controlled drugs: safe use and management*. 2016, National Institute for Health and Care Excellence.

80. Religioni, U., *Cancer incidence and mortality in Poland.* Clinical Epidemiology and Global Health, 2020. **8**(2): p. 329-334.

81. Breivik, H., et al., *Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment.* Eur J Pain, 2006. **10**(4): p. 287-333.

82. *The Office*. 2016 [cited 2020-08-02; Available from: http://www.urpl.gov.pl/en/office.

83. *National Bureau for Drug Prevention*. 2010 [cited 2020-08-08; Available from: https://www.kbpn.gov.pl/portal?id=111568.

84. *Act of Law on Counteracting Drug Addiction*. 2005, Government of Poland: https://www.kbpn.gov.pl/portal?id=113884.

85. *Pharmaceutical Law*. 2001, Government of Poland: Journal of Laws from 2008, No. 45, item 271, https://www.gif.gov.pl/download/3/5000/PharmaceuticalLaw-June2009.pdf.

86. Machota, M., et al., *The prescription is a tool for supervision and control of the turnover of reimbursed drugs - legal regulations.* Journal of Public Health, Nursing and Medical Rescue, 2018(5): p. 1-5.

87. Wordliczek, J., et al., *Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons.* Pol Przegl Chir, 2018. **90**(4): p. 55-84.

88. Szczudlik, A., et al., *Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the study of pain and the Polish Neurological Society - part one.* Neurol Neurochir Pol, 2014. **48**(4): p. 262-71.

89. Szczudlik, A., et al., *Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society - Part Two.* Neurol Neurochir Pol, 2014. **48**(6): p. 423-35.

90. *Poland Country Drug Report 2019*. 2019, European Monitoring Centre for Drugs and Drug Addiction.

91. Dzierzanowski, T. and A. Cialkowska-Rysz, *Accessibility of opioid analgesics and barriers to optimal chronic pain treatment in Poland in 2000-2015.* Support Care Cancer, 2017. **25**(3): p. 775-781.

92. *Cancer-specific statistics 2020*. 2020, Canadian Cancer Society, Government of Canada.

93. Jacquelyn J. Cragg, et al., *Prevalence of chronic pain among individuals with neurological conditions*, in *Health Reports*. 2018, Authority of the Minister responsible for Statistics Canada: Ottawa. p. 11-16.

94. Schopflocher, D., P. Taenzer, and R. Jovey, *The prevalence of chronic pain in Canada.* Pain Res Manag, 2011. **16**(6): p. 445-50.

95. *Controlled Drugs and Substances Act*, in *S.C. 1996, c. 19*. 1996, Government of Canada: https://laws-lois.justice.gc.ca/eng/acts/C-38.8/index.html.

96. *Narcotic Control Regulations*, in *C.R.C., c. 1041*. 2019, Minister of Justice Government of Canada: https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._1041/.

97. *Narcotics Safety and Awareness Act, 2010*, in *S.O. 2010, c. 22 - Bill 101*. 2010, Government of Ontario: https://www.ontario.ca/laws/statute/s10022.

98. *Drug Interchangeability and Dispensing Fee Act*, in *R.S.O. 1990, CHAPTER P.23, Last amendment: 2016, c. 6, Sched. 1, s. 2.* 2016, Government of Ontario: https://www.ontario.ca/laws/statute/90p23.

99. *Ontario Regulation 381/11*, in *under Narcotics Safety and Awareness Act, 2010, S.O. 2010, c. 22*. 2011, Government of Ontario: https://www.ontario.ca/laws/regulation/110381.

100. Busse, J.W., et al., *Guideline for opioid therapy and chronic noncancer pain.* CMAJ, 2017. **189**(18): p. E659-E666.

101. *Cancer Pain*, in *Clinical Practice Guideline*. 2018, Alberta Health Services.

102. Loeffen, E.A.H., et al., *Reducing pain in children with cancer: Methodology for the development of a clinical practice guideline.* Pediatr Blood Cancer, 2019. **66**(6): p. e27698.

103. *Prescription Opioids*, in *Canadian Drug Summary*. 2020, Canadina Centre on Substance Use and Addiction.

104. *Federal Actions on Opioids to Date*. 2020 [cited 2020-07-27; Available from: https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/federal-actions/overview.html.

105. *Royal Assent of Bill C-37 - An Act to amend the Controlled Drugs and Substances Act and to make related amendments to other Acts*. 2017 [cited 2020-07-27; Available from: https://www.canada.ca/en/health-canada/news/2017/05/royal_assent_of_billc-37anacttoamendthecontrolleddrugsandsubstan.html.

106. *Government of Canada Actions on Opioids: 2016 and 2017*, G.o. Canada, Editor. 2017, Health Canada: Ottawa, ON K1A 0K9. p. 1-17.

107. *Authorized Canadian naloxone Nasal Spray (NARCAN) coming to market*. 2017 [cited 2020-07-27; RA-63784:[Available from: https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/63784a-eng.php#public-public.

108. *Special Access Programme - Drugs*. 2018 [cited 2020-07-27; Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/special-access-programme-drugs-1.html.

109. *Government of Canada enables new access to drugs in urgent public health situations*. News Release 2017 [cited 2020-07-27; Available from: https://www.canada.ca/en/health-canada/news/2017/06/government_of_canadaenablesnewaccesstodrugsinurgentpublichealths.html.

110. *Regulations Amending the Precursor Control Regulations (Fentanyl Precursors)*, in *SOR/2016-294, P.C. 2016-982*. 2016, Health Canada: http://www.gazette.gc.ca/rp-pr/p2/2016/2016-11-30/html/sor-dors294-eng.html.

111. *5-year relative survival*. National Cancer Control Indicators 2020 [cited 2020-07-25; Available from: https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/5-year-relative-survival.

112. *Distribution of cancer stage*. Cancer control continuum 2020 [cited 2020-07-25; Available from: https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/5-year-relative-survival.

113. *Cancer data in Australia*. 2020 [cited 2020-07-25; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data.

114. *Chronic pain in Australia*. 2020, Australian Institute of Health and Welfare: Canberra.

115. *Office of Drug Control (ODC)*. [cited 2020-06-11; Available from: https://www.odc.gov.au/about.

116. *Health Products Regulation Group: Regulatory Science Strategy, 2020-2025*. 2020 16 January 2020 [cited 2020-06-11; Version 1.0, November 2019:[Available from:

https://www.tga.gov.au/publication/health-products-regulation-group-regulatory-science-strategy-2020-2025.

117. *Narcotic Drugs Act 1967*, in *Compilation No. 13, Authorised Version C2016C01132*. 2016, Office of Parliamentary Counsel, Canberra: https://www.legislation.gov.au/Details/C2016C01132.

118. *Therapeutic Goods (Charges) Act 1989*, in *Act No. 21/22 of 1990 as amended up to Act No. 8, 2018*. 2018, Australian Government: https://www.legislation.gov.au/Details/C2018C00066.

119. Rebera, A., *Poisons Standard (No. 2) June 2020*, in *made under subsection 52D(2) of the Therapeutic Goods Act 1989*. 2020, Australien Government, delegate of the Secretary to the Department of Health: https://www.legislation.gov.au/Details/F2020L00639.

120. Hua AC, S.F., Ge X., *Correction: State-based legal requirements for Schedule 8 prescriptions: why so complicated?* Med J Aust, 2015. **203**(8): p. 320.

121. Schug, S.A., et al., *Acute Pain Management: Scientific Evidence (4th edition)*. 2015, ANZCA & FPM, Melbourne.

122. *Opioid harm in Australia and comparisons between Australia and Canada*. 2018, Australian Institute of Health and Welfare: Canberra.

123. TGA, *Prescription strong (Schedule 8) opioid use and misuse in Australia – options for a regulatory response*, in *Consultation Paper*. Therapeutic Goods Administration.

124. *Prescription opioids: Information for health professionals*. 2020 29 May 2020 [cited 2020-06-12; Available from: https://www.tga.gov.au/prescription-opioids-information-health-professionals.

125. *Summary of PBS opioid listings for the treatment of pain as of 1 June 2020*. 2020, Department of Health - Australian Government.

126. Jemal A, T.L., Soerjomataram I, Bray F *The Cancer Atlas*, in *The Cancer Atlas*. 2019, The Amercian Cancer Society, INC.

127. Sankaranarayanan, R., K. Ramadas, and Y.L. Qiao, *Managing the changing burden of cancer in Asia.* BMC Med, 2014. **12**: p. 3.

128. Nagao, M. and S. Tsugane, *Cancer in Japan: Prevalence, prevention and the role of heterocyclic amines in human carcinogenesis.* Genes Environ, 2016. **38**: p. 16.

129. Yamaguchi, T., et al., *Recent developments in the management of cancer pain in Japan: education, clinical guidelines and basic research.* Jpn J Clin Oncol, 2012. **42**(12): p. 1120-7.

130. Inoue, S., et al., *Chronic Pain in the Japanese Community--Prevalence, Characteristics and Impact on Quality of Life.* PLoS One, 2015. **10**(6): p. e0129262.

131. *Pharmaceutical Administration and Regulations in Japan*, in *Regulatory Information Task Force Japan Pharmaceutical Manufacturers Association*. 2020, Pharmaceutical Manufacturers Association Japan: http://www.jpma.or.jp/english/parj/pdf/2020.pdf. p. 1-191.

132. *Narcotics and Psychotropics Control Act*, in *Amendment of Act No. 50 of 2015*. 1953, Government of Japan: http://www.japaneselawtranslation.go.jp/law/detail/?printID=&id=2849&amp%3Bvm=04re%3D02&vm=02.

133. Yamaguchi, T., et al., *Clinical guideline for pharmacological management of cancer pain: the Japanese Society of Palliative Medicine recommendations.* Jpn J Clin Oncol, 2013. **43**(9): p. 896-909.

134. Ushida, T., *Burdensome problems of chronic musculoskeletal pain and future prospects.* J Orthop Sci, 2015. **20**(6): p. 958-66.

135. Sumitani, M., et al., *Executive summary of the Clinical Guidelines of Pharmacotherapy for Neuropathic Pain: second edition by the Japanese Society of Pain Clinicians.* J Anesth, 2018. **32**(3): p. 463-478.

136. *Clinical Practice Guideline for Chronic Pain*, J.S.f.t.S.o.P. (JASP), Editor. 2018, The Committee for Clinical Practice Guideline for Chronic Pain.

137. Onishi, E., et al., *Comparison of Opioid Prescribing Patterns in the United States and Japan: Primary Care Physicians' Attitudes and Perceptions.* J Am Board Fam Med, 2017. **30**(2): p. 248-254.

138. Tannoury, C., et al., *Comparison of opioid use and prescribing patterns in orthopedic surgery in Japan and the United States: A JOA-AOA Traveling Fellowship Investigation.* J Orthop Sci, 2020. **25**(3): p. 520-524.

139. Onwuchekwa Uba, R., K. Ankoma-Darko, and S.K. Park, *International comparison of mitigation strategies for addressing opioid misuse: A systematic review.* J Am Pharm Assoc (2003), 2020. **60**(1): p. 195-204.

140. Suga, Y., et al., *Current Status of Adverse Events Related with Opioid Analgesics in Japan: Assessment Based on Japanese Adverse Drug Event Report Database.* Biol Pharm Bull, 2019. **42**(5): p. 801-806.

141. *Cancer Statistics*. 2020 [cited 2020-07-25; Available from: http://cancerindia.org.in/cancer-statistics/.

142. *Cancer Survival Rates by Country 2020*. 2020 [cited 2020-07-25; Available from: https://worldpopulationreview.com/country-rankings/cancer-survival-rates-by-country.

143. Saxena, A.K., P.N. Jain, and S. Bhatnagar, *The Prevalence of Chronic Pain among Adults in India.* Indian J Palliat Care, 2018. **24**(4): p. 472-477.

144. *Functions*. 2020 [cited 2020-07-16; Available from: https://cdsco.gov.in/opencms/opencms/en/About-us/Functions/.

145. *About CBN*. [cited 2020-07-16; Available from: http://cbn.nic.in/html/aboutcbn.htm.

146. *Narcotic Drugs and Psychotropic Substances Act*, in *The Gazette of India*. 1985, Parliament of India: http://www.cbn.nic.in/html/Acts.htm.

147. *Gazette Notification G.S.R. 359(E)*. 2015, Ministry of Finance, Department of Revenue, Government of India Press, Controller of Publications: The Gazette of India: Extraordinary, REGD. NO. D. L.-33004/99, http://www.cbn.nic.in/html/NDPS3rdamend.pdf.

148. *Notification S.O. 1761 (E) and S.O. 3448 (E)*. 2018, Ministry of Finance, Department of Revenue, Government of India Press, Controller of Publications: The Gazette of India: Extraordinary, https://dor.gov.in/.

149. *Notification S.O. 1181 (E)*. 2015, Ministry of Finance, Department of Revenue, Government of India Press, Controller of Publications: The Gazette of India: Extraordinary, http://www.cbn.nic.in/html/END05052015.pdf.

150. Ramanjulu, R., et al., *The Indian Society for Study of Pain, Cancer Pain Special Interest Group guidelines on pharmacological management of cancer pain (Part I).* Indian Journal of Pain, 2019. **33**(4): p. 11-17.

151. Thota, R., et al., *The Indian Society for Study of Pain, Cancer Pain Special Interest Group guidelines on pharmacological management of cancer pain (Part II).* Indian Journal of Pain, 2019. **33**(4): p. 18-29.

152. Ramanjulu, R., et al., *The Indian Society for Study of Pain, Cancer Pain Special Interest Group guidelines on pharmacological management of cancer pain (Part III).* Indian Journal of Pain, 2019. **33**(4): p. 30-36.

153. *Major Trauma*, G.o.I. Ministry of Health & Family Welfare, Editor. 2017, Standard Treatment Guidelines.

154. Menezes, V.H., et al., *Prescription Pattern of Analgesic Drugs for Patients Receiving Palliative Care in a Teaching Hospital in India.* Indian J Palliat Care, 2016. **22**(1): p. 63-6.

155. Mishra, R. and S.S. Keshari, *Prescription pattern of analgesics in outpatient department in a tertiary care teaching hospital in North India.* International Journal of Basic & Clinical Pharmacology, 2017. **6**(10): p. 2372-2374.

156. Joshi, S., et al., *An observational study to evaluate the prescription pattern of analgesics used in the perioperative period in a tertiary care hospital.* Perspectives in Clinical Research.

157. Salgaonkar, S., *At the opioid crossroad for chronic non cancer pain.* Indian Journal of Pain, 2018. **32**(2): p. 57-59.

158. Jemal, A., et al., *Cancer burden in Africa and opportunities for prevention.* Cancer, 2012. **118**(18): p. 4372-84.

159. *South Africa*, T.G.C. Observatory, Editor. 2019, International Agency for Reseach in Cancer, World Health Organization.

160. Vanderpuye, V., et al., *An update on the management of breast cancer in Africa.* Infect Agent Cancer, 2017. **12**: p. 13.

161. Kamerman, P.R., et al., *Almost 1 in 5 South African adults have chronic pain: a prevalence study conducted in a large nationally representative sample.* Pain, 2020. **161**(7): p. 1629-1635.

162. *SAHPRA - Who we are*. 2020 [cited 2020-06-13; Available from: https://www.sahpra.org.za/who-we-are/.

163. *Medicines and Related Substances Act (previously Drugs Control Act) 101 of 1965, as amended*, in *No. 1171*. 2017, South African Government: Government Gazette 40869, 26 May, 2017, https://www.sahpra.org.za/wp-content/uploads/2020/02/Government_Gazette_Medicines_and_Devices_Act_Jun_2017-1.pdf. p. 68-94.

164. *Guide to the Treatment of Cancer Pain in South Africa*. 2015, South African Cancer Pain Working Group, Medspec Publishing.

165. Raff, M., et al., *South African guideline for the use of chronic opioid therapy for chronic non-cancer pain.* S Afr Med J, 2013. **104**(1 Suppl 1): p. 78-89.

166. *Standard Treatment Guidelines and Essential Medicines List for South Africa*, in *Primary Health Care Level*. 2018, Republic of South Africa: National Department of Health.

167. *Standard Treatment Guidelines and Essential Medicines List for South Africa*, in *Hospital Level Paediatrics*. 2017, Republic of South Africa: National Department of Health.

168. *Standard Treatment Guidelines and Essential Medicines List for South Africa*, in *Hospital Level Adults*. 2015, Republic of South Africa: National Department of Health.

169. Harding, R., et al., *Provision of pain- and symptom-relieving drugs for HIV/AIDS in sub-Saharan Africa.* J Pain Symptom Manage, 2010. **40**(3): p. 405-15.

170. Van Hout, M.C., et al., *"Codeine Is My Helper": Misuse of and Dependence on Codeine-Containing Medicines in South Africa.* Qual Health Res, 2017. **27**(3): p. 341-350.

171. SAHPRA. *What is codeine?* 2020 [cited 2020-08-29; Available from: https://www.sahpra.org.za/what-is-codeine/.

172. *Rwanda*, T.G.C. Observatory, Editor. 2019, International Agency for Reseach in Cancer, World Health Organization.

173. *What health problems cause the most disability?* [cited 2020-07-25; Available from: http://www.healthdata.org/rwanda.

174. *About Rwanda FDA*. 2019 [cited 2020-08-29; Available from: https://rwandafda.gov.rw/web/index.php?id=9.

175. *Law N°03/2012 governing narcotic drugs, psychotropic substances and precursors in Rwanda*. 2012, Official Gazette n° 15: http://www.rwandafda.gov.rw/web/fileadmin/narcotic_law_2012__2_.pdf.

176. *Ministerial Order Nº 001/MoH/2019 of 04/03/2019 Establishing the List of Narcotic Drugs and Their Categorisation*. 2019, Official Gazette n° 10: http://www.moh.gov.rw/fileadmin/Publications/Legal_Framework/Ministerial_Order_List_of_narcotics_and_their_categorization-43-57__3_.pdf.

177. *Pain Management Guidelines*. 2012, Ministry of Health, Republic of Rwanda: http://moh.gov.rw/fileadmin/templates/Norms/Pain-Management-Guidelines-15-11-2012-.pdf.

178. Rosa, W.E., et al., *The Advancement of Palliative Care in Rwanda: Transnational Partnerships and Educational Innovation.* J Hosp Palliat Nurs, 2018. **20**(3): p. 304-312.

179. WHO, *Rolling out Rwanda's national palliative care programme.* Bulletin of the World Health Organization, 2018. **96**(11): p. 729-796.

180. Bundesministerium für Justiz und Verbraucherschutz, B.f.J., *Verordnung über das Verschreiben, die Abgabe und den Nachweis des Verbleibs von Betäubungsmitteln (Betäubungsmittel-Verschreibungsverordnung - BtMVV)*, in *Zuletzt geändert durch Art. 2 V v. 2.7.2018 I 1078*. 1998, 2018.

181. Khan, S.P., T.A. Pickens, and D.J. Berlau, *Perspectives on cannabis as a substitute for opioid analgesics.* Pain Management, 2019. **9**(2): p. 191-203.

182. Kaye, A.D., et al., *Novel Pharmacological Nonopioid Therapies in Chronic Pain.* Curr Pain Headache Rep, 2018. **22**(4): p. 31.

183. *Kappa Opioid Receptor Agonists*. Our Pipeline 2020 [cited 2020-08-01; Available from: https://www.caratherapeutics.com/pipeline-technology/our-pipeline/.

184. *Nektar Issues Statement Regarding FDA Advisory Committee Vote for Oxycodegol*. News Releases 2020 [cited 2020-08-01; Available from: https://www.prnewswire.com/news-releases/nektar-issues-statement-regarding-fda-advisory-committee-vote-for-oxycodegol-300987219.html.

185. *U.S. FDA Accepts Regulatory Submission for Tanezumab, a Potential First-in-Class Treatment for Patients with Chronic Pain Due to Moderate-to-Severe Osteoarthritis*. News 2020 [cited 2020-08-01; Available from: https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_accepts_regulatory_submission_for_tanezumab_a_potential_first_in_class_treatment_for_patients_with_chronic_pain_due_to_moderate_to_severe_osteoarthritis.

186. S Asra Husain, M.S.B., Martha A Maurer, *Do national drug control laws ensure the availability of opioids for medical and scientific purposes.* Bull World Health Organ, 2014. **92**: p. 108-116.

187. Rouleau, G., et al., *Nursing Practice to Support People Living With HIV With Antiretroviral Therapy Adherence: A Qualitative Study.* J Assoc Nurses AIDS Care, 2019. **30**(4): p. e20-e37.

188. Cleary, J., et al., *Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in India: a report from the Global Opioid Policy Initiative (GOPI).* Ann Oncol, 2013. **24 Suppl 11**: p. xi33-40.

189. Vargas-Schaffer, G., *Is the WHO analgesic ladder still valid? Twenty-four years of experience.* Can Fam Physician, 2010. **56**(6): p. 514-7, e202-5.

190. Marschall, U., et al., *Long-term opioid therapy for chronic non-cancer pain in Germany.* Eur J Pain, 2016. **20**(5): p. 767-76.

191. Rose A. Rudd, M., et al., *Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014*, in *Morbidity and Mortality Weekly Report*. 2016, US Department of Health and Human Services/Centers for Disease Control and Prevention. p. 1378-1382.

192. Zhu, W., et al., *Initial Opioid Prescriptions among U.S. Commercially Insured Patients, 2012–2017.* New England Journal of Medicine, 2019. **380**(11): p. 1043-1052.

193. Cherny, N.I., et al., *Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative.* Ann Oncol, 2010. **21**(3): p. 615-626.

194. Cleary, J., et al., *Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Africa: a report from the Global Opioid Policy Initiative (GOPI).* Ann Oncol, 2013. **24 Suppl 11**: p. xi14-23.

195. Cleary, J., et al., *Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Asia: a report from the Global Opioid Policy Initiative (GOPI).* Ann Oncol, 2013. **24 Suppl 11**: p. xi24-32.

196. *Prescription Drug Monitoring Program (PDMP)*. 2019 [cited 2020-08-09; Available from: https://www.alabamapublichealth.gov/pdmp/index.html.

197. *One-Page Country Summaries*. The World Factbook 2020 [cited 2020-08-23; Available from: https://www.cia.gov/library/publications/resources/the-world-factbook/docs/one_page_summaries.html.

9. Appendices

Appendix 1: World Health Organization Model List of Essential Medicine 2019, medicines for pain and palliative care, from [18]

2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen a	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. a Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
2.2 Opioid analgesics	
codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr *for the management of cancer pain
□ morphine*	**Granules (slow-release; to mix with water):** 20 mg –200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride **or** morphine sulfate) in 1- mL ampoule. **Oral liquid:** 10 mg (morphine hydrochloride **or** morphine sulfate)/5 mL. **Tablet (slow release):** 10 mg–200mg (morphine hydrochloride **or** morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate). *Alternatives limited to hydromorphone and oxycodone

Complementary list	
*methadone**	***Tablet:** 5 mg; 10 mg (as hydrochloride)* ***Oral liquid:** 5mg/ 5mL; 10mg/ 5mL (as hydrochloride)* ***Concentrate for oral liquid:** 5 mg/ mL; 10mg/ mL (as hydrochloride)* **For the management of cancer pain.*

Non-opioids, non-steroidal anti-inflammatory medicines and opioid analgesics for pain and palliative care from the WHO Model List of Essential Medicine, 21st edition, pages 2-3. The square box symbol (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The boxed **a** symbol indicates that there is an age or weight restriction on the use of the medicine.

Appendix 2: Schedules I and II of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, as at 7 May 2020, from [34]

List of drugs included in Schedule I

Acetorphine	3-*O*-acetyltetrahydro-7*α*-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenooripavine
Acetyl-*alpha*-methylfentanyl	*N*-[1-(*α*-methylphenethyl)-4-piperidyl]acetanilide
Acetylfentanyl	*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]acetamide
Acetylmethadol	3-acetoxy-6-dimethylamino-4,4-diphenylheptane
Acryloylfentanyl (acrylfentanyl)	*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]prop-2-enamide
AH-7921	3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide
Alfentanil	*N*-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl) ethyl]-4-(methoxymethyl)-4-piperidinyl]-*N*-phenylpropanamide
Allylprodine	3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine
Alphacetylmethadol	*α*-3-acetoxy-6-dimethylamino-4,4-diphenylheptane
Alphameprodine	*α*-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine
Alphamethadol	*α*-6-dimethylamino-4,4-diphenyl-3-heptanol
alpha-Methylfentanyl	*N*-[1-(*α*-methylphenethyl)-4-piperidyl]propionanilide
alpha-Methylthiofentanyl	*N*-[1-[1-methyl-2-(2-thienyl)ethyl]-4-piperidyl]propionanilide
Alphaprodine	*α*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine
Anileridine	1-*p*-aminophenethyl-4-phenylpiperidine-4-carboxylic acid ethyl ester
Benzethidine	1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester
Benzylmorphine	3-benzylmorphine
Betacetylmethadol	*β*-3-acetoxy-6-dimethylamino-4,4-diphenylheptane
beta-Hydroxyfentanyl	*N*-[1-(*β*-hydroxyphenethyl)-4-piperidyl]propionanilide
beta-Hydroxy-3-methylfentanyl	*N*-[1-(*β*-hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide
Betameprodine	*β*-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine
Betamethadol	*β*-6-dimethylamino-4,4-diphenyl-3-heptanol
Betaprodine	*β*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine
Bezitramide	1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-3- propionyl-1-benzimidazolinyl)piperidine
Butyrfentanyl	*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]butanamide
Cannabis and cannabis resin and extracts and tinctures of cannabis	
Carfentanil	methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate
Clonitazene	2-(*p*-chlorobenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole
Coca leaf	
Cocaine	methyl ester of benzoylecgonine
Codoxime	dihydrocodeinone-6-carboxymethyloxime
Concentrate of poppy straw (the material arising when poppy straw has entered into a process for the concentration of its alkaloids when such material is made available in trade) ("Poppy straw" means all parts (except the seeds) of the opium poppy after mowing)	
Crotonylfentanyl	(2*E*)-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]but-2-enamide
Cyclopropylfentanyl	*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide
Desomorphine	dihydrodesoxymorphine
Dextromoramide	(+)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine
Diampromide	*N*-[2-(methylphenethylamino)-propyl]propionanilide
Diethylthiambutene	3-diethylamino-1,1-di-(2'thienyl)-1-butene
Difenoxin	1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotic acid
Dihydroetorphine	7,8-dihydro-7*α*-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydrooripavine
Dihydromorphine	
Dimenoxadol	2-dimethylaminoethyl-1-ethoxy-1,1-diphenylacetate
Dimepheptanol	6-dimethylamino-4,4-diphenyl-3-heptanol
Dimethylthiambutene	3-dimethylamino-1,1-di-(2'-thienyl)-1-butene
Dioxaphetyl butyrate	ethyl-4-morpholino-2,2-diphenylbutyrate
Diphenoxylate	1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester
Dipipanone	4,4-diphenyl-6-piperidine-3-heptanone
Drotebanol	3,4-dimethoxy-17-methylmorphinan-6*β*,14-diol
Ecgonine, its esters and derivatives which are convertible to ecgonine and cocaine	
Ethylmethylthiambutene	3-ethylmethylamino-1,1-di-(2'-thienyl)-1-butene
Etonitazene	1-diethylaminoethyl-2-*p*-ethoxybenzyl-5-nitrobenzimidazole
Etorphine	tetrahydro-7*α*-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenooripavine
Etoxeridine	1-[2-(2-hydroxyethoxy)-ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester
Fentanyl	1-phenethyl-4-*N*-propionylanilinopiperidine
4-Fluoroisobutyrfentanyl (4-FIBF, pFIBF)	*N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide
Furanylfentanyl	*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide
Furethidine	1-(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester
Heroin	diacetylmorphine

--- table is continued on next page --

List of drugs included in Schedule I

Hydrocodone	dihydrocodeinone
Hydromorphinol	14-hydroxydihydromorphine
Hydromorphone	dihydromorphinone
Hydroxypethidine	4-*m*-hydroxyphenyl-1-methylpiperidine-4-carboxylic acid ethyl ester
Isomethadone	6-(dimethylamino)-5-methyl-4,4-diphenyl-3-hexanone
Ketobemidone	4-*m*-hydroxyphenyl-1-methyl-4-propionylpiperidine
Levomethorphan[a]	(-)-3-methoxy-*N*-methylmorphinan
Levomoramide	(-)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine
Levophenacylmorphan	(-)-3-hydroxy-*N*-phenacylmorphinan
Levorphanol[a]	(-)-3-hydroxy-*N*-methylmorphinan
Metazocine	2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan
Methadone	6-(dimethylamino)-4,4-diphenyl-3-heptanone
Methadone intermediate	4-cyano-2-dimethylamino-4,4-diphenylbutane
Methoxyacetylfentanyl	2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide
Methyldesorphine	6-methyl-Δ^6-deoxymorphine
Methyldihydromorphine	6-methyldihydromorphine
3-Methylfentanyl	*N*-(3-methyl-1-phenethyl-4-piperidyl)propionanilide
3-Methylthiofentanyl	*N*-[3-methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide
Metopon	5-methyldihydromorphinone
Moramide intermediate	2-methyl-3-morpholino-1,1-diphenylpropane carboxylic acid
Morpheridine	1-(2-morpholinoethyl)-4-phenylpiperidine-4- carboxylic acid ethyl ester
Morphine	
Morphine methobromide and other pentavalent nitrogen morphine derivatives	
Morphine-*N*-oxide	
MPPP	1-methyl-4-phenyl-4-piperidinol propionate (ester)
MT-45	1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
Myrophine	myristylbenzylmorphine
Nicomorphine	3,6-dinicotinylmorphine
Noracymethadol	(±)-*α*-3-acetoxy-6-methylamino-4,4-diphenylheptane
Norlevorphanol	(-)-3-hydroxymorphinan
Normethadone	6-(dimethylamino)-4,4-diphenyl-3-hexanone
Normorphine	demethylmorphine
Norpipanone	4,4-diphenyl-6-piperidino-3-hexanone
Ocfentanil	*N*-(2-fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide
Opium	
Oripavine	O^3-demethylthebaine or 6,7,8,14-tetradehydro-4,5-*alpha*-epoxy-6-methoxy-17-methylmorphinan-3-ol
Orthofluorofentanyl	*N*-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide
Oxycodone	14-hydroxydihydrocodeinone
Oxymorphone	14-hydroxydihydromorphinone
Parafluorobutyrylfentanyl	*N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide
para-Fluorofentanyl	4'-fluoro-*N*-(1-phenethyl-4-piperidyl)propionanilide
PEPAP	1-phenethyl-4-phenyl-4-piperidinol acetate (ester)
Pethidine	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester
Pethidine intermediate A	4-cyano-1-methyl-4-phenylpiperidine
Pethidine intermediate B	4-phenylpiperidine-4-carboxylic acid ethyl ester
Pethidine intermediate C	1-methyl-4-phenylpiperidine-4-carboxylic acid
Phenadoxone	6-morpholino-4,4-diphenyl-3-heptanone
Phenampromide	*N*-(1-methyl-2-piperidinoethyl)propionanilide
Phenazocine	2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan
Phenomorphan	3-hydroxy-*N*-phenethylmorphinan
Phenoperidine	1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester
Piminodine	4-phenyl-1-(3-phenylaminopropyl)-piperidine-4-carboxylic acid ethyl ester
Piritramide	1-(3-cyano-3,3-diphenylpropyl)-4-(1-piperidino)piperidine-4-carboxylic acid amide
Proheptazine	1,3-dimethyl-4-phenyl-4-propionoxyazacycloheptane
Properidine	1-methyl-4-phenylpiperidine-4-carboxylic acid isopropyl ester
Racemethorphan	(±)-3-methoxy-*N*-methylmorphinan
Racemoramide	(±)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine
Racemorphan	(±)-3-hydroxy-*N*-methylmorphinan
Remifentanil	1-(2-methoxycarboniylethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester
Sufentanil	*N*-[4-(methoxymethyl)-1-[2-(2-thienyl)-ethyl]-4-piperidyl]propionanilide
Tetrahydrofuranylfentanyl (THF-F)	*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide
Thebacon	acetyldihydrocodeinone
Thebaine	

--- table is continued on next page --

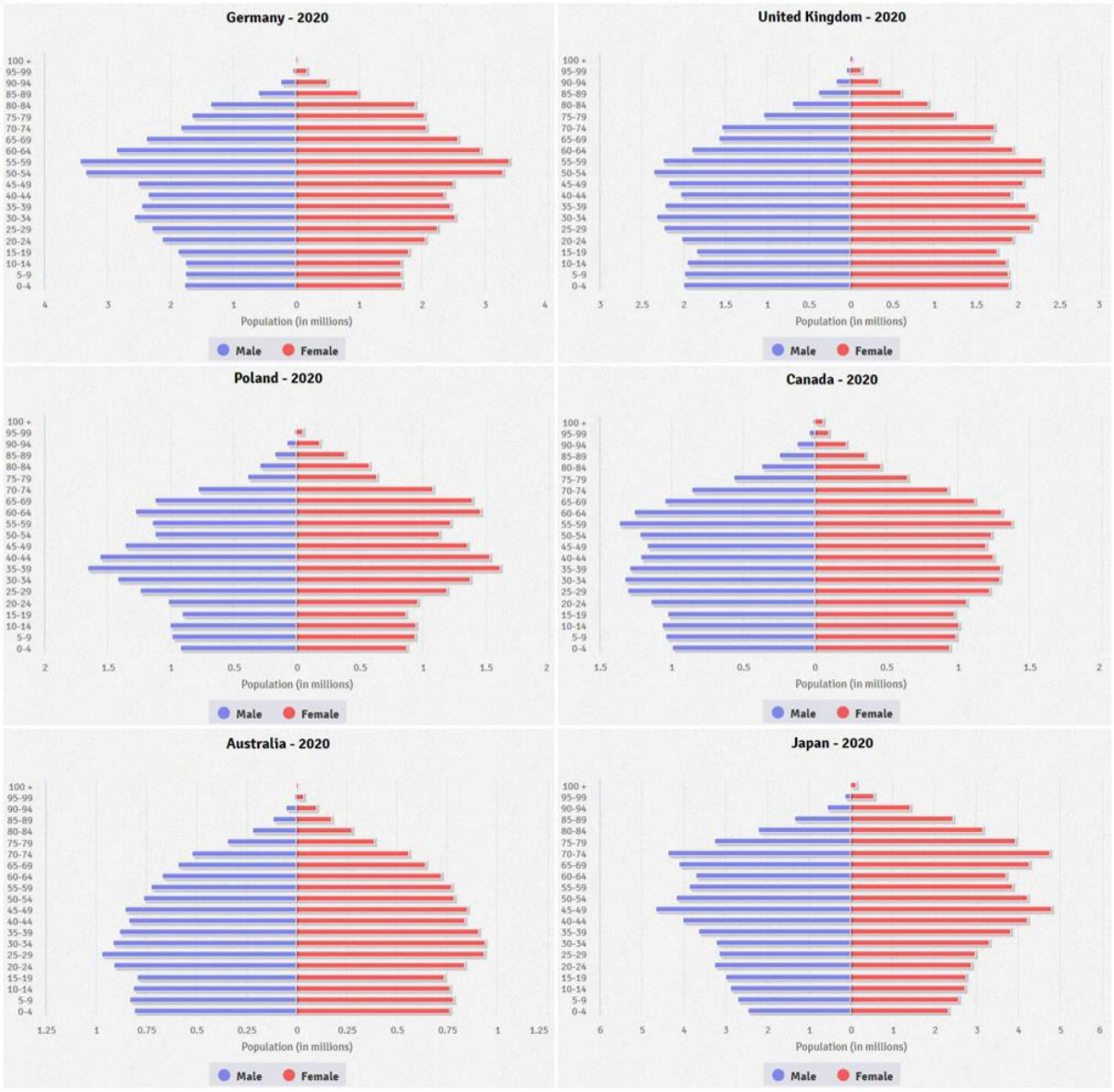
List of drugs included in Schedule I

Thiofentanyl	*N*-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide
Tilidine	(±)-ethyl-*trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate
Trimeperidine	1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine
U-47700	3,4-dichloro-*N*-(2-dimethylamino-cyclohexyl)-*N*-methyl-benzamide
Valerylfentanyl	*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]pentanamide

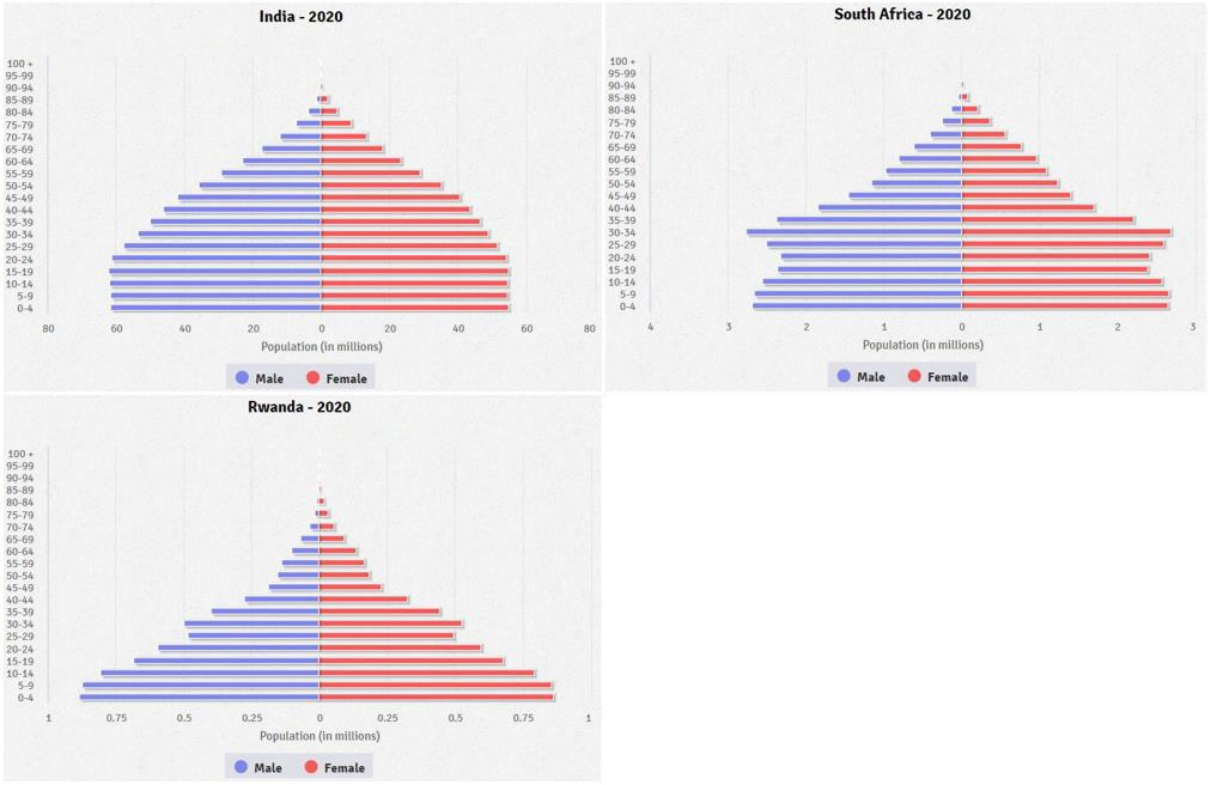
List of drugs included in Schedule II

Acetyldihydrocodeine	
Codeine	3-methylmorphine
Dextropropoxyphene	α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol propionate
Dihydrocodeine	
Ethylmorphine	3-ethylmorphine
Nicocodine	6-nicotinylcodeine
Nicodicodine	6-nicotinyldihydrocodeine
Norcodeine	*N*-demethylcodeine
Pholcodine	morpholinylethylmorphine
Propiram	*N*-(1-methyl-2-piperidinoethyl)-*N*-2-pyridylpropionamide

Appendix 3: Population pyramids 2020 for Germany, United Kingdom, Poland, Canada, Australia, Japan, India, South Africa and Rwanda, from [197]



--- figure is continued on next page --



The population pyramids illustrate the age and sex structure of the population in the nine selected countries for the year 2020. The population is distributed along the horizontal axis, with males shown on the left in blue and females on the right in red. The male and female populations are broken down into 5-year age groups represented as horizontal bars along the vertical axis, with the youngest age groups at the bottom and the oldest at the top.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Düsseldorf, den

Dr. Katja Bendrin