

APPROPRIATE ACCESS TO OPIOID MEDICINES

A legal & policy perspective

Marjolein J.M. Vranken

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APPROPRIATE ACCESS TO OPIOID MEDICINES

A legal & policy perspective

Adequate toegang tot opioïde geneesmiddelen
Een benadering vanuit wetgeving en beleid
(met een samenvatting in het Nederlands)

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CHAPTER 1

INTRODUCTION





CHAPTER 1.1

GENERAL INTRODUCTION



ACCESS TO ESSENTIAL OPIOID MEDICINES

Ensuring adequate access to essential medicines continues to be a challenge for governments and public health authorities worldwide. This challenge may be even more complex for medicines that not only have a high therapeutic value, but additionally have a potential for misuse and abuse (hereinafter also referred to as non-medical use¹). In their efforts to achieve maximum health outcomes, governments need to ensure access for patients in medical need while preventing harm related to non-medical use. Examples of medicines with a high therapeutic value and a potential for harm due to non-medical use include antibiotics (harm as a result of antibiotic resistance, which can be accelerated by misuse), sedatives (e.g. the benzodiazepine diazepam) and analgesics (harm as a result of development of opioid dependence). This thesis focuses on challenges to ensure appropriate access to medical treatment with opioid medicines.

Opioid medicines are an essential pharmaceutical treatment option for various types of pain (opioid analgesia) and for the treatment of opioid dependence (opioid agonist therapy).² Other medical uses include anesthesia, suppression of cough or diarrhea, dyspnoea, dyspnoea related anxiety and reversing opioid overdose.² The World Health Organization (WHO) has recognized this medical necessity by adding several opioids to its list of “essential medicines”: medically necessary medicines that are intended to be available in adequate amounts and at an affordable price to all patients in need of these medicines.³ Examples of essential opioid medicines include codeine, fentanyl, morphine and methadone. In spite of international recognition of their high therapeutic value, patients do not have equitable access to these medicines. In 2010, at least 79% of the global population had no or limited access to opioid medicines for pain relief.⁴

A DUAL OBLIGATION: ENSURING ACCESS AND PREVENTING NON-MEDICAL USE

This disbalance between high medical need and limited access is considered to be associated with measures taken as a consequence of the pharmacological properties of opioids. Although considered safe when used in the right subset of patients and in accordance with established dosage regimens², opioids have the potential to cause opioid dependence and can therefore be harmful for individuals and public health. Due to this potential for developing opioid dependence and harmful use, opioid medicines belong to the group of so-called “controlled medicines”: medicines that contain substances that are controlled under international agreements, including “the Single Convention on Narcotic Drugs”.⁵ Parties to this agreement are obliged to take measures to prevent the non-medical use and diversion by limiting the use

of controlled substances to medical and scientific purposes. In parallel, parties should ensure adequate access for medical and scientific purposes. This dual obligation is also referred to as the “central principle of balance”.² While the current aim is to achieve balance in drug control policies, historically the focus of drug-control systems has moved from a more public-health oriented system to a criminal-law based system.³ In the 1990s, the undertreatment of pain started to receive interest from a broad audience, including the WHO and the American Pain Society.⁴ Recently, this focus has shifted towards concerns about inappropriate use rather than undertreatment due to the so-called opioid epidemic in especially the United States (US).

FACTORS INFLUENCING ACCESS

The challenge for governments to achieve maximum public health outcomes as a result of finding the right balance has not reached its optimum yet. Data from the International Narcotics Control Board (INCB) show that in 2010, only 7.5% of the global population lived in countries where the opioid analgesic consumption level was considered adequate.⁴ The existing literature recognizes the role of drug control policies in limiting access to opioid medicines. Available data indicate that governments and policy makers may prioritize the need to prevent non-medical use and diversion over the need to ensure access to and availability of opioid medicines.^{2,6} Many other factors are considered to have an impact on access to opioid medicines besides drug control policies, including factors relating to economic aspects, knowledge and education, policy aspects, and societal attitudes.² These factors may be interrelated.⁷ For example, misconceptions about opioid use (lack of knowledge) could contribute to fear of using opioid medicines in medical practice (societal attitudes) and hence could restrict access to these medicines. Additionally, this fear might cause governments and policy makers to implement restrictive policies and legislation. Subsequently, these restrictive policies and legislation may create a sense of fear of using opioid medicines, particularly if severe sanctions are involved for unintended violations.

LEGAL AND REGULATORY BARRIERS TO ACCESS

The existence of barriers in national legislation and regulations has been reported in scientific literature⁸⁻¹⁷ and by several international organizations, including the WHO, the INCB and Human Rights Watch.¹⁸⁻²² Examples of reported legal and regulatory barriers include limitations on the amount to be prescribed, the requirement to prescribe in multiple copies or on special forms, restrictions regarding prescribing and dispensing privileges and overly strict requirements for storage and record keeping. The majority of studies that reported on such barriers have conducted surveys^{8-13,21}, or have reviewed legislation and policies using WHO policy guidelines¹⁴⁻¹⁶. Although WHO policy guidelines^{2,23} provide direction

for reviewing legislation, no method is available to analyze legislation and regulations in a systematic manner with detailed information on potential barriers to access. Additionally, the majority of studies focus on the treatment of moderate to severe (cancer) pain, and little is known on these types of barriers affecting other patient groups, such as patients with opioid dependence.

OTHER BARRIERS TO ACCESS

Whereas the number of studies reporting on legal and regulatory barriers is limited, numerous studies have reported on other types of barriers to access to opioids.^{24–30} The large majority of these studies have conducted surveys, focusing on one stakeholder group, such as physicians, nurses or patients. A few studies have also examined the perception of barriers among other types of stakeholders such as healthcare decision and policy makers.^{29,30} Reported barriers include inadequate knowledge of pain management, fear for dependence or diversion, limited financial resources, lack of education and training, physicians' reluctance to prescribe opioids and patients' reluctance to use opioids.

There are no studies comparing healthcare professionals working with opioid medicines in different medical fields, such as pain management, palliative care and harm reduction. The latter - harm reduction - refers to policies, practices and programs aimed at minimizing the negative health, legal and social impact associated with drug use, laws and policies.³¹ In general, access to opioid medicines in a harm reduction setting remains a relatively neglected area of study, in particular in comparison to studies focussing on patients with cancer pain. There is also only a limited number of studies examining differences in the perception of barriers between healthcare professionals and policy makers.^{29,30} These differences may have major impact in practice; as national drug control policies are usually drafted and implemented by stakeholders who do not have clinical experience with these medicines, the potential negative consequences of control measures for healthcare professionals and patients in medical need may not always be recognized. And vice versa, control measures that are expected to interfere with access may not constitute actual barriers in clinical practice, or may have less impact than expected.

RECENT INITIATIVES TO STRENGTHEN APPROPRIATE USE OF OPIOIDS

Several initiatives have been undertaken to improve appropriate access to opioid medicines and to reduce harm associated with non-medical use of opioids. One of these initiatives was the Access To Opioid Medication in Europe (ATOME) project, which started in 2009 as a five-year project funded under the European Union's 7th Framework Programme, with the

aim to improve access to opioids in twelve central and eastern European countries: Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Serbia, Slovakia, Slovenia and Turkey. These countries had in common that there was statistical evidence of inadequate consumption of opioids per capita³², and no major initiatives ongoing to improve access to opioid medicines. The project comprised the publication of new WHO policy guidelines², the analysis of national policies and circumstances that affect the availability of opioid medicines, the development of national action plans to improve access in each country and a proposal for amendments to national legislation and regulations to better balance the need to prevent non-medical use while allowing patients to access opioid medicines.³³

While in several parts of the world initiatives have been launched to improve access, in the US a variety of actions is being taken that focus on the prevention of harm associated with non-medical use. A four-fold increase was seen in the consumption of opioid analgesics between 1999 and 2010 in the US, and this increase was paralleled by an increase in opioid overdose related deaths.³⁴ In response, state legislation has been implemented that limits the number of providers of opioids (“doctor shopping”) and regulates pain clinics (“pill mills”). Additional actions include the implementation of Prescription Drug Monitoring Programs (PDMP) and clinical opioid prescribing guidelines.³⁵ Concerns about increased opioid analgesic use also exist in other high-developed countries, including the Netherlands. Between 2000 and 2014, the opioid analgesics use in the Netherlands increased at an average rate of 8% per year from 3.2 to 9.4 daily defined doses (DDDs) per 1 000 population per day.³⁶

THESIS OBJECTIVE

This thesis aims to study which factors may have a negative impact on access to opioid medicines, focusing on legal, regulatory and policy aspects. These insights may provide directions for implementing effective solutions for lifting barriers, with the ultimate goal to ensure appropriate access to opioid medicines.

Working towards this overall aim, research will be conducted on three complementary themes: 1. studies that focus on legal and regulatory aspects, 2. studies that address the perception of different types of barriers and 3. studies that look at access to opioid medicines in clinical practice in the context of barriers.

THESIS OUTLINE

Following this introduction (**chapter 1.1**), an overview of the legal framework controlling opioid medicines on an international and national level, including frequently used terminology when discussing opioid medicines, will be presented in **chapter 1.2**. This (inter)national legal

framework constitutes the basis for governments to implement control measures in their national systems. Some of these national control measures may potentially impede access to opioid medicines for patients in medical need.

In **Chapter 2**, we aim to analyze national drug control systems in central and eastern European countries participating in the ATOME project with the aim to identify potential legislative and regulatory barriers to access. The chapter starts with a quick scan of potential legal and regulatory barriers in **chapter 2.1**, followed by an in-depth analysis in **chapter 2.2**. In the last chapter (**chapter 2.3**) we further analyze the results of the study presented in chapter 2.2 focusing on one specific group of patients: patients with opioid dependence.

Chapter 3 is divided into three parts. In chapters 3.1 and 3.2, two studies are presented that assess the perception of barriers to adequate opioid use of several stakeholder groups in the countries that participated in the ATOME project. **Chapter 3.1** studies challenges to the availability and accessibility of opioid medicines in participating central and eastern European countries, while **chapter 3.2** analyses whether there are differences in the perception of barriers depending on the stakeholder involved. In the third part (**chapter 3.3**) we discuss the challenge for governments, health authorities and healthcare providers to ensure access to opioids for patients in legitimate medical need while implementing strategies that aim to prevent non-medical use of opioids.

In **Chapter 4**, we aim to position actual access to opioid medicines within the context of different types of potential barriers. **Chapter 4.1** focusses on geographic and inter-practice variation in prescribing patterns of strong opioid analgesics in primary care in the Netherlands. **Chapter 4.2** aims to examine how a period of intense media coverage following a morphine related event affected the prescribing of strong opioid analgesics in primary care in the Netherlands. In **chapter 4.3**, actual opioid consumption will be positioned in the context of the findings presented in Chapter 2: potential legal and regulatory barriers.

Finally, all studies described above will be placed in a broader perspective in the General Discussion in **Chapter 5**, providing policy recommendations and suggestions for future research.

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CHAPTER 1.2

LEGAL FRAMEWORK CONTROLLING OPIOID MEDICINES



INTRODUCTION

For several groups of medicines, tension may exist between access and control, the latter to prevent harm or to manage the costs of healthcare. For example, antibiotics are essential medicines to prevent and treat bacterial infections. At the same time, inadequate use of antibiotics may accelerate antibiotic resistance, which increases the treatment duration, the treatment costs and mortality.¹ Governments and policy makers may decide to regulate access to these types of medicines to achieve maximum health outcomes, by implementing laws, regulations or policies. They may also rely on healthcare professionals or professional organizations to regulate access and control harm or healthcare costs. For example, in the case of antibiotics by drafting and implementing guidelines for the monitoring and reporting of antibiotic resistance or educating patients.¹ Opioid medicines are a key example of medicines where tensions exists between access and control. In contrast to antibiotics, their use is highly regulated on an international level. Due to their potential for developing opioid dependence and harmful use, they belong to the group of so-called “controlled medicines”: medicines that contain substances that are controlled under international drug control conventions.

Parties to these conventions are obliged to take measures to prevent the non-medical use and diversion by limiting the use of controlled substances to medical and scientific purposes. In parallel, parties should ensure adequate access for medical and scientific purposes. This dual obligation is also referred to as the “central principle of balance”.² While the international conventions contain provisions that must be carried out, Parties to these treaties also have the “legislative freedom” to adopt stricter control measures in national policies and legislation than required. Problems may arise when these control measures unintentionally impede access to controlled medicines for patients in medical need in a way that is not proportional to their intended benefit for the prevention of non-medical use and diversion. This chapter aims to provide an overview of the legal framework controlling opioid medicines and its significance for ensuring appropriate access to these medicines, taking the Netherlands as an example. First, we will briefly address frequently used terminology when discussing the control of opioid medicines. Then, the legal framework will be outlined from an international perspective. We will touch upon the international situation from an United Nations (UN) drug control conventions perspective, without the intention to present a conclusive picture. Next, we will focus on a national perspective, discussing the system in place in the Netherlands to control opioids and to ensure their availability for medical and scientific purposes. Finally, we will give brief consideration to the consequences of the (inter)national drug control system for appropriate access to opioid medicines.

DEFINITIONS AND TERMINOLOGY

When discussing opioid medicines, confusion may arise regarding the terminology used, which includes: “opioids”, “opiates”, “controlled substances”, “controlled medicines”, “narcotic drugs”, “psychotropic substances” and “psychoactive substances”. Opioid medicines are medicinal products⁽¹⁾ that contain one or more opioid substances. Opioid substances are substances that act on opioid receptors producing morphine-like effects. A distinction can be made between opiates and opioids, where opiates are natural substances derived from opium and opioids include all substances binding to opioid receptors, both natural and synthetic.³ Opioid substances belong to the group “controlled substances”, which indicates that these substances are listed in the international drug control conventions. Medicines containing controlled substances can be referred to as controlled medicines. Narcotic drugs and psychotropic substances are both legal terms that refer to all substances that are listed in the international drug control conventions.² Psychoactive substances are considered a more neutral term for the whole class of substances of interest to drug policy. It refers to substances that, when taken in or administered into one’s system, affect mental processes including cognition or affect.⁴

In addition to confusion on the terminology used for opioid medicines, in discussions people may not always distinguish between the “abuse” and “misuse” of illicit opioids or prescribed opioids. The term abuse is used in the conventions as a part of the criteria to be applied in deciding on listing substances in one of the Schedules of controlled substances. However, the conventions do not define this term. Previous World Health Organization (WHO) Expert Committee’s on Drug Dependence defined abuse as “persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice”.^{2,5} Confusion may arise as the conventions use the term to refer to patterns at a population level, while the term is also used to refer to behavior at an individual level and commonly in a wider context referring to any *drug* use, particularly of illicit drugs.^{2,5} As the term abuse is considered ambiguous, judgmental and stigmatizing, it is recommended to use the alternatives such as harmful use or non-medical use.⁶ The term abuse can be used in relation to the (objectives of the) conventions. Misuse is defined by WHO policy guidelines as “the non-medical and non-scientific use of substances controlled under the international drug control treaties or under national law”², and is considered less judgmental than the term abuse.⁶

Other frequently used terms in legal documents that are considered stigmatizing by the WHO include referring to patients with dependence as “addicts”, referring to dependence-producing substances as “addictive substances” and referring to controlled medicines as “dangerous

(1) Directive 2001/83/EC Article 1(2) defines medicinal products as substances or a combination of substances that are either presented for treating or preventing disease in human beings, or that may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

drugs”, “drugs of addiction” or “poisons”.^{2,6} For the purpose of this thesis, we will discuss opioid medicines in the context of controlled medicines.

INTERNATIONAL DRUG CONTROL SYSTEM

As mentioned above, opioid medicines belong to the group “controlled substances” which entails they are controlled under the United Nations (UN) conventions. There are three UN conventions that together form the legal framework of the international drug control regime: the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol⁷ (hereinafter: Single Convention), the 1971 Convention on Psychotropic Substances⁸ (hereinafter: Psychotropic Substances Convention), and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances⁹. The objective of the conventions is to limit the use of the substances that are listed in these conventions to “medicinal or scientific purposes”. This objective is amplified in the preamble to the conventions. For example, the preamble to the Single Convention starts by recognising that “addiction to narcotic drugs constitutes a serious evil”. This is followed by the acknowledgment that “the medical use of narcotic drugs continues to be indispensable for the relief of pain”.⁷ States that are Party to these conventions are obliged to supervise trading and production of these substances and at the same time to ensure that opioids are available for medical use. Use for purposes other than medicine or science should be subject to criminal sanctions. In addition, the production (Article 29 of the Single Convention) and distribution (Article 30 of the Single Convention) of narcotic drugs must be subject to a license and supervised, and governments must provide statistics on the quantities required, manufactured, used, and seized (Articles 19 and 20 of the Single Convention).

The Single Convention and the Psychotropic Substances Convention each contain four Schedules in which substances are listed, i.e. the “controlled substances” mentioned above. The listing of substances in one of the Schedules is dynamic; substances can be placed under or removed from international control, or can be transferred between Schedules. As an example, in 2017 the substance butyrfentanyl was included in Schedule I of the Single Convention.¹⁰ The WHO plays a key role in advising on the scheduling of substances (Article 3 of the Single Convention and Article 2 of the Psychotropic Substances Convention). The WHO Expert Committee on Drug Dependence advises on the scheduling of narcotic drugs based on similarity in terms of harmful use and ill effects of substances already controlled. For psychotropic substances, additional criteria and requirements apply (Article 2 of the Psychotropic Substances Convention). Control provisions are most restrictive for narcotic substances listed in Schedule IV, followed by Schedule I, Schedule II and Schedule III. Examples

of substances in Schedule I are cocaine, cannabis, heroin, fentanyl and morphine. Schedule II contains substances with a lower risk of harmful use than the substances in Schedule I, such as codeine. Schedule III contains applications intended for medical use and composed in such a way that the potentially harmful substance cannot easily be extracted. Consequently, these substances are less susceptible to harmful use and a less restrictive regime applies to these substances; they are exempted from certain control measures. Examples include preparations containing less than 0.1% cocaine or less than 2.5% codeine. Finally, Schedule IV contains a selection of the substances in Schedule I. These selected substances are considered to be particularly harmful. Schedule IV includes heroin. A similar classification of substances into Schedules applies for psychotropic substances, with one important (and confusing) difference: for narcotic drugs, Schedule IV is the most restrictive whereas for psychotropic substances Schedule IV is the least restrictive.

DUTCH LEGISLATION ON CONTROLLED MEDICINES: LEGAL FRAMEWORK

To date, 186 countries have ratified the Single Convention. The Netherlands is a Party as of 1987, and is therefore required to apply its provisions. These provisions are regarded as minimum requirements; stricter measures are justified if a Party considers this necessary. This is evidenced by Article 39 of the Single Convention, which provides that “(...) a Party shall not be (...) precluded from adopting measures of control more strict or severe than those provided by this convention (...)”. Article 23 of the Psychotropic Substances Convention contains a similar provision. In addition to the Single Convention, the Netherlands has also ratified the Psychotropic Substances Convention and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The International Narcotics Control Board (INCB) is the regulatory body responsible for supervising compliance with these conventions and does not always agree with the policy conducted by the States. For example, since the 1990s the INCB has been increasingly critical of the Dutch policy of tolerating the use of cannabis in designated establishments known as ‘coffee shops’. In 2001 the INCB stated that the Netherlands had not been complying with its obligations under the conventions for some time: “The Netherlands continues to maintain a policy, introduced in the 1970s, of tolerating the consumption and sale of cannabis products in so-called “coffee shops”, which is not in compliance with the international drug control treaties”.¹¹ In its 2011 annual report the INCB again emphasized that the Netherlands was not in compliance with the conventions: “(...) “coffee shops” are in violation of the provisions of the international drug control conventions”.¹²

The obligations imposed by the conventions have been incorporated in the Dutch legislation on controlled substances: the Opium Act, the Opium Act Decree (“OAD”) and the Opium Act Implementation Regulation. Additional regulations are contained in the “Policy rules on administrative fines by the Minister of Health”, containing rules on sanctions for breaches of various legislation including the Opium Act, and the “Policy rules on Opium Act exemptions”, containing further rules for deciding on applications for Opium Act exemptions. The name Opium Act does not do full justice to the scope of this act. While opium is a good example of a substance with a high potential for developing dependence (and consequently dangerous), many other substances share this characteristic and are also covered by the strict rules in the Opium Act. In the Netherlands these substances are often simply referred to as “drugs”. A more appropriate name is the internationally recognised term “controlled substances”, for which there is not really an accurate Dutch translation. In the context of this chapter, the term “Opium Act drugs” will also be used; the terms “controlled substances” and “Opium Act drugs” will be used interchangeably.

The current Opium Act dates from 1976 but Dutch legislation on controlled substances goes back much further.¹³ In 1912 the “Hague International Opium Convention” was entered into, binding the Netherlands (and the other signatories) to take measures in respect of the sale and production of narcotic drugs. This led to the establishment of the first Opium Act, in 1919. Since that time, the Opium Act has been revised on many occasions, including the implementation of the international obligations arising under the UN drug control conventions.

The system in the Opium Act is as follows. The Opium Act contains two lists specifying certain *drugs*. These *drugs*, and any medicinal products containing these *drugs*, fall within the scope of the Opium Act. This means that, for these Opium Act *drugs* and therefore also for medicinal products containing these substances, certain activities are prohibited under Article 2 (with respect to the substances on List I) and Article 3 (with respect to the substances on List II). *Drugs* can be added to and removed from the lists by governmental decree. In urgent cases the Minister of Health even has the authority to designate a *drug* by ministerial decree. Two legal grounds exist for adding or removing *drugs* by governmental decree: the international obligations and agreements, such as inclusion in the lists for the conventions (Article 3a(1) OA); and a request by the Minister (Article 3a(1) OA). The Minister of Health has this authority if the relevant *drug* influences human consciousness and its use can cause harm to health and to society. These lists are therefore revised regularly when developments give cause to do so; substances are added or removed. This means that on a national level it can be decided to place substances under control in addition to the substances that are controlled based on

international obligations. For example, the new psychoactive substance 4-fluoroamfetamin (4-FA) with effects comparable to ecstasy and amphetamine has been added to List 1 of the Opium Act as of May 25th 2017 following several incidents with 4-FA.¹⁴ However, since 4-FA has been prohibited, two new slightly modified versions of 4-FA entered de market: 2-fluoroamphetamine and 3-fluoramphetamine. As these psychoactive substances have a different chemical composition, they are classified as legal. The Dutch cabinet is planning to amend the Opium Act to prohibit groups of substances instead of individual substances, to ban a whole group of so-called designer drugs.¹⁵

The fundamental principle on which the legislation is based is a broad prohibition on all activities described in Articles 2 and 3 for the *drugs* covered by the legislation. Those activities are described in broad terms and comprise bringing into or out of Dutch territory (Articles 2 and 3(A) OA), growing, preparing, manipulating, processing, selling, delivering, supplying, transporting (Articles 2 and 3(B)), possession (Articles 2 and 3(C)) and manufacturing (Articles 2 and 3(D)). Article 4 OA also refers to the - qualified - prohibition on prescribing an Opium Act drug on prescription and Article 3b refers to disclosures with the manifest object of promoting the sale, delivery or supply of a drug as referred to in Article 2 or Article 3.

So the basic rule is a prohibition with respect to specified activities (Articles 2, 3, 3b and 4 OA) for all Opium Act *drugs*. It is possible to deviate from this basic rule in specific situations and on strict conditions. Some of these exceptions relate to the use of these Opium Act *drugs* in science and medical practice. There are two possible options: either one of the exceptions set out in the legislation is satisfied or an exemption may be granted. The first option is likely to be more appealing as it entails less administrative obligations and costs.⁽²⁾ One of the exceptions set out in the legislation relates to activities necessary in the context of practicing medicine; without this exception the use of Opium Act drugs in medical practice would not be permitted. In addition to this, a lighter regime applies to certain *drugs* and applications; they are partially exempted from the general prohibition in Articles 2 and 3 OA. These *drugs* and applications are listed in Articles 10-15 OAD. For medical practice, Article 11 OAD is relevant, as it exempts preparations that contain no more than 0.5 mg codeine per milliliters or per gram (and do not contain any other substances on List I) from the prohibitions described in Articles 2(B) and 2(C) OA.

(2) See also Administrative Jurisdiction Division of the Council of State, 2 December 2009 (ECLI:NL:RVS:2009:BK5057), Foundation Centre for Human Drug Research/Minister of Health, «JGR» 2010/9, with note by Vranken and Schutjens, in which the central issue was whether an exemption is compulsory when scientific medical research is conducted by physicians with a medical objective. The Division agreed with the District Court (District Court of The Hague dated 9 March 2013, (ECLI:NL:RBSGR:2009:BI0226; reg.no. AWB 08/4459 BESLU)), that a controlled substances exemption was required for the activities that the CHDR wished to carry out.

Article 8 OAD also contains a number of exceptions to the strict requirements imposed on prescription and dispensing on a so-called ‘Opium Act prescription’. The medicinal products listed in this article may be prescribed on a standard prescription and the extra requirements for archiving and administration of Opium Act prescriptions do not apply. The background to this is that the properties of the medicinal products referred to do not justify these relatively onerous requirements. However, these products are still covered by the Opium Act.

Specific requirements for prescribing

Under Article 4(1) OA, prescription of Opium Act *drugs* is allowed if such prescription takes place in the course of the normal conduct of the physician’s or pharmacist’s profession and serves a medicinal purpose. However, this statutory exception only applies for certain *drugs* that have been included in the annexes to the Opium Act Decree⁽³⁾ (Article 4(1) OA in conjunction with Article 2(1) OAD). No other Opium Act *drug* may be prescribed as a medicinal product, except in the context of scientific medical research (Article 2(1) OAD). Annex 1 contains all the drugs on List II to the Opium Act (other than hashish) and a selection of the drugs on List I. Annex 1 also contains derivative substances (salts, esters, ethers and enantiomers) and preparations of these substances. Annex 2 to the Opium Act Decree contains the drugs heroin and diamorphine (and preparations of these drugs). Prescription of the *drugs* in Annex 2 is subject to extra conditions. These *drugs* may only be prescribed in certain institutions or in the context of certain research (Article 2(2) OAD), by physicians employed by a treatment unit (Article 2(3) OAD) for the benefit of patients at this treatment unit (Article 2(4) OAD).

In addition to the conditions mentioned above, the Opium Act Decree also imposes additional requirements to prevent non-medical use. For example, specific requirements apply (in addition to the requirements for a ‘standard’ prescription in Article 1(1)(pp) of the Medicines Act) with respect to the content of the prescription (Article 3 OAD): each Opium Act *drug* must be prescribed on a separate prescription written in indelible ink. Moreover, the prescription must be signed, stating the prescriber’s surname, initials, postal town/city and telephone number and the date of signature, and the name and quantity of the drug must be written out in full in letters.

Sometimes an institution or physician themselves will order specific medicinal products from a pharmacist for use in their medical practice or institution, for example for the “doctor’s bag” in order to administer it to the patient (in manum medici). Article 3 of the Opium Act Implementation Regulation imposes a number of requirements for these kind of orders,

(3) Not to be confused with Lists I and II to the Opium Act.

which are very similar to the requirements that apply for a prescription. For example, the order must be written in indelible letters and signed by the person ordering the drug. A number of items have to be stated on the order, which are similar to the matters required to be stated on a prescription, and here again the rule is that a separate form is required for each Opium Act *drug* ordered.

Specific requirements for dispensing

Dispensing Opium Act *drugs* is permitted under Article 5(1)(a) OA. This subsection provides that pharmacists and general practitioners with an in-house pharmacy are permitted to prepare, manipulate, process, sell, deliver, supply, transport or have in their possession certain *drugs*. Here again, the same conditions and restrictions apply as in respect of prescribing Opium Act *drugs*; this exception only applies with respect to the *drugs* mentioned in the annexes to the Opium Act Decree and only to the extent that activities with these drugs serve a medicinal purpose and take place within the normal course of conducting professional activities (Article 5(1)(a) OA). An additional requirement that measures are taken to prevent non-medical use also applies. The Opium Act Decree describes these measures. For example, different requirements apply with respect to receipt (Article 6 OAD), delivery (Article 4 OAD) and storage (Article 5 OAD) of Opium Act drugs. Under Article 5(1) OAD, prescriptions under which an Opium Act drug is delivered should be stored separately from other prescriptions, organised in a specific way: by name of prescriber, name of substance and date of delivery in succession. If the preparation concerned consists of several substances covered by the Opium Act then a separate copy of the prescription must be made and stored for each substance. In addition to the onerous requirements for the prescription to prevent non-medical use by patients, the Opium Act also contains provisions intended to prevent non-medical use by physicians or other healthcare providers themselves; responsibility for supervising this lies with the pharmacist. For example, pharmacists must provide copies of prescriptions under which Opium Act *drugs* are delivered to the prescriber themselves to the Dutch Healthcare Inspectorate (Article 5(3) OAD). This enables non-medical to be identified. Pharmacists also have to maintain an accurate record of purchasing, dispensing, administering, loss and any manipulation and processing of Opium Act *drugs* (Article 7 OAD). Regular checks also need to be conducted to ensure this record still matches the stocks held at the pharmacy. This is intended to identify non-medical use and prevent pharmacy staff or pharmacists themselves from using or trading in these *drugs* illegally.

Other activities: production, wholesale trading, advertising, possession and usage

To enable opioids to be used for medical applications, prescribing and dispensing medicinal products covered by the Opium Act is permitted under conditions. However, these medicinal products also need to be developed, produced, imported and distributed. Manufacturers and wholesalers of Opium Act medicinal products are not covered by the exceptions that exist for physicians and pharmacists. They have to apply under Article 6 OA for an exemption from the prohibitions described in Articles 2 and 3 OA. Based on Article 6a OA, the Minister of Health, Welfare and Sport can authorize an administrative body to provide these exemptions.

An exemption (Article 6 OA) can be granted if the applicant shows that this is necessary, for example in the interests of public health (Articles 6(1) and 8(1)(a) OA). An exemption is also possible in the context of scientific or analytical chemical research or for instructional purposes (Articles 6(1) and 8(1)(b) OA).⁽⁴⁾ Here again, the applicant must demonstrate the necessity of using Opium Act *drugs*; no necessity will be deemed to exist if the objectives can reasonably be achieved without using Opium Act *drugs*.⁽⁵⁾ For applications for scientific or analytical chemical research, the objective should be supported by scientific evidence, for example using research protocols. An example of the use of Opium Act *drugs* for instructional purposes would be the situation of use by the police as a tool when providing information.¹⁶ Finally, an exemption may be needed for certain activities carried out under an agreement. For example, growing medicinal cannabis on the basis of an agreement with the Minister (Articles 6(1) and 8(2)).

Various bodies are involved in the grant of exemptions. The Office of Medicinal Cannabis (OMC) deals with applications for exemptions for cannabis, hashish, hemp and hemp oil and is also the government body with responsibility for the production of cannabis for medicinal and scientific purposes.¹⁷ Applications relating to other Opium Act *drugs* must be submitted to Farmatec¹⁸ or to the Central Administration Office (CAK)¹⁹, which deal with applications relating to these *drugs* on behalf of the Minister of Health, Welfare and Sport. To bring Opium Act *drugs* into or out of Dutch territory, an import or export exemption is required and here again Farmatec (acting on the instructions of the Healthcare Inspectorate) is the responsible organisation.¹⁸ Farmatec is part of the CIBG: an executive agency of the Ministry of Health, Welfare and Sport. The party applying for the exemption must state the Opium Act *drugs* for which the exemption is being applied for, since it is not a generic, general exemption. When importing and exporting Opium Act *drugs*, a new exemption needs to be applied for in respect of each consignment. This exemption is valid for up to three months; if it is not possible to complete the import or export within this period then a new exemption must be

(4) Administrative Jurisdiction Division of the Council of State 2 December 2009 (ECLI:NL:RVS:2009:BK5057), Foundation Centre for Human Drug Research/Minister of Health, «JGR» 2010/9, with note by Vranken and Schutjens.

(5) Policy rules on Opium Act exemptions, subsection 4.

applied for. In exceptional cases, for example when Opium Act *drugs* come from China, an exemption can be requested for a period of six months.

The prohibition on the possession of *drugs* that fall under the scope of the OA does not apply for those who need these *drugs* for own medical use and have obtained them in a legal manner (Article 5(2) OA). This enables patients to use opioid medicines for their medical treatment. When travelling abroad with these medicines, a Schengen certificate or a medical certificate (for countries outside the Schengen area) is required. In the context of Article 6a OA, the CAK has been designated as the administrative body that handles applications for a certificate that allows patients to travel with medicines that fall under the scope of the Opium Act. Finally, advertising for medicinal products covered by the Opium Act is prohibited, even advertising to healthcare professionals.⁽⁶⁾ However, information without any commercial intention is allowed.

CONSEQUENCES FOR APPROPRIATE ACCESS TO OPIOID MEDICINES

As outlined in the introduction, the Single Convention holds the obligation for national governments to prevent non-medical use and diversion of opioid substances, by implementing administrative and legislative control measures relating to “narcotic drugs” listed in Schedules in their national legislation. At the same time, this legislative framework should also ensure adequate access to controlled medicines for medical and scientific purposes. Unfortunately, the prevention of illicit drug use and diversion often prevails. As a consequence additional control measures are implemented in national legislation that impede access to legitimate medical use of controlled medicines in a way that may not be proportional to their intended impact on the prevention of non-medical use and diversion.²⁰ The Single Convention for example, states that Parties may require that prescriptions for *drugs* in Schedule I should be written on official forms. Many countries however have implemented additional control measures regarding the prescribing and record-keeping, and require not only the use of official forms but also the recordkeeping of multiple copies under specific circumstances (e.g. the use of a special safe). Although other factors are relevant, legal and regulatory control measures are deemed to have an important role in the worldwide problem of inadequate access.^{21–25}

(6) Supreme Court 25 May 2004, NBSTRAF 2004/238; District Court of Amsterdam 10 December 2008, NJFS 2010, 95; Court of Appeal Amsterdam 15 September 2010, NJFS 2010/307. It should be noted here that the first case explicitly talks about a statement that “was made public in any way, circulated publicly or shown openly. This includes commercial statements that have been made publicly, or at least in public or in a public space and/or in another way enabling them to be consulted by the general public (...)”. This raises the question of whether communications that are restricted to specific target audiences and are concealed from the general public are also covered by the prohibition in Article 3b OA.

In the Netherlands, the obligations imposed by the conventions have been incorporated in the Dutch legislation on controlled substances, which includes the Opium Act and the Opium Act Decree. The fundamental principle of the Opium Act is that almost all activities with opioids are prohibited. For the benefit of medical practice, exceptions are made or exemptions can be obtained for those involved in prescribing and dispensing opioid medicinal products. While it is true that, in principle, this ensures medical use is possible, the extra requirements create a substantial increase in the administrative burden for all parties concerned and breaches of these requirements are subject to heavy fines, which can be imposed without warning. The high administrative burden concerned with the Opium Act obligations has been topic of discussion in the Dutch parliament in 2016.²⁶ The Dutch legislation on controlled medicines was considered outdated and not in line with the current electronic possibilities and practices. As a result, the Dutch Health Care Inspectorate (IGJ) agreed on simplifying the control measures by allowing for electronic recordkeeping.²⁷ Additionally, to reduce fear for unannounced inspection visits that focus on the Opium Act obligations, it was decided that the IGJ would also pay attention to the recordkeeping of controlled medicines during regular (announced) visits.²⁷ It is unclear whether the fear for inspection visits, the administrative burden or other requirements have interfered with appropriate access to these medicinal products in the Netherlands or had a negative impact on providing pharmaceutical care in general. It is also not clear to what extent these (and other) requirements have contributed to the prevention of non-medical use and diversion of controlled substances and medicines. It is evident that control measures, that do not have any impact on the prevention of non-medical use and diversion should be removed, as they may interfere with providing high quality patient care.

On a global level, there is still a lot of progress to be made as recent data show that a 44 000 times differences was found in the Adequacy of Opioid Consumption (AOC) Index between the country with the highest (Germany: AOC Index 304) and lowest (Nigeria: AOC Index 0.0069) opioid analgesic consumption in 2015.²⁸ A review of national legislation in the countries with low opioid analgesic consumption could locate provisions that impede access to opioid medicines for patients in a way that is disproportional to their (intended) benefit for the prevention of non-medical use and diversion. Removing or revising these provisions could serve the dual obligation that governments have based on the (inter)national control system: ensuring adequate access for medical and scientific purposes while preventing non-medical use and diversion.

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CHAPTER 2

LEGAL AND REGULATORY BARRIERS TO ACCESS TO OPIOID MEDICINES





CHAPTER 2.1

LEGAL BARRIERS IN ACCESSING OPIOID MEDICINES: RESULTS OF THE ATOME QUICK SCAN OF NATIONAL LEGISLATION OF EASTERN EUROPEAN COUNTRIES

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ABSTRACT

CONTEXT: Overregulation of controlled medicines is one of the factors contributing to limited access to opioid medicines.

OBJECTIVES: The purpose of this study was to identify legal barriers to access to opioid medicines in 12 Eastern European countries participating in the Access to Opioid Medication in Europa project, using a quick scan method.

METHODS: A quick scan method to identify legal barriers was developed focusing on eight different categories of barriers. Key experts in 12 European countries were requested to send relevant legislation. Legislation was quick scanned using World Health Organization guidelines. Overly restrictive provisions and provisions that contain stigmatizing language and incorrect definitions were identified. The selected provisions were scored into two categories: 1) barrier and 2) uncertain, and reviewed by two authors. A barrier was recorded if both authors agreed the selected provision to be a barrier (Category 1).

RESULTS: National legislation was obtained from 11 of 12 countries. All 11 countries showed legal barriers in the areas of prescribing (most frequently observed barrier). Ten countries showed barriers in the areas of dispensing and showed stigmatizing language and incorrect use of definitions in their legislation. Most barriers were identified in the legislation of Bulgaria, Greece, Lithuania, Serbia, and Slovenia. The Cypriot legislation showed the fewest total number of barriers.

CONCLUSION: The selected countries have in common as main barriers prescribing and dispensing restrictions, the use of stigmatizing language, and incorrect use of definitions. The practical impact of these barriers identified using a quick scan method needs to be validated by other means.

INTRODUCTION

Opioid medicines used in the field of harm reduction, palliative care, and pain management are not readily available and accessible to patients in medical need of these medicines in many countries.¹⁻⁸ Various factors are considered to contribute to this limited access, including lack of knowledge and societal attitudes, economic and procurement aspects, and issues relating to policies and legislation.^{9,10} These latter issues can emerge from governments and policy makers focusing on the prevention of abuse and diversion, adopting more strict control measures than required by international conventions. These overly strict control measures may unintentionally impede access to controlled medicines for patients in medical need. Government representatives from 144 countries and territories reported in a survey conducted by the International Narcotics Control Board (INCB) in 2007 that unduly restrictive laws and burdensome regulations were commonly perceived to play a significant role in limiting the availability of opioids.¹⁰

The “legislative freedom” to adopt stricter control measures in national policies and legislation is amplified in the Single Convention on Narcotic Drugs (also referred to as the Single Convention).¹¹ The Single Convention holds the obligation for national governments to prevent illicit drug use and diversion by implementing administrative and legislative control measures relating to “narcotic drugs” listed in Schedules in their national legislation. Narcotic drugs controlled under the Single Convention include among others opium, morphine, codeine, heroin, methadone, pethidine, cannabis, and coca leaf. Parties to the Single Convention are required to undertake measures to limit the production, manufacturing, import, export, trade and distribution, use and possession of narcotic drugs exclusively to scientific and medical purposes.¹² In addition, the production and distribution of narcotic drugs must be subject to a license and supervised, and governments must provide statistics on the quantities required, manufactured, used, and seized.

At the same time, this legislative framework also should ensure adequate access to controlled medicines for medical and scientific purposes, a dual obligation also referred to as “the central principle of balance”.¹³ Unfortunately, the prevention of illicit drug use and diversion often prevails, and as a result additional control measures are implemented in national legislation impeding access to legitimate medical use of controlled medicines such as morphine, codeine, methadone, buprenorphine, and ketamine.¹⁴ As an example, parties to the Single Convention are obliged to “Require medical prescriptions for the supply, or dispensation of drugs to individuals (...)” with the exception of “(...) such drugs as individuals

may lawfully obtain, use, dispense, or administer in connexion with their duly authorized therapeutic functions (...).¹⁵ In addition to the specific requirements, the Single Convention allows for parties to adopt stricter measures than required by the Single Convention, if “parties deem these measures necessary or desirable”.¹⁶ The Single Convention, for example, explicitly states that parties may require “that prescriptions for drugs in Schedule I should be written on official forms (...)”.¹⁵

As a result of this “legislative freedom”, countries across the world implement control measures that impede access to controlled medicines in a way that is often not proportional to their impact on the prevention of abuse and diversion.¹⁴ For example, in many countries, the prescribing of controlled medicines requires not only the use of official forms but also the recordkeeping of multiple copies. The World Health Organization (WHO) Expert Committee on Cancer Pain Relief and Active Support Care commented in its 1990 report¹⁷ that, although multiple-copy prescription programs may reduce careless prescribing and “multiple doctoring”, it also noted that “(...) the extent to which these programmes restrict or inhibit the prescribing of opioids to patients who need them should also be questioned”.^{17,18} The WHO Expert Committee observed a reduction in the prescribing of “(...) covered drugs by 50 percent or more” as a result of multiple-copy prescription program.¹⁸

The WHO is one of the international organizations continuously emphasizing the problem of overregulation. To ensure balanced legislation, recognizing the importance of medical access to controlled medicines while preventing abuse and diversion, the WHO published guidelines that provide guidance for countries to review their policies and legislation to prevent or overcome barriers to access.¹⁹ These guidelines were updated in 2011²⁰ as one of the objectives of the European Commission-funded Access to Opioid Medication in Europa (ATOME) project.²¹ This project started in 2009 with the aim to improve the accessibility and availability of opioid medication in 12 selected Eastern European countries where there is statistical evidence of very low morphine consumption per capita: Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Serbia, Slovakia, Slovenia, and Turkey.²² In addition to the publication of new WHO policy guidelines, the ATOME project, among other goals, aims to analyze national legislation regulating opioid medicines to identify barriers to access and make recommendations on a national level for optimizing legislation. In preparation for this thorough review of legislation, a method was developed using the WHO policy guidelines as an instrument to quick scan relevant legislation. This study aims at identifying legal barriers to accessing opioid medicines in the 12 ATOME countries by using this quick scan method.

METHODS

An external analysis of selected national legislation was undertaken using WHO policy guidelines to identify barriers to accessing opioid medicines.

Selection of relevant legislation

Key experts in the respective countries were approached by the authors to send national legislation used in regulating opioid substances and opioid medicines. These key experts were appointed in consultation with the WHO, based on their expertise in the field of pharmaceutical law and health policy. To ensure adequate selection of relevant information, all key experts, before the request to send legal documents, were trained in identifying relevant information during a one and a half-day workshop in Bucharest, which was held in February 2011.²³

In addition to this training workshop, a guidance document was sent in March 2011 to help identify and select relevant information. This guidance document included a list of 11 topics (e.g., prescribing, dispensing, registration, administration, and reimbursement) and the request to send laws, decrees, regulations, acts, and relevant case law regulating controlled medicines.

Selected information that was only available in the national language was translated into English by a professional translation agency (NOVA Language Services, Barcelona, Spain).

Analysis of selected legislation

A quick scan method to identify legal barriers to accessing opioid medication was developed focusing on eight of the 21 WHO policy guidelines²⁰ relating to legal and regulatory issues (Guidelines 6, 8-12, 18, and 19; Table 1) and eight different categories of barriers. The categories comprise all activities relating to access to medicines in the pharmaceutical supply chain from manufacturing to dispensing (manufacturing, import/export, prescribing, and dispensing) supplemented with three additional categories based on the WHO guidelines (language, storage, and registration). The category “other” was added to include potential barriers that did not fit into one of the seven categories.

Table 1. Selected WHO policy guidelines

Guideline 6	All government agencies, depending on their roles and obligations, should ensure that in the fulfilment of their duties, they do not impede health policies and access to legitimate treatment with controlled medicines. Health authorities should provide relevant information on treatment principles to drug law enforcement and other relevant agencies.
Guideline 8	Governments should ensure that all population groups without discrimination equally benefit from their policies on the availability and accessibility of controlled medicines for rational medical use and the prevention of diversion, abuse, and dependence syndrome.
Guideline 9	Governments should examine their drug control legislation and policies for the presence of overly restrictive provisions that affect delivery of appropriate medical care involving controlled medicines. They should also ensure that provisions aim at optimizing health outcomes and take corrective action as needed. Decisions which are ordinarily medical in nature should be taken by health professionals.
Guideline 10	Terminology in national drug control legislation and policies should be clear and unambiguous in order not to confuse the use of controlled medicines for medical and scientific purposes with misuse.
Guideline 11	Appropriately trained and qualified physicians, and, if applicable, nurses and other health professionals, at all levels of health care should be allowed to prescribe and administer controlled medicines, based on their general professional license, current medical knowledge and good practice without any further license requirements.
Guideline 12	Appropriately trained and qualified pharmacists at all levels of health care should be allowed to dispense controlled medicines, based on their general professional license, current medical knowledge and good practice without any further license requirements.
Guideline 18	Governments should ensure, in cooperation with companies and agencies managing distribution, that the procurement, manufacture, and distribution of controlled medicines are accomplished in a timely manner with good geographical coverage so that there are no shortages of supply, and that such medicines are always available when they are needed while maintaining adequate controls to prevent diversion, abuse, or dependence syndrome.
Guideline 19	Governments should minimize the negative impact of control and safety measures on the affordability and availability of controlled medicines.

The selected legislation was analyzed (quick scanned) by one author (M. J. M. V.). Potential overly restrictive provisions were identified as well as provisions that contain potential stigmatizing language and incorrect use of terminology (e.g., using the term abuse when referring to long-term medical use) and definitions based on the WHO policy guidelines. Provisions were considered to be potentially overly restrictive if they contain stricter rules than required by European and international legislation and if these stricter rules can impede access to controlled medicines in practice in a way that may be disproportional to their potential effect on the prevention of abuse and diversion.

Selected provisions that were considered to be potentially “overly restrictive” were scored using the selected WHO guidelines by two authors (M. J. M. V., M.-H. D. B. S.) into two different categories: 1) barriers and 2) uncertain. Provisions in the first category (barriers) can be expected to impede access to opioids based on the WHO guidelines. The second category (uncertain) consists of provisions that may impede access to opioids, depending

on specific circumstances, additional legislation, or interpretation of the provisions. Further information is required to determine whether provisions in this category are considered to be overly restrictive, the collection of that falls out of the scope of this quick scan. The results were discussed, and a barrier was recorded if both reviewers agreed the selected provision to be a Category 1 provision (barrier). Provisions in Category 2 (uncertain) were not recorded as barriers. The total number of provisions that was recorded as a barrier was calculated for each of the eight issue categories. Repetitions of identical barriers (e.g., the use of stigmatizing terminology throughout one document) were calculated as one barrier per legal document.

RESULTS

Legal barriers identified

National legislation (including laws, acts, decrees, and regulations) was received from 11 of the 12 key experts in the period March–November 2011. None of the key experts provided case law. Overly restrictive provisions were identified in all 11 countries in several categories using the quick scan method (Table 2). The most frequently observed barriers were identified in the category of prescribing (all 11 countries). Ten countries showed barriers in the areas of dispensing and language. No barriers concerning the manufacturing of opioid medicines were identified by this quick scan method in the reviewed legislation. Identified barriers classified in the “other” category concerned among others the possession, reimbursement, or pricing of opioid medicines. In total, five countries showed 25 or more barriers in their legislation (Table 2). Most barriers were identified in the legislation of Bulgaria, Greece, Lithuania, Serbia, and Slovenia. The Cypriot legislation showed the fewest total number of barriers.

Examples of provisions identified

Table 3 contains examples of provisions that have been considered to impede access to opioid medicines for every issue category. Most provisions were identified in the following categories: prescribing, dispensing, and language. Examples of identified barriers in the category of prescribing include restrictions on the maximum daily dosage and the total amount of controlled medicines to be prescribed (limited to a certain period), limited validity of prescriptions, administrative requirements for prescribing, and requirements for special licenses and permits (Table 3). Identified barriers in the category of dispensing include the prohibition to dispense controlled medicines issued by physicians of other cities and county health care institutions, the prohibition to dispense an amount of controlled medicines that exceeds a certain period, and the obligation for patients to visit one designated pharmacy

to receive controlled medicines prescribed by repeat prescriptions (Table 3). Barriers that have been identified in the category language include provisions that do not make a clear distinction between medical use and illicit use or abuse, provisions that use terminology contributing to the prejudice and stigma of the use of controlled medicines (e.g., addictive drugs or dangerous drugs), and provisions that contain incorrect definitions.

Table 2. Identified provisions per category per country that have been considered to impede access to opioid medicines

country	import/export	manufacturing	prescribing	storage	dispensing	registration	language	other	total
Bulgaria	■	■	■	■	■	■	■	■	≥ 25
Cyprus	■	■	■	■	■	■	■	■	< 15
Estonia	■	■	■	■	■	■	■	■	≥ 20 - 25
Greece	■	■	■	■	■	■	■	■	≥ 25
Hungary	■	■	■	■	■	■	■	■	≥ 15 - 20
Latvia	■	■	■	■	■	■	■	■	≥ 15 - 20
Lithuania	■	■	■	■	■	■	■	■	≥ 25
Poland	■	■	■	■	■	■	■	■	
Serbia	■	■	■	■	■	■	■	■	≥ 25
Slovakia	■	■	■	■	■	■	■	■	≥ 15 - 20
Slovenia	■	■	■	■	■	■	■	■	≥ 25
Turkey	■	■	■	■	■	■	■	■	≥ 20 - 25

No data available	0	1-2	3-5	> 5
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Table 3. Examples of identified provisions per category that have been considered to impede access to opioid medicines

Category	Legal provision in national legislation
PRESCRIBING	<p><i>"It is forbidden for pharmacists to provide narcotic drugs for daily use in amounts greater than the daily dose allowed by the (...) pharmacopoeia even when a greater dose is prescribed by a physician, except in cases for which special permission has been granted by the Ministry of Health & Social Solidarity at the opinion of the Narcotics Committee"</i></p> <p><i>"(...) In cases of cancer patients, and only after a relevant permit by the health department of the local prefectural administration, the physician can dispense a special narcotics prescription for an amount that exceeds the maximum daily dose for a five-day (5) treatment. The local prefectural administration's permit is valid for one (1) month."</i></p> <p><i>"If there is no other way to suppress the pain, it shall be allowed to exceed 3 times the norms, indicated in the table of paragraph (...), indicating in the prescription "Special assignment" and confirming it additionally by affixing the physician's signature and personal stamp."</i></p>
DISPENSING	<p><i>"It is prohibited to dispense (sell) narcotic drugs based on prescriptions, issued by physicians of other cities and county health care institutions."</i></p> <p><i>"Proprietary medications or compounds that contain the substances listed in Table (...) are dispensed with a special drug prescription for narcotics in therapeutic doses for one (1) day (...)."</i></p> <p><i>"The family practitioner shall warn the patient or patient's family member that during continuous treatment with a controlled substance, subsequent repeats of the controlled substance shall be dispensed to the patient regularly by the public retail pharmacy where the first prescription was filled."</i></p>
LANGUAGE	<p><i>According to their legal definition, narcotic drugs are artificial or natural substances that act on the central nervous system and cause the individual in question to develop an addiction to them.</i></p> <p><i>" (...) to prevent the use of narcotic and psychotropic substances."</i></p> <p><i>The supply of drugs that contain addictive substances must be controlled in order to limit the development of iatrogenic dependence or its maintenance.</i></p>
IMPORT/ EXPORT	<p><i>"(...) An application for a license for the export or import of a psychoactive controlled substance shall contain the following: (...) The method of transportation, as well as the border crossing on the territory (...)"</i></p>
STORAGE	<p><i>Its external walls (if any) shall be made from reinforced concrete and not less than 250mm brick walls or made from the other material of the same strength. The external walls that do not meet these requirements shall be reinforced with protective grilles. The internal wall shall be no less than 120mm, made from reinforced concrete or not less than 120mm if the brick wall, reinforced with metal grid. The inside walls that do not meet these requirements, shall be reinforced with protective grilles. It shall have not less than 180mm overlays made of reinforced concrete or material similar in strength. If walls and ceilings do not meet these requirements, they shall be reinforced with protective grilles; It shall have doors that meet Class II security requirements, laid forth in the Description. There shall be a protective grille on the Windows (if any), as well as flues and ventilation ducts (if the opening is larger than 180x180mm). Protective shutters may be installed instead of protective grilles. In such case, there shall be motion detectors with curtain lenses installed between the window glass and protective shutters, and protective shutter should be blocked upon opening them.</i></p>
REGISTRATION	<p><i>The physician shall record administration of medication in the patient's medical history form, and if narcotic drugs and compensated medicines are prescribed – shall indicate the prescription series and number.</i></p>
OTHER	<p><i>For the prescription disposal purpose, a permanent commission of no less than 3 persons shall be assembled, based on the pharmacy director's order. The pharmacies, which have two employees on staff, the commission shall be assembled of 2 persons.</i></p>

DISCUSSION

This study shows that overly strict control measures - one of the factors contributing to limited access- can be identified by scanning legislation focusing on eight WHO guidelines. Overregulation of opioid medicines has been previously reported by several authors and international organizations, including the INCB,¹⁰ the WHO,^{9,17-20} and Human Rights Watch.¹ Cherny et al.²⁴ analyzed data obtained from surveys distributed among senior clinicians working in the field of oncology or palliative care, as a joint effort by the European Society for Medical Oncology (ESMO) and the European Association for Palliative Care (EAPC). The surveys contained questions that address the criteria for balanced legislation as described in guidelines published by the WHO in 2000.¹⁹ In total, data were reported from 21 Eastern European countries and 20 Western European countries. Legal restrictions to access, such as the requirement for a permit to prescribe or receive opioids, the requirement to prescribe in multiple copies or on special forms, limitations on the treatment period or on dispensing privileges, the absence of emergency provisions, and the use of stigmatizing language, were reported in the legislation of all countries, in particular in the Eastern European countries.²⁴ All previously reported legal restrictions - with the exception of the absence of emergency provisions- also were identified using this quick scan (Table 3).

Similar results were reported from studies conducted in countries outside Europe. A follow-up of the ESMO/EAPC survey recently revealed that hundreds of millions of patients in Africa, Asia, Latin America, the Caribbean, and the Middle East do not have access to essential medicines for the relief of pain because of restricted formularies of opioids and regulatory barriers.²⁻⁸ The Pain and Policy Studies Group, one of the coordinating partners within the ESMO/EAPC survey, has extensive experience in assisting governments of countries across the world in evaluating their national policies. Their methods, which involve a set of criteria based on “the central principle of balance”, have been used to address legal and regulatory barriers and recommend changes in many countries, including Romania, Italy, and India.²⁵ This criteria-based method also was used by De Lima et al.²⁶ to identify potential barriers to access by reviewing national laws on controlled substances from Argentina, Colombia, Costa Rica, Peru, and the state of Texas. INCB and WHO criteria were transformed into a set of 17 questions, which were used to evaluate the national situation on opioid availability. In total, only 52% of the criteria were met in these countries.²⁶

All studies mentioned previously, including this ATOME Quick Scan, have in common that they either used the WHO guidelines or used criteria evaluating similar content as the WHO

guidelines in their methods to evaluate policies and legislation. There are some differences in the specific WHO criteria used in relation to this quick scan. Some studies^{25,26} include WHO criteria that address “positive language”, such as provisions that recognize the importance of the medical use of opioids (WHO guideline 1).²⁰ Other studies^{2-8,24} also look at provisions that are missing in legislation, for example, provisions that allow pharmacists to correct small technical errors in prescriptions and dispense small amounts of controlled medicines in case of emergencies (WHO guideline 12).²⁰ This quick scan, however, only focuses on current provisions in selected legislation, which allows analyses and comparison of available legislation without the necessity of collecting all existing legislation that is required to identify missing provisions.

Limitations of this study concern the selection and translation of legislation and the scoring of barriers by the authors. Legislation was selected by key experts in the specific countries and - if not available in English - translated into English. Incomplete selection of data or incorrect translation may have caused incorrect or incomplete reporting of barriers. By careful selection, training and guidance of the key experts and by working with a professional translation agency specialized in the area of health and law, the omission of data and inconsistencies in translation have been reduced as much as possible. Nevertheless, there are data missing that may have an impact on access to opioids. For example, case law or legal documents from states, districts, provinces, or other specific regions were not provided by the key experts. Also, not all key experts provided their constitution. In addition, legislation analysis is subject to interpretation of legal texts. It is inevitable that interpretations may vary. However, by using WHO guidelines as an instrument to identify barriers and by involving two reviewers, the chances of divergent interpretations are minimized. Finally, the exclusion of provisions that are categorized as “uncertain” (Category 2) is very likely to have caused underreporting of the total number of legal barriers. However, as this is considered to be a quick scan, allowing the identification of obvious impediments in legal documents using only a set of selected WHO guidelines, the present study is not designed to provide a complete overview of all legal barriers. The ATOME Quick Scan of legislation can be used as a relatively simple method by any person with basic knowledge of the system in place to control narcotic drugs to identify potential hurdles to accessing opioid medicines, using eight of the 21 WHO guidelines as a tool to locate unbalanced legislation. The practical approach of scoring provisions into two categories to identify obvious impediments not only gives insight in “quick wins” in terms of improvement (Category 1 provisions) but also provides a good basis for a more detailed review of legislation (Category 2 provisions). This in-depth review is currently being finalized within the ATOME project. The more detailed review of legislation

will not only give more insight in the qualitative aspects of the potential barriers but also will result in recommendations for improving access in the specific countries.

Although barriers to access have been identified in this quick scan, the reproducibility of this study and the impact of these potential barriers on clinical practice remains unknown. As this quick scan covers only a limited number of countries, additional research in other countries is needed to confirm the results of this pilot study. Additional research also is recommended to assess the correlation between barriers in legislation and limited access to opioids for patients. Taking into account that legislation is considered to be only one part of this problem, a multifaceted approach is necessary evaluating all aspects involved. The ATOME project acknowledges this complexity by its broad approach; national situational analyses are being undertaken, and national conferences are organized in each of the 12 ATOME countries to address not only legal barriers but also, for example, issues relating to policies, economic aspects, education, and attitudes.²⁷

In conclusion, this study has shown that legal barriers to accessing opioids can be identified using a quick scan of legislation. Although legislation is only one of the factors contributing to limited access, the potential impact of overly strict control measures should not be underestimated: a single provision in national legislation can prevent a patient from receiving adequate medical treatment with opioid medicines. In drafting legislation, countries need to adequately review the appropriateness of provisions and balance the effectiveness of such provisions with respect to undesirable misuse of medicines against the negative impact on accessibility of necessary medication. A revision of unbalanced legislation, therefore, is recommended as a first step toward access to opioid medicines for patients in medical need.

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experience in opioid medicine issues; the 10 ATOME partners work with the country teams, including government officials and public health and medicine experts, to carry out legislative and policy reviews, leading to recommendations that will facilitate access for all patients requiring treatment with medicines controlled under international drug conventions. The full workshop reports (including a list of attendees) are available on the ATOME Website.

2.1

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CHAPTER 2.2

BARRIERS TO ACCESS TO OPIOID MEDICINES: A REVIEW OF NATIONAL LEGISLATION AND REGULATIONS OF 11 CENTRAL AND EASTERN EUROPEAN COUNTRIES

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ABSTRACT

Control measures designed to prevent the misuse of opioid medicines can often unintentionally restrict legitimate medical use, leaving patients with cancer in pain. This study aimed to develop and validate an assessment instrument based on WHO policy guidelines to systematically identify legal and regulatory barriers to opioid access in 11 European countries (Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Serbia, Slovakia, Slovenia, and Turkey) as part of the Access to Opioid Medication in Europe project. Relevant legislation and regulations were independently assessed by three reviewers and potential barriers were identified within nine categories including prescribing, penalties, and others. Potential barriers were identified in all countries, ranging from 22 potential barriers (Cyprus) to 128 potential barriers (Lithuania). The total number of barriers in a single category varied from one (Slovenia, usage category) to 49 (Greece, prescribing category). Differences, such as prescription validity, varied within one category, ranging from 5 days (Hungary) to 13 weeks (Cyprus). The results of this Review should give rise to a national review and revision of provisions that impede access to opioids, disproportionate to their (intended) benefit in preventing misuse, in these 11 European countries.

INTRODUCTION

Opioid analgesics are essential for the treatment of moderate to severe cancer pain.¹ The World Health Organization (WHO) recognised this medical need and added morphine to WHO's Model List of Essential Medicines,² which are medically necessary medicines that should be available in sufficient quantity at an affordable price. Despite this internationally acknowledged medical need, at least 79% of the world's population has no or (very) low access to opioid medicines for pain relief.³ WHO estimates that 5.5 million patients with terminal cancer worldwide experience moderate to severe pain because of inadequate access to controlled medicines.⁴ Various factors are thought to contribute to inadequate access, including economic aspects, legislation, policy, a paucity of knowledge, and societal attitudes.⁴⁻⁶ Legislation, policy, and a paucity of knowledge are strongly interrelated: misconceptions about opioids could themselves contribute to an unfounded fear of using opioid medicines in medical practice and hence could restrict access to these medicines. Additionally, this misguided fear might cause governments and policy makers to implement restrictive policies and legislation. Subsequently, these restrictive policies and legislation create a sense of fear of using opioid medicines, particularly if severe sanctions are involved for unintended violations. As a result of the complex interaction of factors affecting access, patients worldwide unnecessarily experience pain and other concomitant clinical consequences that impair their quality of life, including physical, social, and psychological functioning.⁷

Although other factors are relevant, legal and regulatory control measures are deemed to have an important role in the worldwide problem of inadequate access.^{5,6,8-12} Opioid medicines are controlled under an international agreement—the Single Convention on Narcotic Drugs.¹³ Parties to this agreement are obliged to take measures to prevent misuse and diversion by limiting the use of these controlled medicines to medical and scientific purposes. Despite (inter)national control measures, satisfactory levels of prevention of misuse and diversion are not always achieved, which can result in further control actions.¹⁴ In New York City (NY, USA), for example, in response to a progressive increase in overdose and deaths from opioid medicines, clinical guidelines were established that limited the prescribing of opioid analgesics in emergency departments to a 3-day treatment period,¹⁵ and excluded the prescribing of some long-acting opioid analgesics.¹⁴ Although these control measures might sometimes be necessary to reduce risks associated with misuse and diversion, little high-quality evidence exists to support these types of actions.¹⁶ For example, in the USA, strategies focusing on patient and prescriber information were shown to be useful in moderately decreasing

overprescribing and diversion of opioids.^{16–18} However, the problems and solutions in the USA are very specific to that country and, thus, cannot be compared with situations in many other countries around the world.^{19–21} These measures might not reduce misuse and diversion in countries where there is no overprescribing and where there is a different mechanism behind misuse and diversion.

Implementation of further strict control measures might result in the prevention of misuse and diversion, but the downside is that legitimate medical use of opioids might be restricted. As a result, access to opioid medicines is inadequate for patients that rely on their use, including patients with moderate to severe cancer pain. Many studies have reported on legal and regulatory barriers to access to opioid analgesics, mostly in low-income and middle-income countries. Strict control measures were deemed burdensome and complex, and were deemed to interfere with medical practice.^{8,10} Frequently reported legal and regulatory restrictions to access include the requirement for permission to prescribe or receive opioids, limitations on the amount to be prescribed, restrictions regarding dispensing privileges, and the absence of emergency provisions.^{8,9,22–25}

Although, on an international level, the prevention of misuse and diversion has prevailed for decades, more recently this focus has shifted towards ensuring access to essential medicines. In this context, governments were urged by the International Narcotics Control Board and other international organisations and agencies to critically examine their national policies and legislations and remove impediments to the adequate availability of opioid medicines for medical and scientific purposes.^{10,26,27} Governments that now implement control measures are facing a dilemma in their efforts to achieve maximum public health outcome: how to prevent opioid misuse while not negatively affecting access to opioid medicines for patients in medical need. WHO policy guidelines titled, “Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines” were developed to support government representatives and policy makers in assessing their national policies and legislation.⁴ These guidelines were updated at the start of the Access to Opioid Medication in Europe (ATOME) project. The ATOME project aimed to improve access to opioid medicines in 12 central and eastern European countries (Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Serbia, Slovakia, Slovenia, and Turkey) who had statistical evidence of very low morphine consumption per person and no major initiatives in progress to improve access to opioid medicines. Although WHO’s guidelines give direction and include an assessment checklist on access of controlled medicines, no practical assessment instrument is available with detailed information on potential barriers

to assess legislation and regulations. The aim of this study was therefore twofold: to develop and validate an assessment instrument for the systematic analysis of national legislation and regulations; and to conduct a review in line with WHO policy guidelines with the objective to identify potential legal and regulatory barriers to access to opioid medicines for countries participating in the ATOME project.

DATA COLLECTION

Selection of national legislation and regulations

The ATOME review of national legislation and regulations consisted of a two-step method: a quick scan of the legislation²⁸ and, on the basis of these results, a more thorough review. At the start of the ATOME project, country team members were identified by WHO's Regional Office for Europe on the basis of their skills and role in their country to ensure relevance to the project's activities. These country teams included representatives from the national controlled substances authorities and national Ministries of Health, experts representing regulatory and law enforcement authorities, and leading health-care professionals and patient representatives. Within these country teams, a legal expert was appointed to collaborate on the ATOME legislation review. Of the 12 countries in the ATOME project, 11 participated in the legislation review. The Poland ATOME country team decided not to participate and was therefore not included in this legislation review. Key experts in each country selected legislation about controlled substances and opioid medicines for the quick scan review from March 16, 2011, to Nov 1, 2011. This quick scan consisted of the identification of obvious impediments in selected legal documents using eight of the 21 WHO guidelines referring to legal and regulatory aspects of access to controlled substances. In the framework of the more thorough review, the key experts in the selected countries were requested to update information about the legislation and provide information on forthcoming changes in the originally selected legislation. Documents collected initially and additional relevant legislation and regulations (collected until February, 2013) were translated into English by a translation agency (NOVA Language Services, Barcelona, Spain), if it was only available in the national language (see appendix for a full overview of selected and translated legislation and regulations).

Analysis of national legislation and regulations

To review legislation and regulations, we developed a method using an assessment instrument on potential barriers to access to opioid medicines focusing on nine different categories:

prescribing, dispensing, manufacturing, usage, trade and distribution, affordability, penalties, language, and other (to include potential barriers that did not fit into one of the other categories). The assessment instrument was developed by MJMV, JAL, and M-HDBS, and on the basis of WHO's policy guidelines and additional medical literature regarding barriers to access.^{4,8,29-31} A selection of subcategories (referred to as items) of potential barriers in the prescribing and language categories and how they relate to WHO policy guidelines is provided (table 1).

One reviewer (MJMV) analysed all relevant national legislation and regulations, and selected legal or regulatory provisions related to controlled substances and opioid medicines for further review. Three reviewers (MJMV, JAL, and M-HDBS) independently reviewed these selected provisions using the assessment instrument, and identified potential barriers to access to opioid medicines. Differences of views between the reviewers regarding the identification of potential barriers were discussed until a consensus was reached. Newly identified barriers were added to the assessment instrument and the reviewed legislation and regulations were checked retrospectively to complete the process.

Validation of methods and results

We validated the reliability of the selection of legal and regulatory provisions from one reviewer (MJMV) by assessing the inter-rater reliability of the selection of provisions between two reviewers (MJMV and M-HDBS) for a selected number of countries. The two reviewers reviewed the law on controlled substances of three randomly selected countries (Hungary, Serbia, and Slovakia) and independently selected provisions for further review (no guidelines exist for a qualitative content analysis in terms of the percentage of text material needed to be tested for validity before applying the category system to all data; the research team deemed a validity assessment in 25% of the 11 countries to be sufficient to determine the reliability of the initial selection by only one reviewer [MJMV]). We compared the selection by the two reviewers using Cohen's κ statistics, which was rated to be very good ($\kappa=0.87$). After validation of the selection of provisions, the assessment instrument was piloted by all three reviewers to align the review process: selected provisions of one randomly selected country (Greece) were analysed based on the assessment instrument, and the three reviewers met to discuss differences of views that concerned general interpretation of the assessment instrument.

Table 1. Examples of potential barriers in the prescribing and language categories according to item through use of the assessment instrument

Potential barrier	Related WHO policy guideline	Examples identified in legislation
Authorisation to prescribe is restricted	Guideline 11	"If it appears that a patient will need to use a controlled substance for longer than 30 days or will need it repeatedly, the family practitioner only shall be authorized to prescribe it (...)" ³²
Special permit or licence required for prescribing	Guideline 11	"(...) In cases of cancer patients, and only after a relevant permit by the health department of the local prefectural administration, the physician can dispense a special narcotics prescription for an amount that exceeds the maximum daily dose for a five-day (5) treatment. The local prefectural administration's permit is valid for one (1) month" ³³
Special prescription forms required or multiple copies of prescriptions required	Guideline 9	"The persons involved in activities related to narcotic substances shall purchase the special forms from the regional healthcare centres" ³⁴ "The size of the original copy of a prescription for narcotic drugs is 127 x 158 mm, three sheets. The pharmacy shall have the original prescription and one copy thereof and the health care provider shall have one copy" ³⁵
Limited duration of prescription validity	Guideline 9	"Prescriptions issued by physicians are valid for the following periods of time: (...) Narcotic drugs—5 days, including the day the prescription was issued" ³⁶
Amount of controlled medicine to be prescribed is limited	Guideline 9	"If there is no other way to suppress the pain, it shall be allowed to exceed 3 times the norms, indicated in the table of paragraph 31, indicating in the prescription "Special assignment" and confirming it additionally by affixing the physician's signature and personal stamp" ³⁷

Potential barrier	Related WHO policy guideline	Examples identified in legislation
<p>Daily dosage is limited</p> <p>A potential barrier if the maximum dosage is lower than evidence-based medical treatment guidelines advice or individual patient needs might require higher dosages, or both</p>	<p>Guideline 11</p>	<p>“per day of treatment, a general practitioner may only prescribe one tenth of the quantities specified in the previous paragraph per individual patient, while the total quantity of a medicinal product prescribed may not exceed the quantity specified in the previous paragraph”³⁸</p>
<p>No clear distinction between medical use and illicit use or misuse</p> <p>A potential barrier if the language used in legislation does not provide a clear distinction between medical use and illicit use or misuse and, as a result, causes confusion or fear for the use of opioid medicines in medical practice, or both, particularly when severe sanctions are involved for unintended violations</p>	<p>Guideline 10</p>	<p>“Preventive measures (...) in order to reduce the supply of narcotic and psychotropic substances (...)”³⁹</p> <p>“(...) when the use of narcotic and psychotropic substances was the main reason causing death”⁴⁰</p>
<p>Incorrect definitions of all terms are used</p> <p>A potential barrier if the language used contains biased definitions or presuppositions regarding the nature, effect, or rational use of opiates that might encourage distorted knowledge or assumptions or might cause fear for the use of opioid medicines in medical practice, or both, particularly when severe sanctions are involved for unintended violations</p>	<p>Guideline 10</p>	<p>“According to their legal definition, narcotic drugs are artificial or natural substances that act on the central nervous system and cause the individual in question to develop an addiction to them”⁴¹</p>
<p>Unclear language is used</p> <p>A potential barrier if the language used contains wording or terminology that leaves space for interpretation (eg, the use of vague adjectives) and causes confusion or fear for the use of opioid medicines in medical practice, or both, particularly when severe sanctions are involved for unintended violations</p>	<p>Guideline 10</p>	<p>“Medicines containing narcotic drugs can be prescribed only if their use is necessary and if they are marketed under the Law on production and marketing of medicines”⁴²</p>
<p>Controlled medicines are referred to as dangerous, toxic, or addictive drugs</p> <p>A potential barrier if the language used contributes to the stigmatisation of opioid medicines or causes fear for the use of opioid medicines in medical practice, or both</p>	<p>Guideline 10</p>	<p>“For medical products, containing intoxicating substances, the packing must be marked diagonally by two red strips (...)”⁴³</p>

Individual country reports containing the provisional results of the analysis of national legislation and regulations were disseminated to the ATOME country teams and discussed during the ATOME legislation review workshop in Utrecht, Netherlands (Jan 31–Feb 1, 2013).⁴⁴ In total, 14 representatives from nine of the 11 countries participating in the ATOME project (all countries except Bulgaria and Turkey) attended the meeting. Additionally, the country teams were invited to provide written feedback using a form that addressed several questions, including the results and the correctness of the translation (appendix). Written feedback was received from six (Cyprus, Estonia, Greece, Hungary, Lithuania, Serbia) of the 11 countries. As Bulgaria and Turkey did not attend the ATOME legislation review workshop and did not provide feedback in writing, no changes were made to the results of the analysis of national legislation and regulations of both countries. Small changes were made to the results on the basis of this feedback received including small errors in translation, recent amendments in legislation, or differences in the interpretation of definitions or terminology, or both. The changes did not lead to modification of the assessment instrument.

Data analysis

We calculated the number of initially selected provisions per country and the total number of initially selected provisions. Additionally, we assessed the total number of provisions that were deemed to contain at least one potential barrier to access to opioid medicines in relation to the total number of provisions selected for review (per country and in total). We identified potential barriers according to category and according to items within the categories (all categories apart from language). We recorded the presence of potential barriers in the language category qualitatively according to the item to correct for language repetitions. Individual differences between the countries in the prescribing category were highlighted for the following items: limited prescription validity, multiple copies or special prescription forms required, total amount or treatment period, and daily dosage.

FINDINGS

Potential barriers to access, including language, were identified in all 11 countries with the number of categories in which items were reported varying from six categories (Slovenia) to all nine categories (Bulgaria and Latvia; figure 1). Across all 11 countries, 778 potential barriers (excluding the language category) were identified, with the smallest number in Cyprus (n=22) and the largest number in Lithuania (n=128; figure 1). Every country showed potential barriers in the prescribing, dispensing, usage, and language categories, whereas

the total number of barriers in each category (excluding language) varied from one (several countries, several categories; e.g., Slovenia, usage category) to 49 (e.g., Greece, prescribing category).

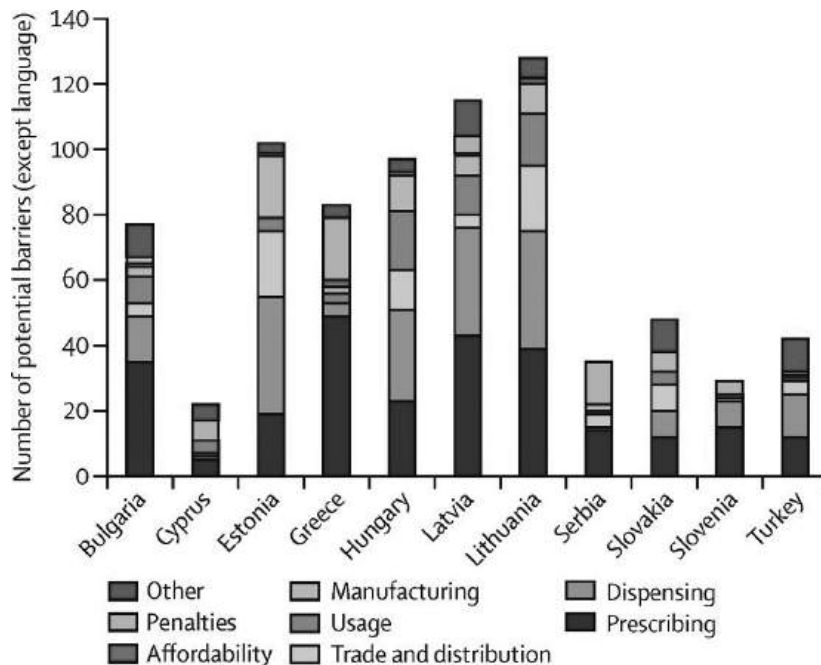


Figure 1. Number of potential barriers quantitatively identified according to category (except language) per country. See the online article for a colour version of this Figure: <https://www.ncbi.nlm.nih.gov/pubmed/26758755>.

Prescribing and dispensing categories

The number of items identified for the prescribing category and dispensing category ranged from five items (Cyprus) to 14 items (Latvia), out of a total 20 items (figure 2). Prescribing and dispensing restrictions and administrative requirements were the most common barriers identified in the prescribing and dispensing categories, with individual differences between countries in the level of impediment (table 2). For example, the prescription validity varied from 5 days (Hungary, Lithuania, Slovakia) to 13 weeks (Cyprus), and special prescription forms were used in duplicate and triplicate for some countries. Restrictions regarding the total amount to be prescribed on a single prescription were identified in the legislation of several countries with quantifications in the number of treatment days or the mass of medicines prescribed. Additional restrictions regarding the daily dose were identified in the legislation of three countries (Greece, Latvia, Slovenia; table 2).

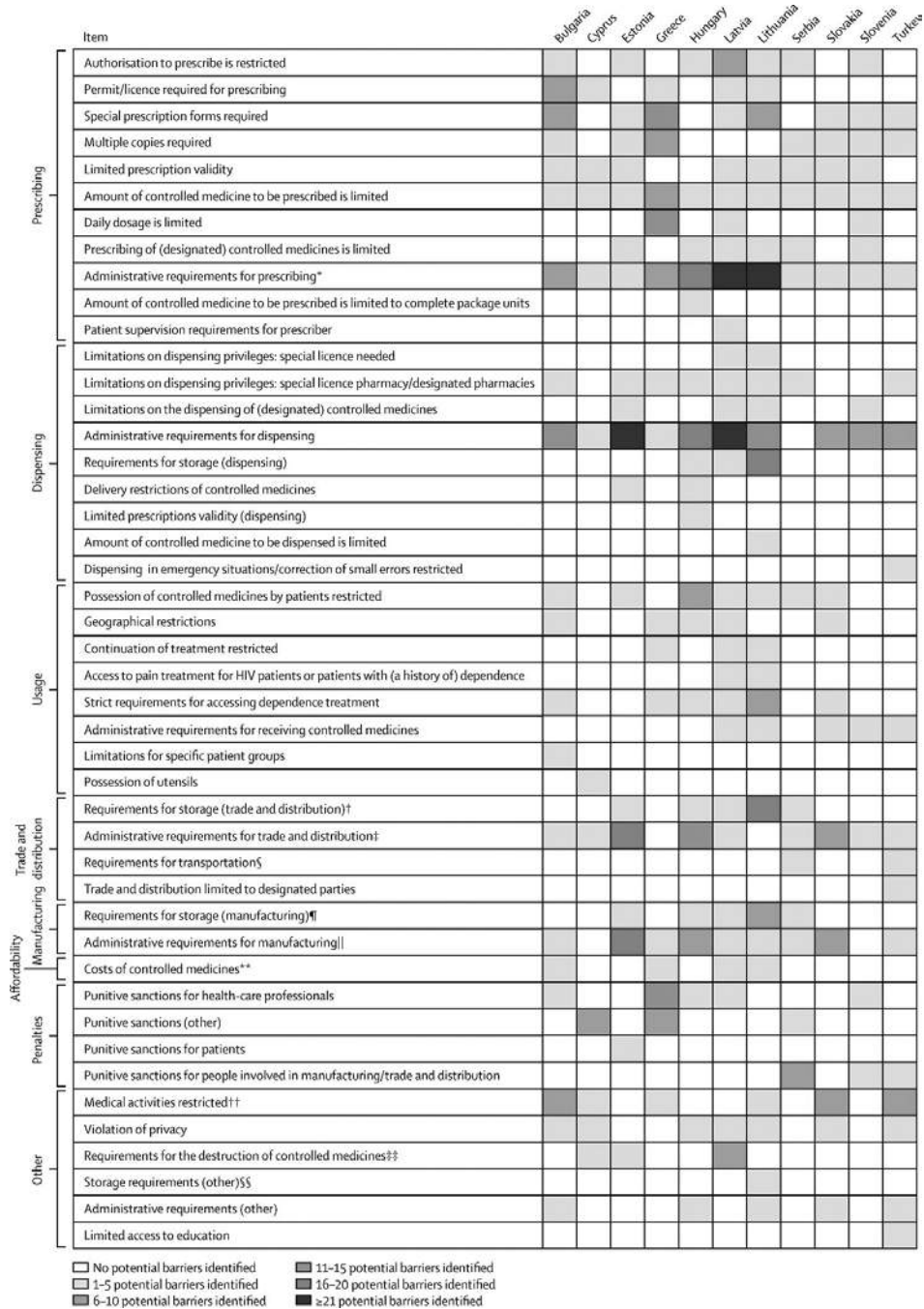


Figure 2. Assessment instrument showing potential barriers according to item (subcategory) in prescribing, dispensing, usage, trade and distribution, manufacturing, affordability, penalties and other, per country. See the online article for a colour version of this Figure: <https://www.ncbi.nlm.nih.gov/pubmed/26758755>.

*Requirements that increase the administrative burden and might cause medical practitioners to be unable or reluctant to treat patients with controlled medicines and do not solely concern any of the other categories. For example, the requirement that physicians are allowed to receive a restricted number of prescription forms that need to be stored in a designated safe. †Requirements that might cause legal entities to be unable or reluctant to store controlled medicines because of the high costs of the security measures. For example, requirements regarding the safes, security systems, or requirements that dictate the thickness of the bars in the windows. ‡Requirements that increase the administrative burden and might cause legal entities to be unable or reluctant to trade in controlled medicines. For example, very strict timelines to complete the application for an import or export licence, particularly if the information requested cannot be easily retrieved. §Requirements that might cause legal entities to be unable or reluctant to transport controlled medicines because of the high costs of these security measures. For example, the requirement that controlled medicines can only be transported in a vehicle that is equipped with metal containers with special security locks. ¶Requirements that might cause legal entities involved in manufacturing to be unable or reluctant to store controlled medicines because of the high costs of the security measures. For example, requirements regarding the safes or security systems, or requirements that dictate the thickness of the bars in the windows. ||Requirements that increase the administrative burden and might cause legal entities to be unable or reluctant to manufacture controlled medicines. For example, very strict timelines for completing the application to receive a permit for manufacturing opioid medicines, particularly if the information requested cannot be easily retrieved. **For example, costs are not reimbursed by statutory funding schemes; high prices or taxes because of state monopoly; high monthly fee for patients to be able to receive dependence treatment. ††Restrictions that have an effect on medical activities and do not solely concern any of the other categories. For example, specific requirements for healthcare institutions providing treatment with controlled medicines. †††Requirements for the destruction of controlled medicines that might deter legal entities or health-care professionals from working with controlled medicines. For example, complex reporting requirements for the disposal of controlled medicines or the requirement that unusable controlled medicines can only be destroyed in the presence of a representative from the government. §§Storage requirements that do not fit any of the other categories. For example, storage of opioid medicines during international transportation.

Table 2. Individual differences between countries in the level of impediment of potential barriers (prescribing category only)

	Duration of prescription validity	Multiple copies or special forms required	Mass of controlled medicine or treatment period	Maximum daily dosage
Bulgaria	7 days from the date of issuance	Three copies: original and two copies in different colours (yellow and green) printed on carbon paper	30 days	Not identified
Cyprus	13 weeks	Not identified	13 weeks	Not identified
Estonia	30 days (non-controlled medicines 60 days)	Three copies, 127 × 158 mm sheets printed in green on red self-copying paper with 80 mm binding holes on the left, a security print on the margins, and a seven-digit number in black in the upper left-hand corner	30 days	Not identified
Greece	Not identified	Two copies, serial numbered, special narcotic drug prescription form needed	The amount to be dispensed on a single prescription varies: 1 day (designated substances listed in tables ⁴¹); 5 days (dextropropoxyphene, methyphenidate, and pentazocine); 15 days (fentanyl transdermal patches); 30 days (treatment of patients with cancer, provided that a permit is granted: permit valid for 1 month)	Maximum daily dosages in legislation (eg, morphine 50 mg); maximum daily dosages can be exceeded for the treatment of patients with cancer, over a maximum of 5 days, provided that a permit is granted
Hungary	5 days	Not identified	15 of 30 days (prescribed by general practitioner) or 90 days (prescribed by general practitioner for patients travelling); repeat prescription allowed by general practitioner for a maximum of 30 days	Not identified
Latvia	30 days (non-controlled medicines 90 days)	Specific margins to be completed by pharmacist	Maximum amounts to be prescribed in Annex 5 of Regulation No 175; treatment period limited to 14 days (buprenorphine), 30 days, or 90 days (only narcotic analgesic products prescribed by a psychiatrist, narcologist, neurologist, or family doctor)	Daily dosage of buprenorphine legally restricted

	Duration of prescription validity	Multiple copies or special forms required	Mass of controlled medicine or treatment period	Maximum daily dosage
Lithuania	5 days, including the day of issuance	Blank form for "narcotic medicines" and blank form for compensated "narcotic medicines" to be completed	Maximum amounts to be prescribed for a patient on a single occasion (eg, morphine 2 g); total amount limited to a 7-day treatment course, transdermal: 30 days	Not identified
Serbia	7 days from the date of issuance	Two copies, serial numbered, with the second copy marked "copy"	Maximum amounts to be prescribed for a patient on a single occasion (eg, morphine 0.2 g), amount limited to treatment period of 30 days; for the treatment of malignant diseases: duration of treatment limited to 14 days	Not identified
Slovakia	5 days	Three copies, special forms required	30 days; no repeat prescriptions allowed	Not identified
Slovenia	5 days, excluding the day of issuance	Two copies, serial numbered, with the second copy marked "copy"	30 days; no repeat prescriptions allowed; maximum amounts to be prescribed specified in legislation	Daily dose cannot exceed a tenth of maximum amounts specified
Turkey	Not identified	Three copies, serial numbered, with special forms for psychotropic substances or narcotic substances	Maximum amounts to be prescribed on a single prescription specified in legislation (eg, morphine [oral] 2700 mg)	Not identified

Language in legislation and regulations

The language used in the legislation for controlled substances and medicines in all 11 countries referred to (patients with) dependence in a disrespectful manner (figure 3). Ten countries (all except Hungary) used incorrect drug definitions or unclear language, or both, in their legislation on controlled medicines. Furthermore, these countries had provisions in their legislation that do not make a clear distinction between medical use and illicit use or misuse.

	Bulgaria	Cyprus	Estonia	Greece	Hungary	Latvia	Lithuania	Serbia	Slovakia	Slovenia	Turkey
Reference to (people with) dependence in a disrespectful manner (eg, addicts or addiction)	■	■	■	■	■	■	■	■	■	■	■
Incorrect definitions of opioids or unclear language, or both	■	■	■	■	□	■	■	■	■	■	■
Absence of a clear distinction between medical use and illicit use or misuse	■	■	■	■	■	■	■	■	■	■	■
Reference to controlled medicines as dangerous, toxic, or addictive drugs	■	■	■	■	■	■	■	■	■	■	■

Not identified
 Identified

Figure 3. Potential barriers in the legislation and regulations of controlled medicines per country (language category only)

DISCUSSION

The reviewed national legislation and regulations contain many potential barriers to access to opioid medicines that are indispensable for the management of cancer pain. Additionally, all countries assessed were deemed to have disrespectful language in their legislation that contributed to the stigmatisation of the use of opioid medicines. Most potential barriers concerned the prescribing and dispensing of opioid medicines, with individual differences between countries in the level of impediment of several important items, such as limitations involving prescription validity, treatment duration, and daily dosage. Although legal and regulatory barriers to access to opioids have previously been identified^{22–25,29,30,31,45–47}, this is, to our knowledge, the first study that provides an in-depth analysis of the qualitative aspects of potential barriers in opioid access of 11 central and eastern European countries by doing a systematic external review of legislation that takes into account all elements in the pharmaceutical supply chain (from manufacturing to usage) by using an assessment instrument based on WHO policy guidelines that can be used in an universal manner.

Other studies describing legal, regulatory, or policy barriers to access to opioid medicines either conducted a survey^{22–26,29,45,46} or assessed legislation and policies by building on similar

content to WHO policy guidelines.^{30,31,47} Regulatory barriers to the accessibility of opioids for cancer pain in central and eastern Europe were previously reported by Cherny and colleagues²⁹ on the basis of surveys distributed among senior clinicians in 2007 and 2008. Results similar to those results reported in this Review were noted for reported limitations on the treatment period and the requirement to use special forms or prescribe in multiple copies. Small differences between findings might be associated with the high level of detail in the present Review and the availability of information on recent amendments. Different results were seen regarding the use of stigmatising language in legislation, which might be the result of under-reporting by the survey's respondents. A worldwide follow-up of the European survey by Cherny and colleagues²⁹ revealed that regulatory barriers and restricted formularies have an important role in inadequate access to opioid medicines for the treatment of cancer pain in Africa, Asia, Latin America, the Caribbean, and the Middle East, affecting millions of patients.^{22–25,45,46} Although the focus of previous surveys— and most other studies—was restricted to a predefined subset of potential barriers, the scope of our study allowed for the identification of every potential barrier encountered by systematically reviewing all selected legislation. As a result of this broad and systematic approach, potential hurdles to accessing opioids were also located in less obvious areas. Additional research is needed to refine the assessment instrument and to assess the intention of the respective legal provisions and their effect on opioid access in clinical practice.

Several limitations of the present external review of legislation should be mentioned. First, legal and regulatory data were analysed on the basis of selection by key experts in each country and, in many cases, after translation into English. Both incorrect translation and incomplete selection of documents might have caused incomplete or incorrect reporting of potential barriers. By training and guiding carefully selected key experts and by following a two-step method with an additional update of legal and regulatory text, the omission of data was minimised. Inconsistencies in translation were reduced as much as possible by working with a professional translation agency that specialised in the area of law and health, and through dissemination of the results to the ATOME country teams with the explicit request to provide feedback on errors in translation. Second, since the methods of this study consisted of an analysis of legal text, variation in the interpretation of legal terminology and text might have occurred. By involving three reviewers and determining the general interpretation of the assessment instrument, the possibility of different interpretations was minimised.

In addition to the usefulness of this external review of national legislation in identifying potential barriers, the detailed level of information provided has resulted in specific

recommendations for improving access to opioid medicines as part of the ATOME project. Several participating countries have since implemented some of these recommendations. For example, in Lithuania, the total number of special prescription forms physicians are allowed to receive has been doubled from ten to 20. In Estonia, the requirement for pharmacies to obtain a special permit, which authorises them to dispense controlled medicines, was removed. Before the removal of this requirement, pharmacies were reluctant to apply for a licence with the result that patients had difficulties identifying a pharmacy that could dispense their opioid medicines.⁴⁸ Although all these recommendations should contribute to better access to opioids for patients, the effect of these revisions on clinical practice has not been assessed and therefore remains unknown. Additional research is recommended to assess the effect of lifting potential barriers to opioid access in these countries. More scientific evidence is needed to assess the level of effect of different types of barriers, since it can be assumed that some barriers are more likely to affect access than others. Finally, scientific data are needed in a broader legislative and regulatory context to gain insight into how a restrictive control system affects access to opioid analgesics compared with a liberal system. So far, only anecdotal evidence exists showing a direct correlation between strict prescribing or dispensing requirements and patients being denied adequate pain treatment.^{49,50} Public health would benefit from data examining how we can reduce drug-related risks and improve clinical outcomes for patients with moderate-to-severe cancer pain by optimising legislation and regulations.

In conclusion, the potential barriers identified by this external review of national legislation should result in a national review and revision of provisions that impede access to opioid medicines for patients with cancer in a way that is disproportional to their (intended) benefit for the prevention of misuse and diversion. To provide a legal framework that focuses on access to opioid medicines with maximum health outcome, these revisions should take place in consultation with healthcare professionals and patient organisations. Several countries participating in the ATOME project are now in the process of revising legislation and implementing recommendations for improvement to access, bringing patients in medical need one step closer towards adequate access to opioid medicines.

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Annex 1. Legal and regulatory documents (partly) translated (printed in bold) and (partly) analysed per country

DOCUMENTS (PARTLY) ANALYSED	CONTROLLED SUBSTANCES LEGISLATION (GENERAL)	MEDICINAL PRODUCTS LEGISLATION	LEGISLATION CONCERNING HEALTHCARE	CONTROLLED SUBSTANCES LEGISLATION (DEPENDENCE)	OTHER
BULGARIA	Law for Control over the Narcotic Substances and Precursors (1999)	Law on the Medicinal Products in Human Medicine (2007)	Ordinance No. 34/2005 on the procedure for state budget funding of the treatment of Bulgarian citizens with regard to diseases beyond the scope of compulsory health insurance	Ordinance No. 24/2000 on the rules and procedures for the implementation of substitution and maintenance programs for the reduction of health damage for persons addicted to narcotic drugs	
	Ordinance No. 21/2000 on the requirements for documentation and reporting during activities involving narcotic substances and their preparations	Ordinance No 4/2009 on the rules and procedures for the prescription and supply of medicinal products			
CYPRUS	The Narcotic Drugs and Psychotropic Substances Law 1977, incorporating amendments up to 1992. The Narcotic Drugs and Psychotropic Substances Regulations 1979, incorporating amendments up to 1987.				

<p style="text-align: center;">CYPRUS</p>	<p>The Narcotic Drugs and Psychotropic Substances (Amendment) Regulations of 1995 (P.I. 79/95)</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Law 91(I) of 2003</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Decree of 1996 (P.I. 4/96)</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Law 24(I) of 2010</p>	<p>Medicinal Products Act (Passed 16 December 2004 (RT I 2005, 2, 4) Entry into force 1 March 2005)</p>	<p>Health Insurance Act</p>		
<p style="text-align: center;">ESTONIA</p>	<p>Act on Narcotic Drugs and Psychotropic Substances and Precursors thereof (passed 11 June 1997, RT I 1997, 52, 834, entered into force 1 November 1997)</p>				<p>The Conditions and Procedure for the Import and Export, Carrying for Personal Use and Sending by Post of Goods Requiring Special Authorisation of the State Agency of Medicines; the Forms of Special Authorisations and the List of Goods Requiring Special Authorisation of the State Agency of Medicines</p> <p>(Passed with Regulation No. 31 on 18.02.2005, RTL 2005, 23, 316, Entered into force 01.03.2005)</p>

<p>Conditions and Procedure for Handling of Narcotic Drugs and Psychotropic Substances for Medical and Research Purposes, and Conditions and Procedure for Maintaining Records and Reporting in that Area and Schedules of Narcotic Drugs and Psychotropic Substances (Regulation No. 73 of the Minister of Social Affairs of 18 May 2005 (RTL 2005, 57, 807), entered into force 5 July 2005)</p>	<p>The Conditions and Procedure for the Issue of Prescriptions for Medicinal Products and for the Dispensing of Medicinal Products by Pharmacies and the Format of Prescriptions (Approved by Regulation No. 30 of the Minister of Social Affairs of 18 February 2005 (RTL 2005, 23, 315), entered into force 01.03.2005)</p> <p>Conditions and Procedure for Wholesale Distribution of Medicinal Products (Approved by Regulation No. 27 of the Minister of Social Affairs of 17 February 2005 (RTL2 2005, 22, 308), entered into force 01.03.2005)</p>		
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<p>GREECE</p>	<p>Act No. 3459/2006 on Legal Codes for Drugs Presidential Decree 148/2007 on the codification of the provisions stipulated in the regulatory decrees and ministerial orders regarding national legislation on drugs Ministerial Order No. A6b/6543/15-07-1988 on the definition of terms and conditions of the availability of substances provided for in article 4 of Act No. 1729/1987 Government Decree 162/2003. (X. 16.) On cultivation, distribution and use of plants suitable for the production of narcotic drugs</p>	<p>Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Laws Regulating the Pharmaceutical Market ESzCSM (Ministry of Health, Social and Family Affairs) Decree 44/2004 (IV. 28) on prescribing and dispensing medicinal products for human use.</p>	<p>Act CLIV of 1997 on Health</p>	<p>Joint Decree 42/2008 (XI. 14.) EüM-SZMM of the Minister of Health and the Minister for Social Affairs and Labour on the rules of treatment for narcotic drug dependence of other services attending to drug use and of prevention and counselling service</p>	
<p>HUNGARY</p>	<p>Government Decree No. 66/2012 (2nd of April) on the activities that may be conducted with narcotic drugs, psychotropic substances and new psychoactive substances, and on the inclusion of such substances in schedules, and on the amendment of such schedules</p>				

LATVIA	<p>EūM (Ministry of Health) Decree 43/2005 (X.15.) on the system for physician's prescriptions, trading in pharmacies, consumption, recording and storage at healthcare providers of medicinal products classified as controlled drugs</p>	<p>National Law On Procedures for the Legal Trade of Narcotic and Psychotropic Substances and Medicinal Products (Including separate amendments 28/10/2010, 10/07/2008, 27/09/2007, 03/05/2007, 11/05/2006)</p>	<p>Cabinet of Ministers 23/03/2010 Regulations No 288 "Regulations Regarding Operating of Pharmacies"</p>	<p>Policy document Oncologic diseases control program for years 2009-2015</p>	<p>Programme for Limiting the Spread of Human Immunodeficiency Virus (HIV) for 2009–2013, approved by Decree of Cabinet of Ministers No 437 of 30/06/2009</p>	<p>Cabinet of Ministers 8/11/2005 Regulations No 847 "Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be controlled in Latvia" (including separate amendments 12/05/2009 and 3/11/2009)</p> <p>Cabinet of Ministers 26/06/2007 Regulations No 416 "Procedures regarding the Distribution and Quality Control of Medicinal Products" (including separate amendment on 27/07/2010).</p> <p>Cabinet of Ministers 31/10/2006 Regulations No 899 "Procedures for the Reimbursement of Expenditures for the Acquisition of Medicinal Products and Medicinal Devices intended for Out-patient Medical Treatment"</p> <p>Cabinet of Ministers 24/09/2002 Regulations No 429 "Procedures for the Treatment of Patients Addicted to Alcohol, Narcotics, Psychotropic and Toxic Substances"</p>
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<p>LATVIA</p> <p>Cabinet of Ministers 17/06/2008 Regulations No 441 "Procedures for the Purchase, Receipt, Storage, Distribution, Dispensation, Accounting and Destruction of Narcotic and Psychotropic Substances and Medicinal Products in Manufacturing of Medicinal Products and Veterinary Medicinal Products, at Drug and Veterinary Drug Wholesalers and Pharmacies"</p> <p>Cabinet of Ministers 13/08/1996 Regulations No 327 "Regulations on the Transit of Narcotic and Psychotropic Substances and Drugs" (including separate amendments 24/07/2007 and 04/08/1998)</p> <p>Cabinet of Ministers 21/04/2008 Regulations No 293 "Procedures by which a Permit for the Utilisation of Plants, Substances and Medicinal Products Included in Schedules I, II or III of Narcotic Substances, Psychotropic Substances and Precursors Controlled in Latvia for Medical and Veterinary Medical Scientific Research, Specification of Physical and Chemical Properties or for Educational Purposes is Issued, Suspended and Revoked"</p>	<p>Medical Treatment Law</p> <p>Cabinet of Ministers 08/03/2005 Regulations No 175 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing out and Storage Prescriptions" (Including separate amendment on 12/04/2011 of Regulations No 175)</p> <p>Cabinet of Ministers 27/03/2007 Regulations No 220 "Procedures for Acquisition, Storage, Use, Registration and Disposal of Medicinal Products in Medical Treatment Institutions and Social Care Institutions" (Including separate amendments on Regulations 220 on 08/04/2008, 10/03/2009, 31/08/2010 and 25/01/2011)</p>	<p>Cabinet of Ministers 19/12/2006 Regulations No 1046 "Procedures for organization and financing of health care"</p>	
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LITHUANIA	<p>Republic of Lithuania Law on the Control of Narcotic and Psychotropic Substances</p> <p>Republic of Lithuania Law on the Control of Precursors of Narcotic Drugs and Psychotropic Substances</p> <p>Government of the Republic of Lithuanian Resolution regarding the approval of regulations of issuing licenses to produce, import and export narcotic and psychotropic substances, and to engage in their wholesale and retail trade (Last amended on 2011 July 22: No. 887, 13.07.2011, Zin, (Official Gazette), 2011, No. 93-4403 (21.07.2011))</p>	<p>Order of the Minister of Health of the Republic of Lithuania No. 112 of 8 March 2002 "On Medical Prescriptions and Disbursement (Sale) of Medicines" (Published: Official Gazette Valstybės Žinios, 16/03/2002, No. 28, Publication No. 1013).</p>		<p>Order No. 204 of the Minister of Health of 3 May 2002 "On the Approval of Standards for Treatment and Rehabilitation of Dependency Diseases" (Official Gazette Žin., 2002, No. 47–1824).</p> <p>Order No. V-653 of the Minister of Health of the Republic of Lithuania of 6 August 2007 "On the Approval of Procedure Descriptions for Assigning Substitution Treatment and its Application to Treat Opiate Dependency, and Prescription, Disbursement, Storage and Accounting of Substitution Opiate Medicinal Preparations in Personal Health Care Institutions"</p>	
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Republic of Lithuania
Government Resolution No.
591 of 30 May 2005 "On the
Approval of the Description of
the Procedure for Monitoring
the Use of Narcotic and
Psychotropic Substances,
Consequences thereof, the
Circulation of the Precursors
of Narcotic and Psychotropic
Substances"

Republic of Lithuania
Government Resolution No.
221 of 9 March 2006 "On the
Approval of the Regulations
for the Licensing of Activities
Involving the Precursors of
Narcotic and Psychotropic
Substances, Registration of
the Place Thereof, Issuance
of Import and Export
Authorisations, and Control of
such Activities"

Order No. 275 of the Minister
of Health of the Republic of
Lithuania of 24 May 2000
"On the Premises for Keeping
Narcotic and Psychotropic
Medicines and Medicinal
Substances in Hospital
Pharmacies"

LITHUANIA

				<p>Order of the Minister of Health of the Republic of Lithuania No. V-2 of 23 April 2003 "On Recommendations for Determining Small, Large and Very Large Amount of Narcotic and Psychotropic Substances" (Published: Official Gazette Valstybės Žinios, 30/04/200, No. 41, Publication No. 1899).</p> <p>Order No. 342/482 of several institutions (Minister of Health of the Republic of Lithuania and Minister of the Interior of the Republic of Lithuania) of 25 August 1998 "On the Approval of the Description of Special Requirements for Premises where Narcotic and/ or Psychotropic Substances of Schedules II and III are Produced and Stored, their Wholesale and Retail Sale Takes Place" (Published: Official Gazette Valstybės Žinios, 02/09/1998, No. 77, Publication No. 2195; Official Gazette Valstybės Žinios, 16/10/2008, No. 119, Publication No. 4521).</p>	LITHUANIA
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<p>LITHUANIA</p>	<p>Order No. 409 of the Minister of Health of the Republic of Lithuania of 25 July 2001 "On the Ensuring of Control of Import and Export of Narcotic and Psychotropic Medicines and Medicinal Substances" (Published: Official Gazette Valstybės Žinios, 01/08/2001, No. 66, Publication No. 24 29; Official Gazette Valstybės Žinios, 14/07/2005, No. 85, Publication No. 3184).</p> <p>Order No. V-138 of the Minister of Health of the Republic of Lithuania of 2 March 2007 "On the Approval of the Description of Procedure for Issuance of the Certificate for Transportation of Narcotic and/or Psychotropic Substances for Personal Usage for Medical Purposes" (Published: Official Gazette Valstybės Žinios, 10/03/2007, No. 30, Publication No. 1109).</p>				
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<p style="text-align: center;">SERBIA</p>	<p>Order No. 294 of the Minister of Health of the Republic of Lithuania of 4 June 1998 "On the Procedure of Keeping Narcotic and Psychotropic Medicines and Medicinal Substances in Means of International Transportation" (Published: Official Gazette Valstybės Žinios, 19/06/1998, No. 56, Publication No. 1568). Law on psychoactive controlled substances</p>	<p>Rulebook on the prescription and dispensing of medicines (FRY Official Gazette No. 16/94, 22/97, 52/02)</p> <p>Rulebook on advertising of medicines and medical devices</p> <p>Law on medicines and medical devices (Official Gazette no 30/10)</p>	<p>Rulebook on contents and scope of health care from compulsory health insurance and on participation for 2012</p> <p>Draft National Palliative Care Strategy</p> <p>Action Plan for Palliative Care in the Republic of Serbia for the Period 2008-2015</p>	<p>The criminal code</p> <p>Law on criminal procedures</p>
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<p>SLOVAKIA</p>	<p>Act. N. 139/1998 on Narcotic Drugs, Psychotropic Substances and Preparations</p> <p>Decree 158/2010 of 23 March 2010 of the Ministry of Health laying down formal requirements for the book of narcotic substances and keeping records of narcotic substances proving receipt and dispensing of narcotic and psychotropic substances</p>	<p>Act. N. 140/1998 on medicinal products and medical devices, replaced by Act. N. 362/2011 on medicinal products and medical devices¹</p> <p>Act. N. 147/2001 on Advertising of Medicinal Products</p>	<p>Regulation regarding standards for diagnosis and treatment</p>	<p>Vocational guidance No. M/0509/2003 on the standards for the diagnosis and treatment of drug dependencies</p>	
<p>SLOVENIA</p>	<p>Order on the Promulgation of the Prevention of the Use of Illicit Drugs and Dealing with consumers of Illicit Drugs Act</p> <p>Production of and Trade in Illicit Drugs Act</p> <p>Decree on the Scheduling of Illicit Drugs</p>				

1 Although Act. N. 140/1998 has been replaced by Act. N. 362/2011, no important changes have been made to the parts that were indicated as relevant by the national counterpart. Therefore, Act. N. 140/1998 has been (partly) reviewed.

<p>SLOVENIA</p>	<p>Rules Governing the Procedures for the Issue of Licences for Illicit Drugs Marketing</p> <p>Rules on Method And Form of Record-keeping and of Reports on Illicit Drugs</p> <p>Rules on Technical And Sanitary Conditions And on the Method of Insurance of Premises for Storage and Dispensing of Illicit Drugs from Groups I and II</p>	<p>Rules on classifying, prescribing and dispensing medicinal products for human use</p>	<p>Law on Health Care and Health Insurance</p> <p>Act(s) Amending the Health Care and Health Insurance Act</p> <p>General agreement 2010</p> <p>Resolution on National plan of health care 2008-2013</p>		<p>The constitution of the Republic of Slovenia</p>
<p>TURKEY</p>	<p>Law No.2313 (12/06/1933) on Supervision of Narcotic Drug</p> <p>Circular No.5725 (26/01/1984) on submitting consumables of controlled substances and pharmaceutical preparations</p> <p>Circular No.5768 (29/05/1985) on the prescription of narcotics, controlled drugs and preparations</p> <p>Circular No.09/2677 (02/01/1986)</p>	<p>Pharmaceuticals Track&Trace System</p> <p>Law No.1262 (26/05/1928) on the Pharmaceuticals and Medicinal products</p>		<p>Regulation No. 25375 on Substance Abuse Treatment Centres (16/03/2004)</p>	<p>Law No.984 (12/03/1927) on stores where toxic and effective chemical substances used in pharmaceutical businesses and in vocational & agriculture businesses are sold</p>

Annex 2. Feedback form ATOME legislation review

Feedback document: ATOME legislation review country report, country X

Date

Is the reviewed legislation (paragraph 6.1) still valid? If not, please specify....

Are the translations correct? This is even more important for the translation of provisions that are identified as potential barriers in the category 'language'. Please specify....

Are there any doubts or disagreements regarding the identification of potential barriers? Please specify....

Are there potential legal or regulatory barriers missing? Please specify...

Are there any doubts or disagreements regarding the proposed recommendations? Please specify...

Are there any recommendations missing that should be added? Please specify...

Are there any other questions, comments or concerns we should take into account? Please specify...



CHAPTER 2.3

BARRIERS TO ACCESS TO OPIOID MEDICINES FOR PATIENTS WITH OPIOID DEPENDENCE: A REVIEW OF LEGISLATION AND REGULATIONS IN ELEVEN CENTRAL AND EASTERN EUROPEAN COUNTRIES

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Willem Scholten, John A. Lisman, Marija Subataite, Marie-Hélène D.B. Schutjens

Addiction, 2017; 112(6): 1069-1076



ABSTRACT

BACKGROUND AND AIMS: Barriers linked to drug control systems are considered to contribute to inequitable access to controlled medicines, leaving millions of people in pain and suffering. Most studies focus on access to opioids for the treatment of severe (cancer) pain. This study aims to identify specific access barriers for patients with opioid dependence in legislation and regulations of 11 central and eastern European countries.

METHODS: This study builds on a previous analysis of legislation and regulations as part of the EU 7th Framework Access To Opioid Medication in Europe (ATOME) project. An in-depth analysis was undertaken to determine specific barriers for patients with opioid dependence in need of opioid analgesics or opioid agonist therapy (OAT). For each country, the number and nature of specific potential barriers for these patients were assessed according to previously established eight categories. An additional key word search was conducted to minimize the omission of barriers. Barriers in the category language were recorded qualitatively.

RESULTS: Ten of the 11 countries (all except Estonia) showed specific potential barriers in their legislation and regulations. The total number varied from two (Slovenia) to 46 (Lithuania); the number of categories varied from one (Slovenia) to five (Lithuania). Most specific potential barriers were shown in the categories 'prescribing', 'usage' and 'other'. The total number in a single category varied from 1 to 18 (Lithuania, prescribing). Individual differences between countries in the same specific potential barrier were shown, for example variation in minimum age criteria for admission to OAT ranging from 15 (Lithuania, in special cases) to 20 years (Greece). All countries had stigmatising language in their legislation.

CONCLUSIONS: Patients with opioid dependence may experience specific barriers to accessing opioids in addition to those experienced by other patients. The impact of lifting these barriers for individual patients and public health needs to be assessed in future research.

INTRODUCTION

The urgent need to establish equitable access to controlled medicines was recently called attention to by the Global Commission on Drug Policy.^{1,2} Each year tens of millions of people suffer from unrelieved pain due to lack of access to controlled medicines.³ It is estimated that 92 percent of the global supply of morphine is consumed by only 17 percent of the world's population.⁴ In its report, the Global Commission on Drug Policy addresses the crucial role played by barriers linked to the international drug control system in limiting access to controlled medicines. As international drug control policies, from a historical perspective, aimed at preventing illicit use and diversion using punitive approaches, public health and human rights are not prioritized. This imbalance in drug control policies has resulted in inequitable access to controlled medicines. A particularly disadvantaged group are people with opioid dependence. Despite strong lobbying efforts from international harm reduction organisations, access to controlled medicines for the treatment of opioid dependence remains a relatively neglected area. When discussing patients in need of controlled medicines, patients with cancer pain tend to be prioritized over patients with opioid dependence.²

Existing literature recognizes the major role of drug control policies in limiting access to opioid medicines in addition to other factors such as economic aspects, lack of knowledge and societal attitudes.³⁻⁵ Available data indicate that when drafting legislation and regulations, the need to prevent non-medical use and diversion is prioritized over the need to ensure access to and availability of opioid medicines.^{2,3} As a consequence, national governments and policy makers frequently implement unduly strict control measures that impede access to opioid medicines in a way that is disproportional to their impact on the prevention of abuse and diversion.⁶ A previous analysis of legislation and regulations as a part of the EU 7th Framework Access To Opioid Medication in Europe (ATOME) project revealed a total of 778 potential barriers to access to opioid medicines in 11 central and eastern European countries with statistical evidence of low morphine consumption per capita (Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Serbia, Slovakia, Slovenia and Turkey).⁷ Frequently reported legal and regulatory restrictions to access included limitations on the treatment period or dosage that can be provided in a prescription, restrictions regarding prescribing or dispensing privileges (for example limited to a certain medical specialty), the use of special prescription forms in multiple copies and burdensome administrative requirements for record-keeping and storage.⁶⁻¹³

While the frequently reported barriers - when encountered - apply to all or the majority of patients, specific patient groups may experience specific barriers in accessing opioid medicines. This is in particular the case for patients with opioid dependence. For example, access to opioid agonist treatment (OAT) is often hindered due to strict admission criteria such as minimum age restrictions that deny access to young people who use drugs.¹⁴ Specific barriers to access for patients with opioid dependence that may be linked to drug control systems include high costs for OAT, limited coverage of harm reduction services, lack of access to OAT through primary care or in prison, long waiting lists, strict supervision requirements upon administration of medicines, lack of confidentiality and privacy and difficulties in accessing adequate pain relief.^{2,3,14-16} The clinical consequences, both at an individual and at a global level, can be immense.^{2,17} Observational studies for example show that access to methadone used for OAT is associated with an average 54% reduction in the risk of HIV transmission among people who inject drugs (PWID).¹⁸ In addition, implementation of OAT is associated with reductions in the risk of hepatitis C infection, opioid overdose, drug related deaths and crimes.^{17,19} Moreover OAT has been shown to increase adherence to tuberculosis treatment and antiretroviral therapy.^{17,19} It is estimated that OAT has a benefit return of four times its treatment costs, with OAT with methadone being among the most cost-effective treatments.^{2,19-21}

Despite solid evidence supporting effectiveness and cost-effectiveness of OAT, coverage of OAT is considered to be very low.^{2,4,22} The International Narcotics Control Board (INCB) reported that narcotic drugs were used in OAT in drug dependence in 68% of the 100 surveyed countries in 2014.⁴ In countries where OAT is available, the quality and coverage of OAT are frequently below international standards.² A systematic review of the literature showed that national and regional coverage of OAT in PWID varied from one to 61 recipients per 100 PWID per year.²² Other data from the INCB show a major imbalance between the consumption of methadone and the prevalence of people who inject drugs in eastern Europe.⁴ In eastern Europe the level of methadone consumption seems to be very low despite a high prevalence of people who inject drugs, which may be related to the fact that several countries in eastern Europe do not recognise the use of methadone.⁴

To date, several studies demonstrated potential barriers to access to opioids that can be linked to the international drug control system. However, the majority of these studies focus on the treatment of moderate to severe (cancer) pain and little is known on these types of barriers affecting patients with opioid dependence. The aim of this study was to identify specific potential barriers to access to opioid medicines for patients with opioid dependence through an in-depth analysis of national legislation and regulations in these countries.

METHODS

The methods used to systematically review national legislation and regulations have been described in detail in a previous study.⁷ An additional in-depth analysis was undertaken within the results of the previous study (all provisions that were considered to contain at least one potential barrier to access to opioid medicines) to identify all specific potential barriers to access to opioid medicines for patients with opioid dependence. No analytical software was used for the retrieval and coding of data in the previous study nor in the additional in-depth analysis.

General review: selection of potential barriers to access to opioid medicines (all patient groups)⁷

In short, legislation and regulations concerning opioid medicines were selected by key experts in each country in the period March 2011 until February 2013. Legislation and regulations were translated into English by a professional translation agency specialised in the field of health and law (NOVA Language Services, Barcelona, Spain) if it was only available in the national language. In order to review selected legislation and regulations, a method was developed using a template with potential barriers to access to opioid medicines focusing on eight different categories (prescribing; dispensing; manufacturing; usage; trade and distribution; affordability; penalties; and other) and language issues. The template was developed based on WHO policy guidelines and additional literature regarding barriers to access.^{3,9,11,23,24}

A total of 93 relevant legal and regulatory documents were (partly) analysed by one reviewer (author M.J.M.V.) ranging from three (Greece) to 15 (Latvia) documents per country (see Table S2). Legal or regulatory provisions related to controlled substances and opioid medicines were selected and were subsequently further reviewed using the template by three reviewers independently (authors J.A.L., M.D.B.S. and M.J.M.V.). Potential barriers to access to opioid medicines were identified and differences in views between the reviewers regarding the identification of potential barriers were discussed until consensus was reached. Newly identified barriers were added to the template and the reviewed legislation and regulations were checked retrospectively to complete the process.

The reliability of the selection of provisions for further review by one reviewer (author M.J.M.V.) was validated by assessing the inter-rater reliability of the selection of provisions between two reviewers (authors M.D.B.S. and M.J.M.V.) for a selected number of countries. The controlled substances law of three randomly selected countries (Hungary, Serbia and

Slovakia) was reviewed by the two reviewers and provisions were independently selected for further review. The selection by the two reviewers was compared using Cohen's kappa statistics and was rated to be very good (kappa= 0.87). Following validation of the selection of provisions, the assessment instrument was piloted by all three reviewers to align the review process: selected provisions of one country (Greece) were analysed based on the assessment instrument and the three reviewers met to discuss differences of views which concerned general interpretation of the assessment instrument.

Current analysis: identification of specific potential barriers for patients with opioid dependence

For the purpose of this paper, an in-depth analysis was made by reviewing all previously identified 778 potential barriers to access (ranging from 22 in Cyprus to 128 in Lithuania, see Figure 1) that were identified in eight categories (all except language) to identify potential barriers that are applicable for patients with opioid dependence exclusively. For each provision the patient group that could be affected was determined (author M.J.M.V.), and provisions were selected if this patient group was limited to patients with opioid dependence. The selected provisions were checked by one reviewer (author M.D.B.S.) and were recorded as potential barriers to access to opioid medicines for patients with opioid dependence exclusively. An additional search was made within all 778 potential barriers that were identified in the previous study using a set of keywords ("substitution", "substitute", "OAT", "OST", "methadone", "buprenorphine", "prison", "detention", "harm reduction" and "substance abuse") to reduce the omission of potential barriers for patients with opioid dependence. Additionally, all potential barriers in the category language identified in the previous study were reviewed and potential barriers that contribute to the stigmatisation of patients with opioid dependence were recorded qualitatively. The validation of methods and results have been described in detail in the previous study.⁷ No changes were made to the results of the additional analysis based on the keyword search.

Data analysis

The total number of specific potential barriers for patients with opioid dependence was calculated by country and by category (all categories except 'language'). The total number of specific barriers was also calculated in relation to the total number of barriers identified in the previous analysis. The presence of potential barriers in the category language was recorded qualitatively per country. Examples of potential barriers were highlighted for the categories prescribing, usage, affordability, other and language.

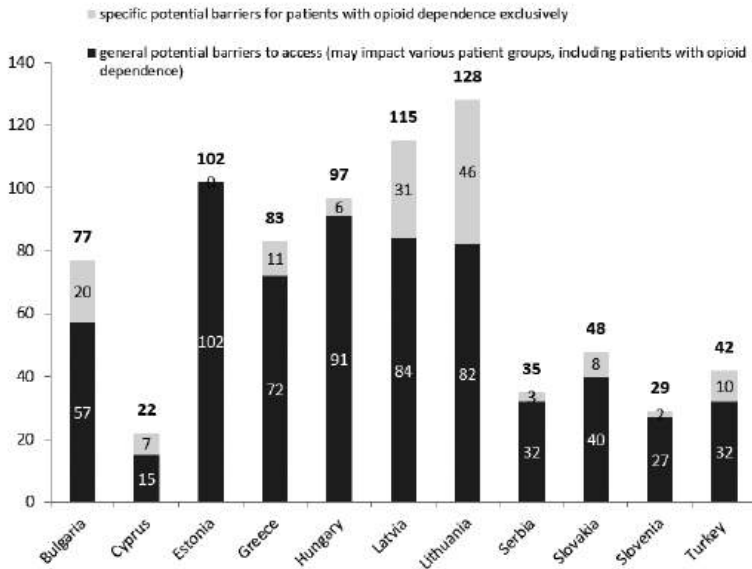


Figure 1. Number of specific potential barriers for patients with opioid dependence exclusively in relation to the number of general potential barriers identified per country (except category language)

RESULTS

Specific potential barriers for patients with opioid dependence

In total, 778 potential barriers to access to opioids were reviewed in 11 countries varying from 22 (Cyprus) to 128 (Lithuania). Of these 778 potential barriers, a total of 144 barriers (19%) in ten countries (all except Estonia) were considered potential barriers exclusively for patients with opioid dependence with the smallest number in Slovenia ($n = 2$, 7%) and the largest number in Lithuania ($n = 46$, 36%) (Figure 1). The number of categories where dependence-related items were found varied between one (Slovenia) to five (Lithuania) of the eight categories (Figure 2). Nine countries showed potential barriers in the category 'prescribing', while the total number of barriers in each category varied from one (several countries, several categories) to 18 (Lithuania, prescribing) (Figure 2). Most barriers were identified in the categories prescribing, usage and other. All 11 countries use language in their legislation that contributes to the stigmatisation of patients with opioid dependence (see Supporting information, Table S1).

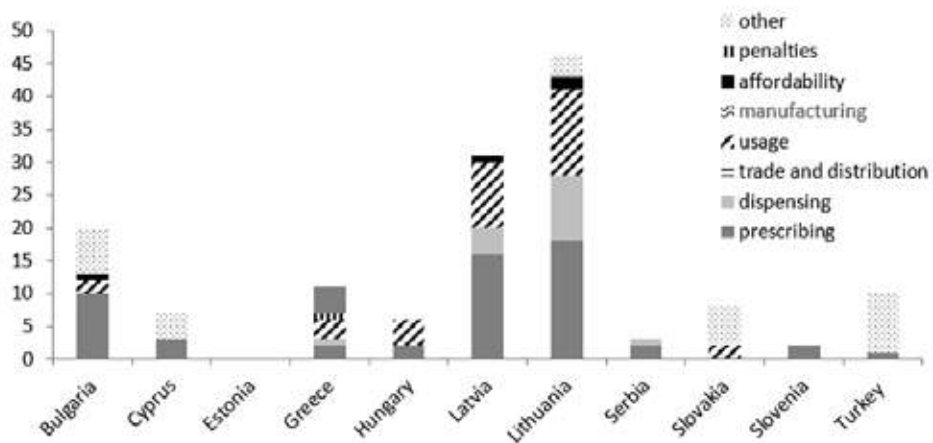


Figure 2. Total number of specific potential barriers for patients with opioid dependence identified per country according to category (except category language). See the online article for a colour version of this Figure: <https://www.ncbi.nlm.nih.gov/pubmed/28087986>.

Examples of provisions identified (categories prescribing, usage, affordability, other and language)

Examples of potential barriers concerning the usage of opioid medicines included strict admission and exclusion criteria for accessing OAT such as minimum age criteria varying from 15 to 20 years (Bulgaria, Greece, Latvia and Lithuania), the requirement of evidence of repeated failure to successfully complete a therapeutic treatment programme aiming at abstinence (Bulgaria and Latvia), or the requirement of being opioid dependent for a minimum period of time (Latvia) (see Table S1). Examples of potential barriers concerning the prescribing of opioid medicines included limitations regarding the authorisation to prescribe opioid medicines or assign OAT (Bulgaria, Latvia, Lithuania, Serbia, Slovakia), administrative requirements for prescribing opioid medicines or assigning OAT (Cyprus, Greece, Hungary, Latvia, Lithuania and Serbia) and limitations regarding the dosage or amount to be prescribed (Latvia, Serbia, Slovenia and Turkey) (see Table S1). Examples of other potential barriers included the availability and affordability of OAT (Bulgaria, Latvia, Lithuania, Serbia and Turkey) and requirements that may interfere with the privacy of patients (Bulgaria, Cyprus, Lithuania, Slovakia and Turkey) (see Table S1). Examples of language used in legislation and regulations that contributes to the stigmatisation of patients with opioid dependence include referring to patients with opioid dependence as ‘addicts’ (all except Hungary and Lithuania), referring to dependence as ‘addiction’ (all countries) or referring to medicines used in OAT as substances to be used as a substitute for addictive narcotics (see Table S1).

DISCUSSION

The results of this study showed that patients with opioid dependence may experience specific barriers to access to opioid medicines that can be linked to drug control systems. The majority of these potential barriers concerned the prescribing and usage of opioid medicines such as minimum age criteria for admission to harm reduction treatment services and other admission criteria for accessing OAT. Additionally, all countries use language in their legislation and regulations that contributes to the stigmatisation of opioid dependence.

This is the first in-depth analysis of national legislation and regulations focussing on potential barriers to access to opioid medicines for patients with opioid dependence. Barriers to access to harm reduction services have been previously reported by other studies that used different methods such as survey research, a review of literature and descriptive studies.^{14-16,20,25} The majority of these studies addressed several types of barriers including barriers that may be linked to drug control systems. For example, a survey by Schulte et al. revealed that physicians in Germany considered strict legislation and regulations in combination with complex documentation requirements the main obstacles for the provision of OAT.¹⁶

Other reported barriers by Schulte et al. included financial remuneration, insufficient medical qualification of professionals providing OAT and inadequate interdisciplinary cooperation.¹⁶ Results of previous studies that were similar to the results of the current study included age restrictions for accessing harm reduction services, strict admission criteria, treatment costs and strict exclusion criteria.^{14-16,20,25} Different results were for example described for fear of legal sanctions for violating controlled substances legislation or regulations. Although overly strict legal sanctions were identified in the previous analysis⁷, these sanctions were considered to be aimed at preventing non-medical use of opioids and diversion in general and were therefore not identified as potential barriers for patients with opioid dependence.

A considerable proportion of the potential barriers to opioid medicines that can be linked to the drug control system primarily affects patients with opioid dependence. As a result of these legal and regulatory barriers, healthcare professionals may be unable or reluctant to prescribe or dispense opioid medicines. Fear for sanctions for unintended violations and (high costs associated with) strict requirements may deter healthcare providers from initiating or continuing treatment. Likewise, patients with opioid dependence may be unable or unwilling to use opioid medicines due to the stigma associated with opioids and opioid dependence, the high treatment costs and access restrictions. Government representatives, policy makers and other stakeholders should recognize this vulnerable patient group while drafting new legislation and regulations. This is even more important considering that international

lobbying efforts for this patient group due to the stigma related to opioid dependence fall short compared to other patient groups in need of opioid medicines. Misconceptions and even prejudices about opioid dependence being a wilful choice or a moral weakness often prevail and opioid dependence is rarely acknowledged as a medical condition.²⁶ The language used in legislation and regulations revealed in this in-depth analysis confirms an attitude towards people with opioid dependence characterised by stigmatisation and criminalisation (see examples in Table S1). Additionally, given that a chain is only as strong as its weakest link other factors that limit access should be taken into account while developing strategies to improve access to opioid medicines. These factors may be interlinked: the fear for non-medical use and diversion of opioid substances may result in overly strict drug control measures and overly strict control measures may cause fear among patients, healthcare professionals and policy makers for using opioid medicines. This may in particular be the case for patients with (a history of) dependence in need of treatment with opioid analgesics; due to the fear that they are more susceptible to developing opioid dependence they may face more difficulties in accessing adequate pain relief.² More scientific data are needed to assess the different types of barriers that limit access to opioid medicines and the impact of lifting these potential barriers in clinical practice for individual patients with opioid dependence and for public health. To increase insight in the impact of potential barriers in clinical practice, a survey could be undertaken among patients with opioid dependence and their healthcare providers in the European countries that participated in the ATOME project. This survey could focus on the quality of the treatment provided, both from a patient and healthcare provider perspective, and on barriers that were encountered that hampered adequate treatment. In addition to the current study which comprises a static analysis of legislation and regulations, future studies could also look into the dynamic process of development of legislation and regulations while taking into account evolving evidence based medical treatment insights and changes in concerns that existed within society regarding opioid dependence. Further studies could also generate an overview of best practice examples from countries that successfully revised their outdated legislation while providing information on the characteristics of their legal system; this information may be beneficial to other countries with a similar legal system.

Several limitations of this in-depth analysis should be mentioned, which primarily concern limitations that were reported in the previous study.⁷ The results of this study showed a variation between countries in the total number of potential barriers for patients with opioid dependence. This variation may be the result of differences in the level of impediment of national drug control systems. The differences may also be associated with the level at which certain requirements are set out. For example, admission criteria for accessing OAT may be

set out in national laws, regulations, ministerial decrees and guidelines, or may be left at the discretion of individual treatment centres. The variation in potential barriers between countries could (partly) be the result of incomplete selection of legislation and regulations in the 11 countries, which is a limitation of this study. Legislation regulating opioid substances and medicines was provided by key experts in 11 countries (see Table S2). Underreporting of potential barriers due to incomplete selection of legislation and regulations cannot be precluded. A second limitation of this study is the translation of legal and regulatory data, which may have caused incomplete or incorrect reporting of potential barriers. Actions were undertaken to minimize incomplete selection of documents and incorrect translation such as training and support of the key experts and dissemination of the results among the national counterparts with the explicit request to provide feedback.⁷ A third limitation of this study concerns the analysis; as the methods of this study comprise an analysis of legal text, inevitably variation of interpretation may occur. By involving multiple reviewers the chances of divergent interpretations have been minimised.

In conclusion, the results of this in-depth analysis of national legislation and regulations of central and eastern European countries showed that patients with opioid dependence may experience particular challenges in accessing treatment with opioid medicines in addition to those experienced by other patients. As most other analysis of legal and regulatory texts have focussed on access to opioid medicines used in (cancer) pain management, access to opioid medicines for the treatment of opioid dependence remains a neglected area of study. More research is therefore needed to assess the relation between barriers linked to drug control systems and access to treatment with opioid medicines for patients with opioid dependence. As these findings suggest that a considerable proportion of the drug control provisions may primarily interfere with the adequate treatment of patients with opioid dependence, government representatives and policy makers should keep this vulnerable patient group in mind and possibly reconsider existing legislation from this angle.

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Table S1. Examples of potential barriers for patients with dependence (categories prescribing, usage, affordability and other)

COUNTRY	AGE RESTRICTIONS FOR ACCESSING HARM REDUCTION	OTHER STRICT ADMISSION CRITERIA (examples)	SANCTIONS FOR VIOLATING TREATMENT RULES (examples)	VIOLATION OF PRIVACY
BULGARIA	18 years	“(…) at least three formally documented treatment programmes before (…)”		<p>“The National centre of drug addictions shall establish and maintain an official data base of persons, included in programmes for treatment with agonists and agonist-anti-agonists.”</p> <p>“The data base under para 1 shall contain:</p> <ol style="list-style-type: none"> 1. unique identification code of the person; 2. medical product, used for the treatment of the person; 3. data of placement and the name of the medical establishment, carrying out the treatment programme with agonists and agonist-anti-agonists; 4. date of discharge from the treatment programme with agonists and agonist-anti-agonists;”
CYPRUS				<p>“Subject to paragraph (2), any medical practitioner who treats any person whom he considers or has reasonable grounds to consider to be addicted to any controlled drug specified in the Sixth Schedule, shall, within seven days from the first visit, furnish in writing a medical officer designated by the Minister of Health, with such of the following particulars relating to that person as may be known to the medical practitioner, that is; the name, address, sex, date of birth and number of identity card of the said person, the date of the medical visit and the name of the relevant drug.”</p>
ESTONIA				

<p>GREECE</p>	<p>20 years</p>	<p>“The inclusion conditions for addicts in rehabilitation programmes are the following: a) (...) b) The addict must have been doing long-term intravenous use of heroin or another opioid substance; c) This use has caused a physical and mental addiction; (...) f) The addict must not experience any severe psychopathological symptoms that make him/her ineligible to participate in the programme.”</p>		
<p>HUNGARY</p>		<p>“If the drug dependence of an involved person has been established by a forensic medical expert in a criminal procedure, the treatment or service can commence within six months of the issuance of the opinion without early status assessment. If the treatment or service does not commence within the six-month period, the involved person shall participate in early status assessment. If the early status assessment differs from the results of the previous forensic medical expert opinion, the institution performing early status assessment shall inform the court, public prosecutor or investigating authority proceeding in the case.”</p>		

<p>LATVIA</p>	<p>18 years</p>	<p>“The doctor’s council established by the State limited liability company Rīga Psychiatry and Narcology Centre (hereinafter – doctor’s council) shall decide on:</p> <p>2.1.1. the commencement of the replacement treatment, if a patient addicted to narcotic substances is a pregnant female or suffers from HIV, AIDS, hepatitis B or hepatitis C, syphilis, tuberculosis or other severe chronic diseases, due to which it is not possible to stop using narcotic substances, and if a patient addicted to narcotic substances:</p> <p>2.1.1.1. is more than 18 years old;</p> <p>2.1.1.2. is addicted to narcotic substances for not less than five years; or</p> <p>2.1.1.3. has undergone treatment unsuccessfully at least two times;</p> <p>2.1.2. medicines used in the replacement treatment and daily intake thereof; and</p> <p>2.1.3. change of medicines used in the replacement treatment or on increase of the daily intake.”</p>	<p>“The replacement treatment of a patient addicted to narcotic substances shall be terminated, if:</p> <p>40.1. carrying out the analyses; it is determined, that a patient addicted to narcotic substances is using alcohol, other narcotic or psychotropic substances and medicines or medicines without a doctor’s order during medical treatment;</p> <p>40.2. serious side effects from the use of the medicines have been observed in a patient addicted to narcotic substances;</p> <p>40.3. a patient addicted to narcotic substances without a justifiable reason fails to attend at the State limited liability company Rīga Psychiatry and Narcology Centre or to the outpatient department of the medical treatment institution referred to in Paragraph 25 of these Regulations for more than five days or does not attend a narcologist at the specified time; or</p> <p>40.4. if a patient addicted to narcotic substances uses the medicines, not taking into account the instructions on the use of the medicines, or distributes them to other persons.”</p>	
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<p>LITHUANIA</p>	<p>18 years (15-18 years only in special cases)</p>	<p>“Patients are referred to the rehabilitation centre based on the selection criteria for rehabilitation, if they express in writing their wish to give up their addictions, and there are reference letters written by the psychiatrist, the psychologist and the group mentor of that correctional institution, where they serve their time and the administration of this correctional institution approved such recommendations.”</p> <p>“Substitution maintenance therapy is applied only after soliciting personal identification documents.”</p>	<p>-</p>	<p>“HCI provides information about persons who have initiated the substitution maintenance therapy or completed such therapy, following the procedure established by the Ministry of Health of the Republic of Lithuania.”</p>
<p>SERBIA</p>	<p>-</p>	<p>-</p>	<p>-</p>	<p>-</p>
<p>SLOVAKIA</p>	<p>-</p>	<p>-</p>	<p>“Exclusion criteria a) Lack of patient cooperation If a clinician objectively finds the patient to be insufficiently cooperative (for example, a further diagnosis of the patient at the stage of decompensation of severe mental illness, the patient lives too far from the dispensary and clinic for maintenance treatment, a pending unconditional imprisonment without the possibility of providing methadone in prison, etc.).</p>	<p>-</p>

<p>SLOVAKIA</p>			<p>b) Health reasons Severe hepatic, renal, or cardiopulmonary insufficiency and possibly other reasons arising from the patient's physical disorders, at the doctor's discretion. c) Other criteria Other criteria may be established on the basis of the specific methadone programme regimen in a given centre for drug treatment (the patient does not have health insurance, distance problems and others)."</p>	<p>"(...) Evidence and treatment of patients in the MMT may have indirect negative impacts on the patient, for example loss of civil rights. The patient registry aims to allow effective organization of work in the MMT, avoid methadone prescription duplication and prevent narcotics from being used illegally. Records of dispensing methadone must be kept in a form that is suitable for recording opiate administration in medical facilities. The substance must be stored in a secure place to ensure its protection against unauthorized access. The entire dispensary and MMT workplace must be also secured against physical threats."</p>
<p>SLOVENIA</p>			<p>-</p>	<p>-</p>
<p>TURKEY</p>			<p>-</p>	<p>"The examination, diagnosis and treatment of patients admitted to the medical and administrative procedures at the centres, with respect to the records, must be kept in an orderly manner in accordance with the relevant legislation. Based on their needs, centres may store any registration system on their computers. For this purpose, the computer system must start out with the first number in the new system and this must be approved by the head of the institution. Keeping records in a computer environment does not eliminate the requirement for having a written record system. (...)"</p>

COUNTRY	AVAILABILITY OF OAT	AFFORDABILITY OF OAT	DOSAGE OR QUANTITY RESTRICTIONS	USE OF STIGMATISING LANGUAGE
BULGARIA	<p>"The substitution and maintenance programmes implemented by medical institutions without state and/or municipal interest, may apply for receiving the opioid agonists and agonists-antagonists under Art. 11, Para 1, if the persons included in the programme provide services in accordance with Annex No. 3."</p> <p>"Annex No. 1 under Art. 2 (New, SG, issue 70, dated 2007) List of narcotic substances and their preparations (opioid agonists and agonists-antagonists); morphine and methadone"</p>	<p>"A minimum package of services provided for persons addicted to narcotic substances, included in substitution and maintenance programmes. (...) For the provision of treatment under items 1-12 the patients shall pay a monthly fee at the amount of one third of the minimum salary for the country."</p>		<p>"The control on the territory of the country over treatment of persons, addicted to narcotic substances shall be exercised by officials of the regional health inspectorates, having higher medical education."</p>
CYPRUS	-	-	-	<p>"For the purpose of these Regulations a person shall be deemed to be addicted to a controlled drug prescribed in the Sixth Schedule if, as a result of the repeated administration of a controlled drug, he has the irresistible wish to continue to take the same."</p>
ESTONIA	-	-	-	<p>"Hospitalization of drug addicts who pose a danger to themselves or others due to a mental disorder, regardless of their will, shall be effected pursuant to legislation regulating mental health care."</p>

GREECE				<p>-</p>	<p>"The administration of substances to be used as a substitute for addictive narcotics is prohibited. By exception, the issuance of such substances shall be allowed by: a) (...); b) (...)."</p>
HUNGARY				<p>-</p>	<p>"The early status assessment shall be performed by a psychiatrist, addiction medicine specialist or clinical psychologist (hereinafter: institution performing the status assessment) of a health service provider referred to in Section 3 (...)."</p>
LATVIA	<p>-</p>	<p>"(...) Up to now, maintenance pharmacological treatment of opioid addiction has been available only in Riga. In view of the present epidemiological situation the availability of pharmacotherapy for treating opioid addicts should be increased through extending it to more patients in all the regions. The experience in long term pharmacological treatment of opioid addiction accumulated at the state company Riga Centre for Psychiatry and Addiction Disorders will serve as a basis for developing a help network for addicts, supplying the service providers with the required resources, including training of health practitioners."</p>	<p>Buprenorphine is not listed as a medicinal product that is reimbursed</p>	<p>"After evaluation of the psychic, somatic and neurological state of a patient addicted to narcotic substances for whom a card has been issued and the determination of non-compliance with the criteria specified in Paragraph 40 of these Regulations, the narcologist shall prescribe the medicines containing buprenorphine on a special prescription form for outpatient treatment not more than once in two weeks, and not exceeding the daily intake of buprenorphine specified by the doctors' council."</p>	<p>"To provide harm reduction measures, including continued pharmacotherapy for opioid addicts in prisons."</p>

LITHUANIA		<p>“Centres for dependence diseases provide treatment based on their own budget.”</p> <p>“Opioid substitute medications and narcotic drug screening tests for people who have compulsory health insurance are covered from the funds of the Compulsory Health Insurance Fund Budget allocated for them and for uninsured persons – from municipal or county budgets, other programmes.”</p>		<p>“Patients are referred to the rehabilitation centre based on the selection criteria for rehabilitation, if they express in writing their wish to give up their addictions, and there are reference letters written by the psychiatrist, the psychologist and the group mentor of that correctional institution, where they serve their time and the administration of this correctional institution approved such recommendations.”</p>
SERBIA			<p>“(1) For one-time dispensing, the doctor may prescribe a medicine that contains at most: (...) 4) 0.2 g of methadone chloride; (...)”</p>	<p>“Compulsory Treatment of Narcotics Addicts (1) The court shall order compulsory treatment to an offender who has committed a criminal offence due to addiction to narcotic media and if there exists a serious danger that he may continue committing criminal offences due to this addiction.”</p>
SLOVAKIA				<p>“(…) There is an urgent need for Slovakia to include methadone maintenance treatment in systematic medical practice in drug addiction. The main objective of methadone maintenance treatment is to medically help patients addicted to opiates, which leads not only to improving their mental and physical health, but at the same time to improving relations and arranging their families to improve their work productivity, social inclusion, to reducing drug-related crime and thus to increasing security in society.(…)”</p>

COUNTRY	AUTHORISATION TO PRESCRIBE/ ASSIGN OAT (examples)	PROCEDURES PRESCRIBING/ASSIGNING (examples)	
SLOVENIA		<p>"For single dispensing, a general practitioner may prescribe a medicinal product for a single user in quantities for treatment up to 30 days, namely: (...). The specified quantities refer to the amount of a medicinal product in the pharmaceutical form. The quantities from the first paragraph hereunder do not apply to the treatment of addiction, and if they are prescribed by means of a special order form for use in health institutes and by legal and natural persons practicing medical activity."</p>	<p>"The quantities from the first paragraph hereunder do not apply to the <i>treatment of addiction</i> (...)."</p>
TURKEY		<p>"Maximum Doses That Can Be Prescribed For Narcotic Drugs (Preparations) (...) Methadone 125 mg (...)"</p>	<p>"The purpose of this regulation is the treatment and rehabilitation of <i>drug addicts</i> at institutions and organisations within the public and private health care system or substance abuse treatment centres which are established as self-contained facilities, services, and the staff has been identified, and the criteria to open up its activities, to regulate the principles and procedures for auditing and closures specified."</p>

<p>BULGARIA</p>	<p>“A substitution and maintenance therapy programme shall be led by physicians with recognized qualifications in psychiatry or toxicology or internal diseases.”</p> <p>“When the head of programme is not a physician with recognized qualifications in psychiatry, the treatment shall be prescribed by a physician with recognized qualifications in psychiatry, who has attended a training based on a curriculum, approved by the National Centre on Drug Abuse.”</p> <p>“The substitution and maintenance programmes which use opiates (opioid agonists and agonists-antagonists) may be implemented by individual psychiatric care practices, specialized psychiatric care group practices, medical centres, diagnostic and consultancy centres, psychiatric dispensaries or medical institutions which provide psychiatric care, in which a medical specialist with recognized qualifications in psychiatry or toxicology or internal diseases is available.”</p>			
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<p>CYPRUS</p>	<p>-</p>	<p>"Subject to paragraph (2), any medical practitioner who treats any person whom he considers or has reasonable grounds to consider to be addicted to any controlled drug specified in the Sixth Schedule, shall, within seven days from the first visit, furnish in writing a medical officer designated by the Minister of Health, with such of the following particulars relating to that person as may be known to the medical practitioner, that is, the name, address, sex, date of birth and number of identity card of the said person, the date of the medical visit and the name of the relevant drug."</p>	<p>-</p>	<p>-</p>
<p>ESTONIA</p>	<p>-</p>	<p>-</p>	<p>-</p>	<p>-</p>
<p>GREECE</p>	<p>"The administration of substances to be used as a substitute for addictive narcotics is prohibited. By exception, the issuance of such substances shall be allowed by: a) public units that specialize in such cases which have been issued a special license at the behest of the Minister for Health and Social Solidarity after an opinion has been submitted by the Organisation Against Drugs (known by its Greek acronym, OKANA); b) OKANA upon the issuance of a relevant license at the behest of the Ministry of Health & Social Solidarity. The above decisions shall determine in particular the substances that shall be allowed to be issued and the terms governing their issuance."</p>	<p>"Proprietary medications which contain opioid agonist substances are dispensed with an agonist substance prescription. This prescription is written in duplicate form and carries the following information: "AGONIST SUBSTANCE PRESCRIPTION", along with the serial number and the full name, specialization, address and telephone number of the physician who dispenses the prescription."</p>	<p>-</p>	<p>-</p>

<p>"An involved person whose drug dependence has been established by a forensic medical expert in a criminal procedure – in consideration of the provisions of Paragraph (3) – may participate only in treatment for drug addiction."</p>	<p>"In the written notification pursuant to Subsection (2), the discharging institution must provide a statement of the reasons which necessitated the change of the institution providing the treatment or service, and certify the duration of the treatment or service it has delivered to the involved person. The institution shall supply the involved person with a discharge summary, or a treatment report of identical contents therewith."</p> <p>"The institution providing the treatment or services shall issue a certificate laid down in Annex 2 and attesting to the participation of the involved person in the treatment or service, in five original copies, which shall qualify as an authentic act. One original copy of the certificate shall form part of the health documentation. The involved person shall receive four copies of the certificate."</p>	<p>"After evaluation of the psychic, somatic and neurological state of a patient addicted to narcotic substances for whom a card has been issued and the determination of non-compliance with the criteria specified in Paragraph 40 of these Regulations, the narcologist shall prescribe the medicines containing buprenorphine on a special prescription form for outpatient treatment not more than once in two weeks, and not exceeding the daily intake of buprenorphine specified by the doctors' council."</p>
<p>HUNGARY</p>		<p>"Replacement treatment with methadone shall be performed by the narcologist of the narcological treatment institution who is in contractual relations with the State Mandatory Health Insurance Agency. The narcologist shall ensure that a patient addicted to narcotic substances receives the daily intake of methadone specified in the decision of the doctors' council in the presence of a medical practitioner."</p> <p>LATVIA</p>

		<p>“If the card is lost, a narcologist shall submit a submission to the State limited liability company Riga Psychiatry and Narcology Centre with a request to issue a duplicate of the card. A submission shall be appended with an explanation from the patient addicted to narcotic substances regarding the reasons for losing the card. A card shall be issued within three days after receipt of a submission.”</p> <p>“If the term of validity of a card has terminated, then in order to receive a replacement card, a narcologist shall send the patient addicted to narcotic substances to the doctors’ council and provide information regarding the course of replacement treatment.”</p>	
		<p>“Opioid substitute medications shall be dispensed only in accordance with the HCl requirements to assigned HCl personnel upon presenting an authorization, issued for no more than 3 months’ time period. The request shall contain the exact trade name of the medication, strength, pharmaceutical form, number of doses contained in words and in digits. The authorisation shall be signed by the HCl head AND the chief accountant and sealed with the HCl seal.”</p>	
<p>“Replacement treatment of a patient addicted to narcotic substances with buprenorphine shall be commenced in the inpatient or outpatient department of the State limited liability company Riga Psychiatry and Narcology Centre, ensuring the receipt of the daily intake of buprenorphine specified in the decision of the doctors’ council in the presence of a medical practitioner, and carry out the observation of the patient addicted to narcotic substances. The narcologist shall decide on the duration of observation upon evaluation of the state of health of the patient addicted to narcotic substances.”</p>	<p>“Substitution maintenance therapy is assigned by the decision of a consulting panel of physicians after evaluating the validity of the diagnosis and indications for maintenance therapy made by a psychiatrist.”</p>		
<p>LITHUANIA</p>			

			<p>“Methadone hydrochloride, buprenorphine hydrochloride and other medical preparations, which contain substances listed in Schedule II of narcotic drugs and psychotropic substances, approved by the Order No. 5, 6 January, 2000 by the Minister of Health of the Republic of Lithuania Regarding Approval of Schedules of Narcotic Drugs and Psychotropic Substances (Žin. (Official Gazette), 2000, No. 4-113); requests for listed substances shall be made out on a special request form in 2 copies with an affixed seal of a health care institution (hereinafter HC) and signed by a head or deputy of this institution; it is necessary to indicate the department/ward name as well as purpose for use of this medicinal preparation. The endorsed medicinal preparation order shall contain the date, the surnames and signatures of the receiver and the dispenser.”</p> <p>“Before initiating a substitution maintenance treatment, a physician prepares an individual treatment and testing plan. Based on the specific clinical and social situation, before initiating a substitution maintenance treatment and during its course, this plan should include the following:</p> <p>13.1. Tuberculosis, hepatitis B and C, HIV venereal and other disease screening tests;</p>		<p>“In case of a serious somatic condition, substitution maintenance therapy may be assigned by a practicing psychiatrist. This decision has to be approved by CPP within two weeks.”</p> <p>“Separate positions shall be created for a physician and a nurse responsible for prescribing, dispensing, safekeeping and accounting of opioid substitute medications in mental health centres providing substitution maintenance treatment services.”</p>
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LITHUANIA

	<p>13.2. Treatment of medical complications and intercurrent diseases;</p> <p>13.3. Psychological and social rehabilitation aids;</p> <p>13.4. Psychotropic substance detection in body fluids”</p>	
	<p>“Practitioners, responsible for fulfilment of this treatment and screening plan, no less than once per 3 month verify this plan and register changes in the medical records. If necessary the patient is referred to CPP. No less than once per year SPP will evaluate the effectiveness of substitution maintenance treatment based on the Substitution Maintenance Treatment Assessment Questionnaire enclosed as Annex No. 1 in Description of the Procedure is (hereinafter – Questionnaire). The person authorized by the head of HCI is responsible for implementation of treatment and screening plan prepared for a specific patient.”</p>	
	<p>“The Questionnaire has to be filled for each patient, who is assigned substitution maintenance treatment. For the first time it has to be filled out within 10 days following initiated treatment and repeatedly filled out every 12 months.</p>	

LITHUANIA		<p>The Questionnaire has to be filled out by the practitioner responsible for implementation of such plan and signed by an attending physician. The completed Questionnaires have to be submitted to CPP. They have to be stored at HCI with other patient's records. Based on data presented in the Questionnaires, HCI prepares a review of the evaluation of substitution maintenance treatment effectiveness, which once per year has to be submitted to the State Mental Health Centre."</p>		
SERBIA	<p>"(...) The treatment of dependence through the use of psychoactive controlled substances shall be prohibited outside of healthcare institutions or private practices, and by other legal entities who perform healthcare activities in accordance with the regulations governing healthcare.(...)"</p>	<p>"(...) Healthcare institutions and private practices shall be required to submit, at the request of the Ministry, a special report about the consumption of psychoactive controlled substances for the purpose of treating dependence no later than 10 days after receipt of the Ministry's request."</p>		
SLOVAKIA	<p>"Restrictions: maintenance treatment can only be provided by a psychiatrist in specialized CTDD outpatient programmes, or in drug dependence outpatient facilities."</p>			
SLOVENIA				
TURKEY				

Table S2. Legal and regulatory documents (partly) translated (printed in bold) and (partly) analysed per country

DOCUMENTS (PARTLY) ANALYZED	CONTROLLED SUBSTANCES LEGISLATION (GENERAL)	MEDICINAL PRODUCTS LEGISLATION	LEGISLATION CONCERNING HEALTHCARE	CONTROLLED SUBSTANCES LEGISLATION (DEPENDENCE)	OTHER
BULGARIA	<p>Law for Control over the Narcotic Substances and Precursors (1999)</p> <p>Ordinance No. 21/2000 on the requirements for documentation and reporting during activities involving narcotic substances and their preparations</p>	<p>Law on the Medicinal Products in Human Medicine (2007)</p> <p>Ordinance No 4/2009 on the rules and procedures for the prescription and supply of medicinal products</p>	Ordinance No. 34/2005 on the procedure for state budget funding of the treatment of Bulgarian citizens with regard to diseases beyond the scope of compulsory health insurance	Ordinance No. 24/2000 on the rules and procedures for the implementation of substitution and maintenance programs for the reduction of health damage for persons addicted to narcotic drugs	
CYPRUS	<p>The Narcotic Drugs and Psychotropic Substances Law 1977, incorporating amendments up to 1992.</p> <p>The Narcotic Drugs and Psychotropic Substances Regulations 1979, incorporating amendments up to 1987.</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Regulations of 1995 (Pl. 79/95)</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Law 91(I) of 2003</p>				

	<p>The Narcotic Drugs and Psychotropic Substances (Amendment) Decree of 1996 (P.I. 4/96)</p> <p>The Narcotic Drugs and Psychotropic Substances (Amendment) Law 24(I) of 2010</p>				
ESTONIA	<p>Act on Narcotic Drugs and Psychotropic Substances and Precursors thereof (passed 11 June 1997, RT I 1997, 52, 834, entered into force 1 November 1997)</p> <p>Conditions and Procedure for Handling of Narcotic Drugs and Psychotropic Substances for Medical and Research Purposes, and Conditions and Procedure for Maintaining Records and Reporting in that Area and Schedules of Narcotic Drugs and Psychotropic Substances</p> <p>(Regulation No. 73 of the Minister of Social Affairs of 18 May 2005 (RTL 2005, 57, 807), entered into force 5 July 2005)</p>	<p>Medicinal Products Act</p> <p>(Passed 16 December 2004 (RT I 2005, 2, 4) Entry into force 1 March 2005)</p> <p>The Conditions and Procedure for the Issue of Prescriptions for Medicinal Products and for the Dispensing of Medicinal Products by Pharmacies and the Format of Prescriptions</p> <p>(Approved by Regulation No. 30 of the Minister of Social Affairs of 18 February 2005 (RTL 2005, 23, 315), entered into force 01.03.2005)</p>	<p>Health Insurance Act</p>		<p>The Conditions and Procedure for the Import and Export, Carrying for Personal Use and Sending by Post of Goods Requiring Special Authorisation of the State Agency of Medicines, the Forms of Special Authorisations and the List of Goods Requiring Special Authorisation of the State Agency of Medicines</p> <p>(Passed with Regulation No. 31 on 18.02.2005, RTL 2005, 23, 316, Entered into force 01.03.2005)</p>

	<p>Act No. 3459/2006 on Legal Codes for Drugs</p> <p>Presidential Decree 148/2007 on the codification of the provisions stipulated in the regulatory decrees and ministerial orders regarding national legislation on drugs</p> <p>Ministerial Order No. A6b/6543/15-07-1988 on the definition of terms and conditions of the availability of substances provided for in article 4 of Act No. 1729/1987</p>	<p>Conditions and Procedure for Wholesale Distribution of Medicinal Products</p> <p>(Approved by Regulation No. 27 of the Minister of Social Affairs of 17 February 2005 (RTL2 2005, 22, 308), entered into force 01.03.2005)</p>			
GREECE			<p>Act CLIV of 1997 on Health</p>	<p>Joint Decree 42/2008 (XI. 14.) EüM-SZMM of the Minister of Health and the Minister for Social Affairs and Labour on the rules of treatment for narcotic drug dependence of other services attending to drug use and of prevention and counselling service</p>	
HUNGARY	<p>Government Decree 162/2003. (X. 16.) On cultivation, distribution and use of plants suitable for the production of narcotic drugs</p>	<p>Act XCIV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Laws Regulating the Pharmaceutical Market</p>			

	<p>Government Decree No. 66/2012 (2nd of April) on the activities that may be conducted with narcotic drugs, psychotropic substances and new psychoactive substances, and on the inclusion of such substances in schedules, and on the amendment of such schedules</p> <p>EÜM (Ministry of Health) Decree 43/2005 (X.15.) on the system for physician's prescriptions, trading in pharmacies, consumption, recording and storage at healthcare providers of medicinal products classified as controlled drugs</p>	<p>ESzCsM (Ministry of Health, Social and Family Affairs) Decree 44/2004 (IV. 28) on prescribing and dispensing medicinal products for human use.</p>	<p>Cabinet of Ministers 23/03/2010 Regulations No 288 "Regulations Regarding Operating of Pharmacies"</p> <p>Cabinet of Ministers 26/06/2007 Regulations No 416 "Procedures regarding the Distribution and Quality Control of Medicinal Products" (including separate amendment on 27/07/2010).</p>	<p>Policy document Oncologic diseases control program for years 2009-2015</p> <p>Cabinet of Ministers 31/10/2006 Regulations No 899 "Procedures for the Reimbursement of Expenditures for the Acquisition of Medicinal Products and Medicinal Devices Intended for Out-patient Medical Treatment"</p>	<p>Programme for Limiting the Spread of Human Immunodeficiency Virus (HIV) for 2009-2013, approved by Decree of Cabinet of Ministers No 437 of 30/06/2009</p> <p>Cabinet of Ministers 24/09/2002 Regulations No 429 "Procedures for the Treatment of Patients Addicted to Alcohol, Narcotics, Psychotropic and Toxic Substances"</p>
<p>LATVIA</p>	<p>National Law On Procedures for the Legal Trade of Narcotic and Psychotropic Substances and Medicinal Products (Including separate amendments 28/10/2010, 10/07/2008, 27/09/2007, 03/05/2007, 11/05/2006)</p> <p>Cabinet of Ministers 8/11/2005 Regulations No 847 "Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be controlled in Latvia" (including separate amendments 12/05/2009 and 3/11/2009)</p>				

<p>Cabinet of Ministers 17/06/2008 Regulations No 441 "Procedures for the Purchase, Receipt, Storage, Distribution, Dispensation, Accounting and Destruction of Narcotic and Psychotropic Substances and Medicinal Products in Manufacturing of Medicinal Products and Veterinary Medical Products, at Drug and Veterinary Drug Wholesalers and Pharmacies"</p> <p>Cabinet of Ministers 13/08/1996 Regulations No 327 "Regulations on the Transit of Narcotic and Psychotropic Substances and Drugs" (including separate amendments 24/07/2007 and 04/08/1998)</p> <p>Cabinet of Ministers 21/04/2008 Regulations No 293 "procedures by which a Permit for the Utilisation of Plants, Substances and Medicinal Products Included in Schedules I, II or III of Narcotic Substances, Psychotropic Substances and Precursors Controlled in Latvia for Medical and Veterinary Medical Scientific Research, Specification of Physical and Chemical Properties or for Educational Purposes is Issued, Suspended and Revoked"</p>	<p>Medical Treatment Law</p> <p>Cabinet of Ministers 08/03/2005 Regulations No 175 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing out and Storage Prescriptions" (Including separate amendment on 12/04/2011 of Regulations No 175)</p> <p>Cabinet of Ministers 27/03/2007 Regulations No 220 "Procedures for Acquisition, Storage, Use, Registration and Disposal of Medicinal Products in Medical Treatment Institutions and Social Care Institutions" (Including separate amendments on Regulations 220 on 08/04/2008, 10/03/2009, 31/08/2010 and 25/01/2011)</p>	<p>Cabinet of Ministers 19/12/2006 Regulations No 1046 "Procedures for organization and financing of health care"</p>	
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<p>LITHUANIA</p>	<p>Republic of Lithuania Law on the Control of Narcotic and Psychotropic Substances</p> <p>Republic of Lithuania Law on the Control of Precursors of Narcotic Drugs and Psychotropic Substances</p> <p>Government of the Republic of Lithuanian Resolution regarding the approval of regulations of issuing licenses to produce, import and export narcotic and psychotropic substances, and to engage in their wholesale and retail trade (Last amended on 2011 July 22: No. 887, 13.07.2011, Žin. (Official Gazette), 2011, No. 93-4403 (21.07.2011))</p>	<p>Order of the Minister of Health of the Republic of Lithuania No. 112 of 8 March 2002 "On Medical Prescriptions and Disbursement (Sale) of Medicines" (Published: Official Gazette Valstybės Žinios, 16/03/2002, No. 28; Publication No. 1013).</p>	<p>Order No. 204 of the Minister of Health of 3 May 2002 "On the Approval of Standards for Treatment and Rehabilitation of Dependency Diseases" (Official Gazette Žin., 2002, No. 47–1824).</p> <p>Order No. V-653 of the Minister of Health of the Republic of Lithuania of 6 August 2007 "On the Approval of Procedure Descriptions for Assigning Substitution Treatment and its Application to Treat Opiate Dependency, and Prescription, Disbursement, Storage and Accounting of Substitution Opiate Medicinal Preparations in Personal Health Care Institutions"</p>	
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Republic of Lithuania Government
Resolution No. 591 of 30 May 2005
“On the Approval of the Description
of the Procedure for Monitoring the
Use of Narcotic and Psychotropic
Substances, Consequences thereof,
the Circulation of the Precursors of
Narcotic and Psychotropic Substances”

Republic of Lithuania Government
Resolution No. 221 of 9 March 2006
“On the Approval of the Regulations
for the Licensing of Activities Involving
the Precursors of Narcotic and
Psychotropic Substances, Registration
of the Place Thereof, Issuance of
Import and Export Authorisations, and
Control of such Activities”

Order No. 275 of the Minister of
Health of the Republic of Lithuania
of 24 May 2000 “On the Premises for
Keeping Narcotic and Psychotropic
Medicines and Medicinal Substances
in Hospital Pharmacies”

Order of the Minister of Health of
the Republic of Lithuania No. V-2 of
23 April 2003 “On Recommendations
for Determining Small, Large and
Very Large Amount of Narcotic and
Psychotropic Substances” (Published:
Official Gazette Valstybės žinios,
30/04/200, No. 41, Publication No.
1899).

Order No. 342/482 of several institutions (Minister of Health of the Republic of Lithuania and Minister of the Interior of the Republic of Lithuania) of 25 August 1998 "On the Approval of the Description of Special Requirements for Premises where Narcotic and/or Psychotropic Substances of Schedules II and III are Produced and Stored, their Wholesale and Retail Sale Takes Place" (Published: Official Gazette Valstybės Žinios, 02/09/1998, No. 77, Publication No. 2195; Official Gazette Valstybės Žinios, 16/10/2008, No. 119, Publication No. 4521).

Order No. 409 of the Minister of Health of the Republic of Lithuania of 25 July 2001 "On the Ensuring of Control of Import and Export of Narcotic and Psychotropic Medicines and Medicinal Substances" (Published: Official Gazette Valstybės Žinios, 01/08/2001, No. 66, Publication No. 2429; Official Gazette Valstybės Žinios, 14/07/2005, No. 85, Publication No. 3184).

	<p>Order No. V-138 of the Minister of Health of the Republic of Lithuania of 2 March 2007 "On the Approval of the Description of Procedure for Issuance of the Certificate for Transportation of Narcotic and/or Psychotropic Substances for Personal Usage for Medical Purposes" (Published: Official Gazette Valstybės Žinios, 10/03/2007, No. 30, Publication No. 1109).</p> <p>Order No. 294 of the Minister of Health of the Republic of Lithuania of 4 June 1998 "On the Procedure of Keeping Narcotic and Psychotropic Medicines and Medicinal Substances in Means of International Transportation" (Published: Official Gazette Valstybės Žinios, 19/06/1998, No. 56, Publication No. 1568).</p>				
SERBIA	<p>Law on psychoactive controlled substances</p>	<p>Rulebook on the prescription and dispensing of medicines (FRY Official Gazette No. 16/94, 22/97, 52/02)</p> <p>Rulebook on advertising of medicines and medical devices</p> <p>Law on medicines and medical devices (Official Gazette no 30/10)</p>	<p>Rulebook on contents and scope of health care from compulsory health insurance and on participation for 2012</p> <p>Draft National Palliative Care Strategy</p> <p>Action Plan for Palliative Care in the Republic of Serbia for the Period 2008-2015</p>		<p>The criminal code</p> <p>Law on criminal procedures</p>

SLOVAKIA	<p>Act. N. 139/1998 on Narcotic Drugs, Psychotropic Substances and Preparations</p> <p>Decree 158/2010 of 23 March 2010 of the Ministry of Health laying down formal requirements for the book of narcotic substances and keeping records of narcotic substances proving receipt and dispensing of narcotic and psychotropic substances</p>	<p>Act. N. 140/1998 on medicinal products and medical devices, replaced by Act. N. 362/2011 on medicinal products and medical devices²</p> <p>Act. N. 147/2001 on Advertising of Medicinal Products</p>	<p>Regulation regarding standards for diagnosis and treatment</p>	<p>Vocational guidance No. M/0509/2003 on the standards for the diagnosis and treatment of drug dependencies</p>	<p>The constitution of the Republic of Slovenia</p>
SLOVENIA	<p>Order on the Promulgation of the Prevention of the Use of Illicit Drugs and Dealing with consumers of Illicit Drugs Act</p> <p>Production of and Trade in Illicit Drugs Act</p> <p>Decree on the Scheduling of Illicit Drugs</p> <p>Rules Governing the Procedures for the Issue of Licences for Illicit Drugs Marketing</p>	<p>Rules on classifying, prescribing and dispensing medicinal products for human use</p>	<p>Law on Health Care and Health Insurance</p> <p>Act(s) Amending the Health Care and Health Insurance Act</p> <p>General agreement 2010</p> <p>Resolution on National plan of health care 2008-2013</p>		

² Although Act. N. 140/1998 has been replaced by Act. N. 362/2011, no important changes have been made to the parts that were indicated as relevant by the national counterpart. Therefore, Act. N. 140/1998 has been (partly) reviewed.

	<p>Rules on Method And Form of Record-keeping and of Reports on Illicit Drugs</p> <p>Rules on Technical And Sanitary Conditions And on the Method of Insurance of Premises for Storage and Dispensing of Illicit Drugs from Groups I and II</p>			
TURKEY	<p>Law No.2313 (12/06/1933) on Supervision of Narcotic Drug</p> <p>Circular No.5725 (26/01/1984) on submitting consumables of controlled substances and pharmaceutical preparations</p> <p>Circular No.5768 (29/05/1985) on the prescription of narcotics, controlled drugs and preparations</p> <p>Circular No.09/2677 (02/01/1986)</p>	<p>Pharmaceuticals Track&Trace System</p> <p>Law No.1262 (26/05/1928) on the Pharmaceuticals and Medicinal products</p>	<p>Regulation No. 25375 on Substance Abuse Treatment Centres (16/03/2004)</p>	<p>Law No.984 (12/03/1927) on stores where toxic and effective chemical substances used in pharmaceutical businesses and in vocational & agriculture businesses are sold</p>



CHAPTER 3

PERCEPTION OF OPIOID USE & POLICY
BARRIERS TO ACCESS TO OPIOID MEDICINES





CHAPTER 3.1

IDENTIFICATION OF CHALLENGES TO THE AVAILABILITY AND ACCESSIBILITY OF OPIOIDS IN TWELVE EUROPEAN COUNTRIES: CONCLUSIONS FROM TWO ATOME SIX-COUNTRY WORKSHOPS

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ABSTRACT

BACKGROUND: Access to many controlled medicines is inadequate in a number of European countries. This leads to deficits in the treatment of moderate to severe pain as well as in opioid agonist therapy.

OBJECTIVE: The study objective was to elaborate the reasons for this inadequacy. The work plan of the Access to Opioid Medication in Europe (ATOME) project included two six-country workshops. These workshops comprised a national situational analysis, drafting tailor-made recommendations for improvement and developing action plans for their implementation.

METHODS: In total, 84 representatives of the national Ministries of Health, national controlled substances authorities, experts representing regulatory and law enforcement authorities, leading healthcare professionals, and patient representatives from 13 European countries participated in either one of the workshops. The delegates used breakout sessions to identify key common challenges. Content analysis was used for the evaluation of protocols and field notes.

RESULTS: A number of challenges to opioid accessibility in the countries was identified in the domains of knowledge and educational, regulatory, legislative, as well as public awareness and training barriers that limit opioid prescription. In addition, short validity of prescriptions and bureaucratic practices resulting in overregulation impeded availability of some essential medicines. Stigmatization and criminalisation of people who use drugs remained the major impediment to increasing opioid agonist program coverage.

CONCLUSIONS: The challenges identified during outcomes of the workshops were used as the basis for subsequent dissemination and implementation activities in the ATOME project, and in some countries the workshop proceedings already served as a stepping-stone for the first changes in regulations and legislation.

INTRODUCTION

With the exception of some Western industrialized countries, access to many controlled medicines is inadequate around the world.^{1,2} The World Health Organization (WHO) estimates that approximately five billion people live in countries with low or no access to controlled medicines³ and insufficient access to treatment for moderate to severe pain is reported in more than 150 countries. In 12 countries of the European Union (EU), opioid analgesic consumption is described as ‘low to very low’.⁴

In addition to pain management, opioids are also needed in the treatment of opioid dependence, mainly for opioid agonist therapy (OAT). Access to OAT in the EU varies dramatically. In some central and eastern European countries, less than 10% of people who would benefit from opioid agonist therapy are reached. Where harm reduction programs exist, access is impeded by lengthy waiting lists, strict admission criteria, and lack of evidence-based standards for provision and quality of care; those at the greatest risk of exclusion are women, young people, and migrants.⁵

The European Commission’s 7th Framework program funded the Access to Opioid Medication in Europe (ATOME) project (2009–2014, www.atome-project.eu). Its objective was to improve access to opioids in 12 European countries where there has been statistical evidence of low per capita morphine consumption at the time of the project submission (September 2009): Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia, Serbia, and Turkey.

The work plan of the ATOME project (see Fig. 1) included two international six-country workshops as the foundation of subsequent activities directed at improving national policies related to opioid access. This article aims to describe the main challenges to opioid availability and accessibility identified during these two workshops and the recommendations for improving access to opioids that were made by the participants of the workshops.



Figure 1. ATOME work plan. (*From Lynch T, Payne S, Scholten W, et al. ATOME training of lawyers and national counterparts workshop: a report. *European Journal of Palliative Care* 2011; 18: 293–297.)

METHODS

Country teams had been composed at the outset of the work program to ensure country-specific relevance and applicability of the project activities; the teams included representatives of the national Ministries of Health; national controlled substances authorities; experts representing regulatory and law enforcement authorities; leading healthcare professionals; and patient representatives. The six-country workshops were held in Bucharest, Romania in September and November 2011, with the purpose to (1) assist expert delegations to undertake national situational analyses; (2) disseminate tailor-made recommendations to their national governments for improving the accessibility, availability, and affordability of controlled medicines; and (3) plan how to implement these improvements.

The principle of balance, i.e., the obligation of each government to ensure availability and accessibility of opioids while preventing abuse and diversion, was the guiding principle in both workshops. The workshops were designed as two-and-a-half-day events with a combination of lectures from international experts (total duration 5h) and discussion groups to analyze the national situation regarding access to opioids, identify potential problems, and decide on action steps to improve the situation (total duration 8h). Representatives from the ATOME consortium and the workshop faculty assisted the group work as facilitators. The country teams presented the outcomes of their group work in plenary, followed by a discussion and feedback from the other delegations (total duration 3.5h). Tools such as the WHO checklist for national situation analysis;⁶ a case example of a patient in order to discuss the national situation in a problem-based manner; and a strategic action planning worksheet were used in the discussion groups in order to guide the process of tailoring country-specific solutions. Material relevant to the accessibility and availability of opioids, such as scientific articles or position papers, was provided to participants prior to the workshop. The results of this article were condensed from the country teams' presentations, action plans, and minutes from the group work sessions. The workshops were evaluated by a pre- and post-workshop questionnaire.

RESULTS

Participants

In total, 39 representatives from Bulgaria, Cyprus, Greece, Turkey, Serbia, and Slovenia attended the first workshop, and 45 delegates from Estonia, Hungary, Latvia, Lithuania,

Poland, and Slovakia the second one. Ukraine (which was not among of the target countries) sent observers to the second workshop. The national delegations used breakout sessions to analyse country-specific key challenges to opioid accessibility and to elaborate strategic action plans for improvement, which were subsequently presented and discussed in plenary.

Key challenges

Lack of education; excessive regulations relating to the prescribing of opioids; “opiophobia” — fear from opioids; and lack of reimbursement were identified as challenges to access to opioids by 50% to 75% of the country teams. Table 1 shows the most frequently identified challenges and recommendations for improvement made by the participants.

Table 1. Challenges concerning access to opioids identified by the country teams

Identified challenge	No. of country teams	Recommendations elaborated among the country teams
<p>Lack of education: Inadequate training of physicians in pain management. Many general practitioners therefore refer the prescription of opioids to oncologists resulting in underprescription.</p>	9	Implement opioid prescribing examination, improve education in the field of pain management, educate regulatory authorities to underline that access to pain relief is a human right, and develop a network to educate multidisciplinary teams in prescribing.
<p>Lack of knowledge about opioids amongst patients, their family and society: Fears and beliefs as well as mis-information and misunderstanding. Perception that suffering is normal, necessary or heroic. Negative stereotypes about opioids (“drugs”) reinforce the fear of patients and physicians.</p>	7	Raise public awareness about the beneficial effects of opioids.
<p>Lack of recognition of pain management: Chronic pain and other non-oncological diagnoses are often not being recognised by healthcare professionals.</p>	5	Develop policy guidelines in pain management in collaboration with the respective ministry, recognise/ acknowledge chronic pain and pain of non-cancer as a clinical problem (with an ICD code if possible).
<p>Lack of reimbursement: Due to high costs opioids are not being reimbursed for acute or chronic conditions. The lack of recognition of chronic non-cancer pain as a medical condition makes reimbursement impossible.</p>	6	Achieve adequate reimbursed through pressure from professional organisations, trade unions, patient organisations and professional bodies in order to influence political will.
<p>Limitations to the available range of opioids: Lack of choice of opioids such as injectable morphine, slow-release oral morphine, buprenorphine and methadone.</p>	5	Bring the revised WHO list of essential medicines to the adherence of government representatives and the pharmaceutical industry.

<p>Pharmaceutical company reluctance to manufacture opioids:</p> <p>Some pharmaceutical companies have little interest in procuring opioids as there is only a small market where cost of procurement and projected incomes are disproportional.</p>	3	Establish a reliable supply of slow-release oral morphine (if needed via import) and improve access to immediate-release opioids.
<p>Excessive regulations relating to the prescribing of opioids:</p> <p>Special prescription forms that need to be stored with special security measures, restrictions regarding the authorisation to prescribe, excessive reporting requirements of opioid prescriptions, complicated administrative requirements for filling out the prescriptions and limited prescription.</p>	8	E-prescription forms should be introduced to enable every physician to prescribe opioids without having to complete a special prescription form.
<p>Excessive regulations relating to storage and dispensing of opioids:</p> <p>Not all pharmacies are allowed to store opioids and special storage conditions are required.</p>	5	Special licensing for dispensing opioids should be abolished, and all pharmacies should be legally obliged to dispense them.
<p>Lack of opioid legislation/ inappropriate legislation:</p> <p>Lack of legislation and outdated terminology impede an adequate supply.</p>	5	Revise legislation with the aim of addressing fears and myths relating to the use of opioids.
<p>Focus on suppression rather than availability of opioids:</p> <p>Government agencies tend to focus more on prevention of diversion and misuse rather than medical availability of opioids and have little recognition that opioids are necessary for pain relief.</p>	3	Education/training sessions and opioid workshops amongst regulatory authorities that stress access to pain relief as a 'human right'.
<p>Other challenges identified:</p> <p>Difficulties in accessing opioids out-of-hours (rural areas) and a lack of trained specialists.</p>	1	All pharmacies should be permitted to stock opioids.

National approaches to solution

To develop national action plans, the country teams completed so-called strategic planning worksheets in group work (see Table 2). Process observations during both events by representatives of the ATOME consortium confirmed the benefit of the workshop method. The six-country workshops had brought together stakeholders from different areas who usually would not have the opportunity to exchange and share their perspectives. This also resulted in concrete positive effects, such as in one country, clarification of misunderstandings about the legal restrictions and unawareness of regulatory leeway regarding methadone prescription for pain treatment (Cyprus).

Table 2. Strategy planning worksheet – example “education”

What?	A. State the problem	Education
Why?	B. State the underlying reason(s) for the problem	No standard training in opioid analgesia in the basic curriculum in physicians and other healthcare professionals No comprehensive continuing education and training of executives involved with the subject
What?	C. State the objective(s) that would address the problem. Which objectives are top priorities	Inclusion of PC and opioid management in the basic training of physicians and paramedics To overcome opiophobia
How?	D. What action steps are needed to achieve the objective?	Target population of education : Physicians, Nurses, Social workers, Pharmacists, Patients and Families, Public
Who?	E. List those who have the authority and/or responsibility to take the necessary action	Ministry of Education Ministry of Health Ministry of Justice
When?	F. Timeline for completion of action steps	September 2011-October 2012
How much?	G. What technical and financial assistance will be needed to achieve each objective	1. Ministry of Health 2. Ministry of Education 3. Pharmaceutical Companies 4. NGOs

3.1

Workshop evaluation

Forty-four percent (n=37) of the 84 participants completed both pre- and post-workshop questionnaires (see Table 3). Thirty-five of the 37 respondents (95%) reported that their knowledge about accessibility of controlled medicines had been enhanced by attending the workshop, and 21 (57%) reported that their attitudes in relation to the accessibility of controlled medicines had been changed by attending the workshop.

Respondents made suggestions in the questionnaire to improve the situation; countries mentioned here can be seen as exemplary; the suggestions are likely to relate to other countries as well. Raising public awareness about the beneficial effects of opioids in order to reduce the fear of prescribing opioid medicines was suggested by several teams. Concrete measures were proposed, such as the initiation of social campaigns to counteract myths and

stereotypes about opioids (Poland, Serbia, Slovakia, and Turkey), or raising pressure from professional organizations, trade unions, patient organizations, and professional bodies to influence political will and ensure adequate reimbursement of opioids (Hungary).

The acknowledgment of chronic pain as a clinical problem was deemed of paramount importance (highlighted by a delegate from Bulgaria), and the development of policy guidelines in pain management in collaboration with the ministry of health to overcome barriers related to excessive regulations was proposed by a representative from Cyprus.

Table 3. Extract of results from the post-workshop questionnaire

1.	What was the most valuable aspect of the workshop?
	Opportunity to collaborate with the government on a project
	Exchanging information with other countries
	Meeting people working in the same field in other countries
	Experience of other countries and recommendations
	I was able to convince my country team and raise awareness especially in the Ministry of Health
	Country action plans gave a good overview of the problematic situation
2.	What was the least valuable aspect of the workshop?
	Too hard working the whole day requiring full concentration
	Too crowded schedule was so exhausting – one more day would be needed to improve the quality of work
	Too much time is spent on the action plan
3.	Please write down any additional comments or suggestions
	It would be useful to know the opinions of authorities for restrictions if these are not due to financial problems
	Everything was well organized; maybe more teaching, films, case examples can be included in the programme
	Good balance of theory and information and practical work
	'Report of status of...' should be prepared before the workshop

DISCUSSION

The results of the workshops underline that lack of access to opioids is multifactorial in nature. Barriers exist on numerous levels which are interlocked and partially reinforced by each other. A strength of these workshops was therefore that stakeholders representing as many relevant fields as possible in relation to access to opioids were addressed.

Common challenges identified during the ATOME workshops were a number of educational, regulatory, legislative, and training barriers that limit the ability of both physicians and nurses to prescribe the necessary doses of opioids to patients. These findings are in line with the main barriers to opioid accessibility reported in previous publications by leading researchers in the field.⁷⁻¹⁰

Frequently reported challenges were related to short validity of prescriptions and excessive bureaucratic practices when prescribing. Similar results have been identified in the legislation analysis by Utrecht University during the ATOME project as well as in the individual country reports. The issue of overregulation of opioids was also reviewed by Cherny et al.,¹¹⁻¹³ who reported on some elements of the legal and regulatory barriers to opioid availability and accessibility throughout Europe and the world. Unduly restrictive legislation that limits the distribution, prescription, dispensation, and use of opioids has been described by Joranson and Ryan¹⁴ and Human Rights Watch.¹⁵ These authors agree that in most cases the problem is not the lack of availability of opioids in the country, but rather the combination of many bureaucratic and legislative regulations that impede opioid prescription and dispensing. Many medical professionals, particularly family doctors, appear to be afraid of prescribing opioid medications, often related to these regulatory barriers.¹⁶ Lynch et al.¹⁷ reported complicated procedures relating to the prescription of opioids in the countries of Central and Eastern Europe and the Commonwealth of Independent States, where it was very difficult to obtain a license to prescribe opioids.

Limited knowledge about opioid analgesics was reported in a number of countries in Western Europe,¹⁸ where lack of professional knowledge about the prescription of strong opioids may result in reluctance on the part of physicians to prescribe them. The relevance of such challenges to a plethora of diverse sociocultural, economic, educational, and health policy settings should be fully and adequately considered. Next to establishing national, regional, or local under- and postgraduate education opportunities for healthcare professionals, guidelines or other guidance can be a feasible way to address unawareness and misinformation, such as the evidence-based guidelines by the European Association for Palliative Care (EAPC) on the

use of opioid analgesics for the treatment of cancer pain.¹⁹

In relation to opioid agonist therapy, stigmatization and criminalization of people who use drugs remains the major impediment to increasing program coverage, particularly in prison settings. This manifests a lack of interest among policy makers in investing in evidence-based harm reduction approaches, despite the proven effectiveness of these programs in preventing HIV transmission. Fear of arrest and police harassment among drug users may deter many from accessing these services.⁵

The aims of the workshops to assist the country teams to analyze their national situation, disseminate country-specific national action plans, and raise awareness about tools and resources have been realized. The challenges reported in the workshops have been analyzed and have been considered in subsequent steps of the program, such as the national follow-up conferences.

There are a number of limitations associated with this paper. First of all, the selection of experts and participants attending the workshops was a potential source of bias, as their views may not represent the situation in the countries concerned. However, the participants (ATOME country team members) were carefully selected to ensure that as many relevant fields as possible in relation to access to opioids were represented. This is crucial, as improving access to opioids requires a multilevel approach, since it is the outcome of a complex interaction of national legislation, policies and regulations, education, economy, healthcare practice, attitudes, and social norms. In addition, close collaboration with the country teams during all phases of the ATOME project, including the workshops, ensured ownership of the proposed strategies, which is an important prerequisite for successful implementation. There may have been some unintended negative effects during the workshops—for example, the fact that challenges reported by participants or country teams could potentially have been suppressed by competitive tendencies between neighbouring countries. However, the invitation of six different countries to each workshop was also believed to facilitate exchange, reduce stigma, and enhance the creative development of solutions by learning from models in other countries, since many countries do encounter similar problems.

Importantly, the challenges identified during each workshop only reflect what was explicitly discussed; this does not necessarily mean that the respective issues do not also apply to other countries—the barriers identified are not exclusive to the countries that reported them.

Workshops with similar setup have been used to compare the development of healthcare policy across both countries and regions and have come to similar results; most notably, those undertaken by the Open Society Foundation's International Palliative Care Initiative and

regional or national palliative care associations such as the African Palliative Care Association (APCA)²⁰⁻²² and the International Association for Hospice & Palliative Care (IAHPC).²³ The international comparison of barriers with the possibility of establishing new contacts in a similar field of expertise seems to be a fruitful way of resolving widespread difficulties.

CONCLUSIONS

The participants of the country teams made use of the two six-country workshops to identify key challenges to access to opioids in their country and to elaborate tailor-made strategic action plans for improvement. Findings from the country workshops reported here were triangulated with outcomes from related activities in the ATOME project, most importantly the recommendations resulting from the quick scan and in-depth analysis of legislation.^{24,25} The results of these workshops therefore delivered an important contribution to a comprehensive analysis and informed the subsequent work of the country teams during a series of national follow-up conferences, as well as the development of tailor-made recommendations and solutions for each of the 12 participating countries.²⁶ These recommendations could serve as guidance for other countries in the world as well.

The WHO resolution on strengthening palliative care, which was adopted at the World Health Assembly in May 2014 in Geneva,²⁷ gives hope that a global improvement of pain treatment gains the focus of politicians and healthcare decision makers. The action steps resulting from the identified challenges of the ATOME program with tailor-made solutions for each of the 12 participating countries could set an example for other countries in the world that want to improve access to controlled medicines following the WHO resolution.

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CHAPTER 3.2

THE PERCEPTION OF BARRIERS CONCERNING OPIOID MEDICINES: DIFFERENCES BETWEEN POLICY MAKERS, HEALTHCARE PROFESSIONALS AND OTHER STAKEHOLDERS

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Submitted



ABSTRACT

BACKGROUND: In many countries the consumption of opioid medicines is too low to meet population needs. Discussions within the Access To Opioid Medication in Europe (ATOME) project indicated that there may be significant differences in the perception of barriers for their adequate use, depending on the stakeholders.

AIM: This study examined the perception of barriers concerning opioid medicines, comparing policy makers, healthcare professionals working in the field of pain management, palliative care or harm reduction and other stakeholders.

DESIGN: Data were collected using a questionnaire partially constructed from existing surveys, reviewed for content validity by 4 experts and pilot-tested in Latvia.

SETTING/PARTICIPANTS: Participants of the ATOME national conferences were invited to complete the questionnaire. Stakeholder groups were compared using non-parametric rank-sum tests.

RESULTS: In total, 199 participants (54%) in seven countries completed the questionnaire. Most frequently rated major barriers included lack of financial resources and inadequate knowledge, skills and training among policy makers (55-66%). Overall, policy makers perceived issues less often as major barriers or having major impact (29% barrier, 32% impact) compared to other stakeholders (36-42% barrier, 39-51% impact). Significant differences were seen on several aspects. For example, excessive regulation/bureaucracy for prescribing was rated as having major impact by 55-57% of healthcare professionals in contrast to only 20% of the policy makers ($p = 0.0020$).

CONCLUSIONS: Multiple barriers may play an important role, partly depending on the perspective of the stakeholder involved. Hence, when addressing perceived barriers, it is important to include all relevant stakeholder groups. Only then, effective and widely supported solutions can be implemented.

BACKGROUND

Opioid analgesics are considered the cornerstone of the treatment of moderate to severe chronic (cancer) pain. Despite their widely recognized analgesic properties, the use of these medicines has been a key topic in international debates over the past decade. Discussions have predominantly focused on the risks associated with these medicines. For example, public media and scientific literature have reported repeatedly about the increase in the number of patients with opioid dependence and opioid-induced death that was seen in the United States since 1999.^{1,2} This increase in the number of deaths has reached a new peak in 2017 with an estimated 72 000 drug overdose deaths, of which more than two-thirds involved opioids.^{3,4}

To prevent illegitimate use of opioid medicines, governments and policy makers have undertaken control measures which often have a legal or regulatory foundation. This increased level of control may be justified if it aims at controlling traffic of the illicitly produced substances at the root of the problem. However, in discussions addressing the “opioid epidemic”, in many cases no clear distinction is made between overdoses from prescribed opioids, use of illicit opioids and illegal diversion or misuse of prescription opioids. This confusion results in a disproportionate generalized fear of opioids, and additional control measures may in practice also reduce legitimate opioid use, limiting access for patients in medical need.⁵

Although an increase in use of opioid analgesics has been seen in most high income countries, on a global scale there is still a high level of inequity.^{6,7} Data from the International Narcotics Control Board show that 95.7% of the global consumption of opioid analgesics in 2011-2013 was consumed by only 15% of the global population.⁶ Only 7.5% of the global population lives in countries where the consumption of opioid analgesics is considered adequate.⁸ National drug control systems containing rules that are more strict than required by international drug control conventions are considered to contribute to this inequity, in addition to other factors such as a lack of knowledge and education, societal attitudes and economic issues.⁹ While it is beyond doubt that non-medical use and diversion should be reduced, it is paramount to balance strategies to ensure access to pharmaceutical products that are legitimately on the market for patients in medical need.⁹

Identifying barriers to legitimate opioid use is a crucial first step in ensuring access. Numerous studies have reported on barriers to access, mostly focusing on one stakeholder group, such as patients, physicians or nurses. Reported barriers include patients’ reluctance to use opioids, inadequate staff knowledge of pain management, physicians’ reluctance to prescribe opioids and complicated regulations.¹⁰⁻²⁰ A few studies have also examined the perception

of barriers among healthcare decision and policy makers.^{6,19,20} Identified barriers include lack of education and training, fear of dependence or diversion, limited financial resources and problems in opioid manufacturing, storage and distributions.^{6,19,20} Discussions within the Access To Opioid Medication in Europe (ATOME) project suggested that considerable differences may exist in the perception of barriers between policy makers and healthcare professionals working in various medical fields, i.e. pain management and harm reduction. These differences may have major impact in practice; as national drug control policies are usually drafted and implemented by stakeholders who do not have clinical experience with these medicines, the potential negative consequences of control measures for healthcare professionals and patients in medical need may not always be recognized.

This study aimed to examine the perception of barriers concerning opioid medicines among various stakeholder groups, comparing healthcare decisions makers, healthcare professionals working in the field of pain management, palliative care or harm reduction and other stakeholders including patient representatives.

METHODS

Sample and data collection

A convenience sample was recruited consisting of participants of the ATOME national conferences in seven countries (Estonia, Hungary, Latvia, Lithuania, Poland, Serbia, and Slovakia) between March 2013 (Latvia) and April 2014 (Poland). Invited participants included representatives from governmental bodies and organizations (e.g. the healthcare inspectorate in charge of controlled medicines and governmental agencies in charge of drug control legislation), healthcare professional organizations, consumer and patient organizations and representatives from non-governmental organizations (e.g. relevant activists or program staff). Data were collected using a questionnaire that was handed out at conference registration; participants were asked to complete the survey before the official beginning of the conference.

Instrument

The questionnaire was developed partly based on existing surveys, such as the Abstinence Orientation Scale developed by Caplehorn et al. and the Barriers II Questionnaire developed by Gunnarsdottir et al.²¹⁻²³ Questions from existing surveys were reformulated to avoid the use of stigmatizing language according to WHO policy guidelines⁹ and to address all potential barriers which might be experienced by distinct stakeholders (e.g. healthcare professionals

and policy makers) working in different fields (pain management, palliative care and harm reduction). The questionnaire comprised four sections: 1. knowledge and attitudes, 2. barriers, 3. feasibility of the questionnaire, and 4. personal / professional background (see Annex 1). In this paper, we focus on sections 2 and 4.

Section 2 consisted of a list of 34 potential barriers covering 5 areas: 1. knowledge, education and guidance, 2. regulation of opioids, 3. information/guidelines, 4. attitudes/concerns, and 5. resources and access to opioid medicines. Participants were asked to indicate the degree to which each item represented a barrier in their practice or country on a scale of 0 (not a barrier) to 3 (= major barrier) with an additional “don’t know/uncertain”-option. An open-ended question sought information on additional barriers. Furthermore, participants were asked to rate the level of impact that this aspect has or had in their work or practice, using a scale of 0 (no impact) to 3 (major impact) with an additional “don’t know/uncertain”-option. To explore possible changes and developments in each country, participants were asked whether the situation in their view had changed during the past five years using a filter question (yes; no; don’t know/uncertain; if yes, has the situation worsened or improved?). Section 4 consisted of a series of questions on background characteristics of the participant including gender, age, education and occupation (see Annex 1).

Instrument validation

The questionnaire was reviewed for content validity by four experts in pain management, palliative care, harm reduction and policy (authors AKM, LR, SP and WS). A pilot test was conducted in one country (Latvia) to evaluate the feasibility of the questionnaire using an additional set of seven questions. Small changes in wording were made based on the respondents’ feedback to the feasibility questions. As the changes were small, data from Latvia were included in the overall analysis. The questionnaire was translated into the languages of the involved countries by Nova Language Services (Barcelona, Spain) to facilitate response. Translations were back-translated into English on a random basis to verify correct translation.

Data analysis

Respondents were categorized into five different groups based on the question “Which group represents your current position best?” (See Annex 1, section D): 1. palliative care/pain management healthcare professionals (PC/PAIN HCP), 2. harm reduction healthcare professionals (HR HCP), 3. other healthcare professionals (OTHER HCP), 4. policy makers (PM) and 4. others (OTHER). The group PM included ‘Government officers’ and ‘Politicians’ and ‘Other healthcare decision makers’. The group OTHER included ‘Other (please specify)’ and ‘Patients or patient representatives’. Although only one answer was supposed to be given,

seven respondents provided multiple answers to this question. These respondents were categorized based on the following: the answer option PM prevailed in combination with other answer options. Additionally, the answer options PC/PAIN HCP and HR HCP prevailed in combination with OTHER HCP as these positions were considered a specialization. Ten respondents were excluded from the sample as they did not state their current position.

Data analysis included descriptive statistics (percentages and mean values) for the total sample, and for each stakeholder group. For the barriers and their impact questions (Annex 1, section B) non-parametric rank-sum tests were used to compare the five groups. Data on the percentage of respondents that perceived a potential issue as a major barrier or as having major impact were presented in total and for each group separately. An average of 1.7% (range 0%-4.5% per question) of the barriers/impact values were missing. Overall, more data were missing regarding the impact questions: 1.8% impact versus 1.6% barriers questions. Missing data were assumed to be missing at random and were handled with pairwise deletion. Differences between the groups were analyzed using Kruskal-Wallis tests. Data were analyzed using IBM SPSS statistics 23.0. A p-value ≤ 0.05 was considered statistically significant. This study was approved by the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands. Confidentiality and anonymity were maintained throughout the study.

RESULTS

Demographic Characteristics

Data were collected from 199 (54%) of the 366 participants of ATOME conferences in seven countries. Respondents were healthcare professionals (22%), healthcare professionals working in the field of pain management/palliative care (35%), harm reduction (11%), policy makers (19%) and other stakeholders (13%). The group OTHER included medical students, lecturers, representatives from non-governmental organizations, social workers, patient representatives and representatives from pharmaceutical companies. The sample included more females (74%) than males. The majority of the respondents (32%) was between 41 and 50 years of age and the majority of the respondents (36%) had > 20 years of professional working experience (Table 1).

Table 1. Characteristics of the sample (n=199: Estonia (54%), Hungary (53%), Latvia (72%), Lithuania (52%), Poland (49%), Serbia (44%) and Slovakia (53%))

		n	n%
GENDER	Male	41	20.6%
	Female	148	74.4%
	Missing	10	5.0%
AGE GROUP (YEARS)	< 21	1	0.5%
	21- 30	23	11.6%
	31- 40	47	23.6%
	41- 50	63	31.7%
	51- 60	41	20.6%
	> 60	16	8.0%
	Missing	8	4.0%
PROFESSIONAL (WORKING) EXPERIENCE (YEARS)	< 1 year	8	4.0%
	1- 5 years	23	11.6%
	6- 10 years	27	13.6%
	11 - 20 years	59	29.6%
	> 20 years	71	35.7%
	Missing	11	5.5%
CURRENT POSITION	PC / PAIN HCP	68	34.2%
	HR HCP	21	10.6%
	HCP OTHER	44	22.1%
	PM	40	20.1%
	OTHER	26	13.1%

Barriers towards opioid medicine use and their impact

In total, 29 potential barriers to access to opioid medicines and their impact on professional practice were rated (section B, annex 1). Overall, 36% of the issues were rated as a major barrier and 43% of the issues were perceived as having major impact on professional practice (see Figure 1). The issues that overall were most frequently perceived as a major barrier or as having major impact were lack of financial resources at an institutional level (66% barrier; 70% impact) and at governmental level (63% barrier; 66% impact), followed by inadequate knowledge, skills and training regarding opioid medicines among policy makers/government representatives (55% barrier; 70% impact) (see Figures 2 and 3). Overall, all issues were

perceived to have more impact than they were seen as an actual barrier (Figure 1, Annex 2).

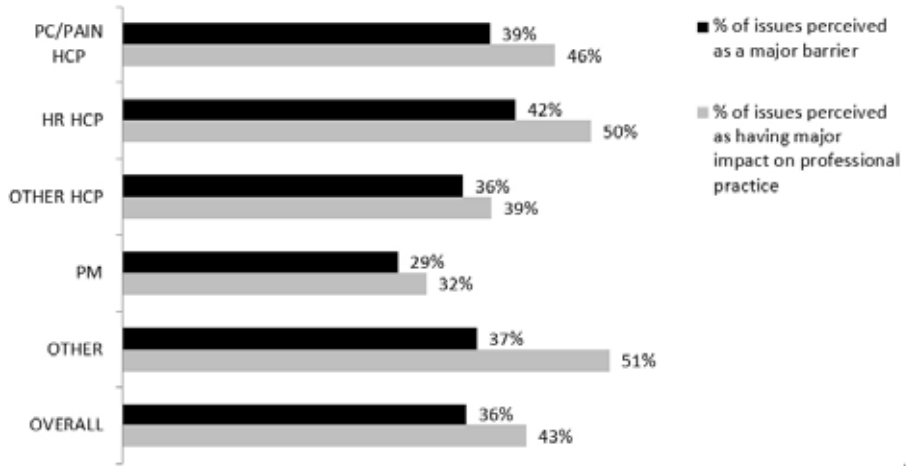


Figure 1. Percentage of issues perceived as a major barrier or as having major impact per stakeholder group and overall (n=199)

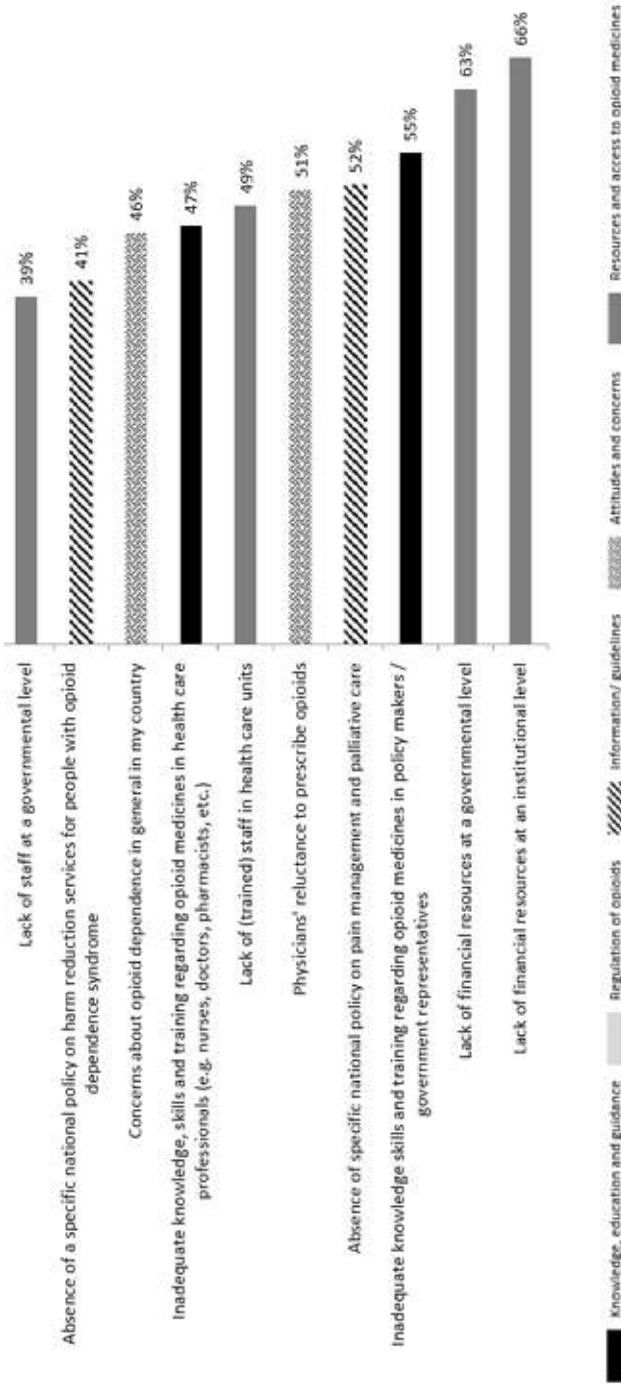


Figure 2. Top 10 issues perceived as major barriers (all stakeholder groups; n=199)

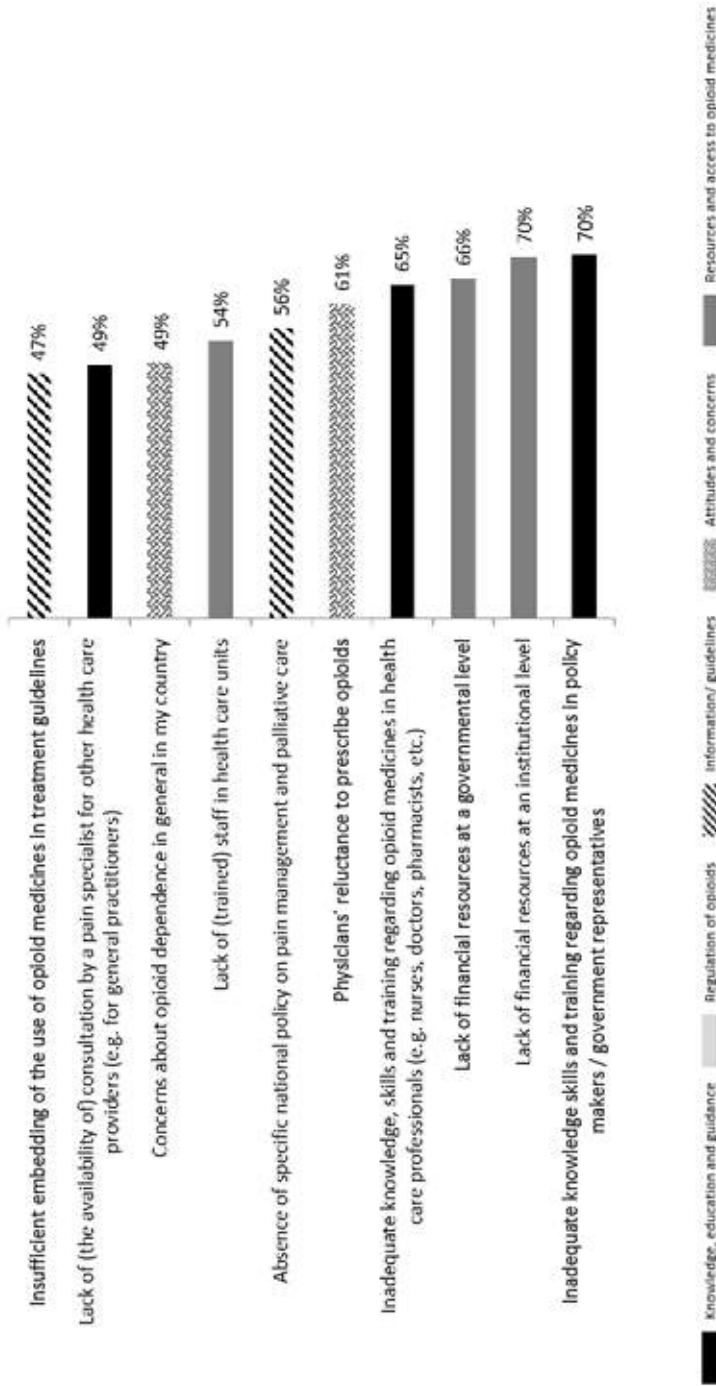


Figure 3. Top 10 issues perceived as having major impact on professional practice (all stakeholder groups; n=199)

Differences in the perception of barriers between groups

Comparing stakeholder groups, issues were overall least often rated as major barriers or as having major impact by PM (29% barrier, 32% impact) and most often by harm reduction healthcare professionals (HR HCP: 42% barrier, 50% impact) followed by the group OTHER (37% barrier, 51% impact) (Figure 1). Significant differences were seen on specific aspects (see Table 2). For example, physicians' reluctance to prescribe opioids was less often perceived as a major barrier or as having major impact by PM (32% barrier; 39% impact) in comparison to other stakeholders (48%-62% barrier, $p = 0.0230$; 57-76% impact, $p = 0.0170$). PC/PAIN HCP regarded lack of (trained) staff in healthcare units frequently as a major barrier or as having major impact (65% barrier; 68% impact) while this issue was not as often perceived as a problem by the groups OTHER and HCP OTHER (31%/40% barrier, $p = 0.0160$; 50%/41% impact, $p = 0.0080$). Expressed in absolute figures, the largest difference was seen for the impact that excessive regulation / bureaucracy of opioids may have on professional practice ($p = 0.020$), which was rated as a major barrier by 67% of HR HCP in contrast to only 25% of PM.

Also, the top ten issues differed between the various stakeholder groups (Annex 3). We observed for example that the "regulation of opioids" was not reflected in the top ten issues of the groups PM and PC/PAIN HCP. Additionally, for all groups except PM, lack of financial resources was perceived most frequently as a major barrier (range: 57%-76%), but lack of knowledge, education and training in policy makers/government representatives was more frequently judged to have a major impact on professional practice (range: 70%-88%).

Additional barriers to access

Ten respondents, nine healthcare professionals and one non-governmental organization representative, mentioned additional barriers in the open-ended questions. Examples of reported barriers include regulations on the reimbursement of medication (Poland) and the requirement of authorization by a second medical specialist when prescribing opioid analgesics for patients with chronic non-cancer pain (Hungary).

Table 2. Significant differences in the proportion of respondents reporting issues as major barriers or as having major impact (n = 199). A complete overview of all potential barriers (barriers + impact) for each stakeholder group is provided in Annex 2.

POTENTIAL BARRIER	PC / Pain HCP	HR HCP	HCP (other)	PM	Other	Overall	P
Lack of (the availability of) consultation by a pain specialist for other healthcare providers (barrier)	28%	48%	35%	23%	27%	30%	0.0010
Inadequate knowledge, skills and training regarding opioid medicines in policy makers/ government representatives (impact)	74%	81%	70%	48%	88%	70%	0.0020
Excessive regulation / bureaucracy of opioids (barrier)	31%	57%	36%	23%	48%	36%	0.0500
Excessive regulation / bureaucracy of opioids (impact)	32%	67%	36%	25%	56%	38%	0.0050
Excessive regulation / bureaucracy of opioids for prescribing procedures (barrier)	37%	52%	45%	23%	38%	38%	0.0270
Excessive regulation / bureaucracy of opioids for prescribing procedures (impact)	44%	57%	57%	20%	46%	44%	0.0020
Disproportional sanctions for unintended violations in medical or pharmaceutical practice (barrier)	28%	33%	32%	20%	19%	27%	0.0010
Disproportional sanctions for unintended violations in medical or pharmaceutical practice (impact)	34%	43%	27%	18%	44%	31%	0.0060
Administrative burden for regulators, physicians, nurses, or pharmacists (impact)	40%	48%	36%	18%	50%	37%	0.0240
Lack of acknowledged treatment guidelines on pain management and palliative care (barrier)	31%	24%	30%	21%	35%	29%	0.0070
Lack of acknowledged treatment guidelines on pain management and palliative care (impact)	35%	38%	33%	32%	48%	36%	0.0020
Physicians' reluctance to prescribe opioids (barrier)	57%	62%	57%	32%	48%	51%	0.0230
Physicians' reluctance to prescribe opioids (impact)	72%	76%	57%	39%	59%	61%	0.0170
Patients' reluctance to take opioids (impact)	46%	29%	32%	32%	38%	37%	0.0320
Patients' relatives' reluctance to permit patients to take opioids (barrier)	41%	24%	36%	26%	20%	33%	0.0010
Patients' relatives' reluctance to permit patients to take opioids (impact)	54%	38%	37%	26%	33%	41%	0.0010

Nursing staff reluctance to administer opioids (barrier)	26%	24%	30%	16%	24%	24%	0.0020
Nursing staff reluctance to administer opioids (impact)	27%	29%	33%	18%	29%	27%	0.0010
Patients' reluctance to report pain (barrier)	15%	19%	20%	24%	25%	19%	0.0090
Patients' reluctance to report pain (impact)	13%	19%	26%	32%	30%	22%	0.0350
Concerns about opioid dependence in general in my country (impact)	52%	71%	44%	32%	61%	49%	0.0110
Lack of equipment, e.g. medical devices used in pain management and palliative care (barrier)	28%	5%	16%	28%	35%	24%	<0.0001
Lack of equipment, e.g. medical devices used in pain management and palliative care (impact)	36%	10%	21%	26%	50%	30%	<0.0001
Lack of (trained) staff in healthcare units (barrier)	65%	57%	40%	43%	31%	49%	0.0160
Lack of (trained) staff in healthcare units (impact)	68%	62%	41%	43%	50%	54%	0.0080
Lack of staff at a governmental level (impact)	48%	48%	34%	30%	65%	43%	0.0440
Lack of access to a wide range of dosage forms of opioids and to a variety of substances (barrier)	34%	48%	26%	40%	58%	38%	<0.0001
Lack of access to a wide range of dosage forms of opioids and to a variety of substances (impact)	41%	48%	28%	38%	62%	41%	<0.0001
Difficulties in supply or distribution (barrier)	22%	10%	26%	23%	27%	22%	0.0460
Difficulties in supply or distribution (impact)	24%	10%	24%	26%	38%	25%	0.0150

DISCUSSION

This study shows that there are significant differences in the perception of barriers between policy makers, healthcare professionals working in the field of harm reduction, pain management and palliative care, and other stakeholders. The aspects that were most frequently perceived as a major barrier or as having major impact were lack of training, lack of financial resources and physicians' reluctance to prescribe opioids.

Overall, policy makers perceived issues less often as major problems compared to other stakeholders. For example, a high proportion of healthcare professionals (44%-57%) reported that excessive regulation or bureaucracy of prescribing procedures had a major impact on accessing opioids, while this was seen as a major issue by only 20% of the policy makers. The regulatory burden perceived by healthcare professionals may be the reason for the reported reluctance to prescribe opioids. The perception of this regulatory barrier was most prominent amongst harm reduction professionals (76%). Overall, this latter group perceived issues most

frequently as major barriers. This specific finding is in line with the results of a recent analysis of national legislation and regulations that showed that patients with opioid dependence may experience specific barriers to accessing opioids in addition to those experienced by non-dependent patients.²⁴ Additionally, the results of that legislation analysis showed that legal and regulatory documents contain language that contributes to the stigmatization of opioid dependence²⁴, which may be one of the reasons why concerns about opioid dependence were frequently rated as a major barrier by harm reduction professionals in the current study.

Lack of financial resources was most frequently perceived as a major barrier, but lack of knowledge was more frequently judged to have a major impact on professional practice. Though lack of financial resources is certainly an omnipresent problem, it does not imply that national action should primarily focus on this problem. Some low and middle income countries for example, have successfully attained constructive solutions to improve access to opioid medicines even with limited financial resources.²⁵ Overall, the sample of the current study was too small to make comparisons between countries with respect to the perception of barriers in different stakeholder groups.

Only a limited number of studies have examined differences in the perception of barriers between healthcare professionals and policy makers. Srisawang et al. examined barriers experienced by policy makers/regulators and healthcare professionals regarding the use of opioid medicines in Thailand.¹⁹ Lack of education and training in cancer pain management for healthcare professionals was regarded the main barrier among physicians, which was also noted among our palliative care/pain professionals. Moreover, Srisawang et al. found that in contrast with our findings policy makers/regulators perceived all potential issues more frequently as serious problems compared to physicians.¹⁹ A possible explanation might be the underreporting of problems by physicians due to selection bias: participating physicians were selected by the hospital director. Another study, conducted by Leon et al. in Colombia, found that insufficient human resources, deficiencies in filling out official forms, fear of expiration of medication and insufficient safety conditions for storage were frequently reported as barriers by officers from Regional Competent Authorities.²⁰ The main barriers reported by physicians were complicated procedures to authorize medication by the Health Maintenance Organizations, followed by poor accessibility in hospitals/pharmacies due to limited hours for dispensing medicines. The sample size of the Colombian study was very small and the study was not set up to compare both groups.²⁰ There are no other studies comparing healthcare professionals working in the field of harm reduction, pain management and palliative care, which is a strength of the current study. Physicians working in different medical specialties and government officials have been shown to experience different types of barriers and also

a different magnitude of barriers. A complete understanding of the impediments to access to opioid medicines in a country or region can therefore not be obtained by researching only one stakeholder group.

Limitations

A convenience sample was recruited for this study consisting of (mostly invited) participants of the ATOME national conferences. Participants were invited based on their interest and/or expertise in aspects that concern the usage of opioid medicines, which may limit the generalizability of the findings. Moreover, not all conference participants completed the survey, mostly due to organizational reasons (e.g. late arrival and registration, or distraction from questionnaire completion due to different priorities at the outset of the conference). Additionally, as this questionnaire is a modified version of existing questionnaires and has not been validated, future research should be conducted to confirm the validity of the questionnaire. Finally, this study relies on self-reporting which may lead to social desirability. By assuring anonymity and confidentiality we expect to have decreased the likelihood of receiving socially desirable answers.

Despite these limitations, we believe the results to be of significant value in that they provide insight into the barriers that are encountered by stakeholders. The results suggest that access to opioid medicines can be improved by providing more education and training for healthcare professionals and policy makers, and by ensuring the availability of financial resources at different levels such as in hospitals and other treatment facilities but also in governmental bodies. In addition, lifting legal and regulatory barriers could contribute to better access, in particular for patients in need of harm reduction. As these data do not explain the reasons behind the differences in the perception of barriers, intensified dialogue is necessary to develop mutual understanding and effective solutions. Further qualitative studies could facilitate these discussions. The results also show the importance of involving government officials and policy makers in these discussions to increase awareness of the impact of certain legislation, regulations and policies on clinical practice.

CONCLUSION

This study shows that different barriers play an important role in access to opioid medicines, depending on the stakeholders involved. When addressing these perceived barriers, intensified dialogue between all stakeholder groups is necessary to facilitate a mutual understanding and develop widely supported solutions to improve access to opioid medicines.

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Access To Opioids Questionnaire (ATOQ)

Opioid medicines used in pain management, palliative care and harm reduction are not widely available and accessible. Certain barriers have been identified that can contribute to limited access. The Access To Opioid Medication in Europe (ATOME) project funded under the European Commission's 7th Framework Programme undertakes applied research into reasons why access is limited in twelve European countries and aims at improving access to these medicines. With this questionnaire, we aim to explore your perception of barriers to opioid accessibility and availability in your country.

You contribution to this survey will be important for the quality of patient care.

All information used in this questionnaire or generated by this questionnaire will be collected and reported anonymously.

Thank you very much in advance for taking your time.



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Section A: Knowledge and attitudes

Please indicate your level of agreement with each of the following statements, using the scale provided:

True	False	Don't know/ uncertain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please select only one answer for each statement.

A1) Knowledge:

		True	False	Don't know/ uncertain
1.	Long term pain treatment with opioids may produce physical dependency symptoms, but not abuse, drug craving or other signs of opioid dependence syndrome.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	Patients receiving opioid medicines for cancer pain treatment rarely develop psychological drug dependence (or drug craving).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	When prescribed and administered according to good medical practice, opioid medicines are not likely to cause abuse.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Strong opioids should not be used to control pain unless a patient is dying, as these drugs will not be effective if used over a prolonged period of time.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	A patient's request for increasing opioid dosage to control pain in most cases indicates increasing pain due to progression of disease.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	Opioids are more efficacious when given intramuscularly, compared to oral application.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	Intramuscular administration of opioids is painful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	Adequate treatment with opioids, e.g. morphine, administered according to good medical practice in palliative care may hasten the end of life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	A patient with pre-existing opioid dependence and severe pain from another disease such as cancer should not be treated with opioid analgesics while experiencing severe pain.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A2) Attitudes:

		True	False	Don't know/ uncertain
1.	All competent and trained physicians should be able to prescribe opioid medicines, without any further (license) requirements.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	All patients in my country who need medical treatment with opioid medicines can have access to treatment with these medicines.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	In order to prevent abuse of opioid medicines, the daily dose or the total amount prescribed needs to be limited.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Physical pain is an inevitable experience that belongs to a severe illness and to the end of life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	Focusing on pain therapy will lead to a neglect of curative treatments to heal the patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	It is unethical to deny methadone maintenance to a patient with dependency syndrome.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	Methadone services should be expanded so all patients with dependency syndrome who want methadone maintenance, can receive it.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	Being free of drugs (substances of abuse) is the only reasonable goal of treatment efforts for people with opioid dependence.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	Safe injecting rooms should be established wherever large numbers of people with opioid dependence use in the streets.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	In all places with large numbers of injecting drugs users, needle and syringe exchange programmes should be established.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Section B: Barriers

It is well known that many factors can pose a problem to accessing opioid medicines.

In the following section, you will be presented a number of aspects that can pose a barrier to opioid availability. We would like to know whether these aspects in your view pose a barrier to opioid availability **in your country**.

Please indicate your rating of the level of impediment in your country for each of the following aspects using the following scale:

Not a barrier	Minor barrier	Moderate barrier	Major barrier	Don't know/uncertain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In addition, please rate the level of impact this aspect has or has had in your practice / work using the following scale:

No impact	Minor impact	Moderate impact	Major impact	Don't know/uncertain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

B1) Knowledge, education and guidance:

		No	Minor	Moderate	Major	Don't know/ uncertain
1.	Lack of (the availability of) consultation by a pain specialist for other health care providers (e.g. for general practitioners).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	Inadequate knowledge, skills and training regarding opioid medicines in health care professionals (e.g. nurses, doctors, pharmacists etc.).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	Inadequate knowledge skills and training regarding opioid medicines in policy makers/ government representatives.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Other:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

B2) Regulation of opioids:

			No	Minor	Moderate	Major	Don't know/ uncertain
5.	Excessive regulation/bureaucracy of opioids.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	Excessive regulation/bureaucracy of opioids in pharmacy.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	Excessive regulation/bureaucracy for prescribing procedures.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	Complicated international requirements.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	Disproportional sanctions for unintended violations in medical or pharmaceutical practice.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	Administrative burden for regulators, physicians, nurses or pharmacists.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11.	Other						

B3) Information/ guidelines:

			No	Minor	Moderate	Major	Don't know/ uncertain
12.	Insufficient embedding of the use of opioid medicines in treatment guidelines.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13a.	Absence of a specific national policy on pain management and palliative care.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13b.	Absence of a specific national policy on harm reduction services for people with opioid dependence syndrome.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14a.	Lack of acknowledged treatment guidelines on pain management and palliative care.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14b.	Lack of acknowledged treatment guidelines on harm reduction services for people with opioid dependence syndrome.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15.	Insufficient embedding of opioid medicines in acknowledged treatment guidelines.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.	Other:						

B4) Attitudes and concerns:

		No	Minor	Moderate	Major	Don't know/ uncertain	
17.	Physicians' reluctance to prescribe opioids.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18.	Patient's reluctance to take opioids.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19.	Patients' relatives' reluctance to permit patients to take opioids.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20.	Nursing staff reluctance to administer opioids.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21.	Patients' reluctance to report pain.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22.	Concerns about opioid dependence in general in my country.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23.	Other:						

B5) Resources and access to opioid medicines:

		No	Minor	Moderate	Major	Don't know/ uncertain	
24.	Lack of equipment, e.g. medical devices used in pain management and palliative care.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25.	Lack of equipment, e.g. medical devices used in and harm reduction.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26.	Lack of (trained) staff in health care units.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27.	Lack of staff at a governmental level.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28.	Lack of financial resources at a governmental level.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29.	Lack of financial resources at an institutional level.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30.	Lack of access to wide range of dosage forms of opioids and to a variety of substances.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31.	Difficulties in supply or distribution.	Barrier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Impact	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32.	Other:						

B6) Recent changes in your country:

33. In your opinion, has the situation regarding barriers to accessing opioids changed in the past five years? Please use one of the following response options:

- Yes No Don't know/uncertain

33a. If yes, has the situation worsened or improved?

Please use one of the following response options:

- Worsened Improved Don't know/uncertain

33b. Please specify the problem that improved or worsened and specify how the situation changed:

Section C: Feasibility questionnaire

Please indicate your level of agreement with each of the following statements, using the scale provided:

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know/uncertain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please select only one answer for each statement.

		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree	Don't know/uncertain
1.	The questions were clear.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	Questions were unambiguous.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	It was easy to answer the questions.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	I felt uncomfortable answering one or more questions.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	The effort and time investment to complete the questionnaire are reasonable.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	How long did it take to complete the questionnaire? ____ minutes						
7.	Are there any questions that need improvement?						
	Please specify question number and recommendations for improvement.						

Section D: Background

1. Which group represents your current position best?

Please select only one answer.

- Palliative care/ pain management professionals
- Harm reduction professionals
- Other health care professionals
- Government officers
- Politicians
- Other health care decision makers
- Patients or patient representatives
- Other (please specify):

2. Please state your background:

Please select one or more answers.

- Physician
- Nurse
- Pharmacist
- Pharmacy technician
- Social worker
- Lawyer
- Economist
- Researcher
- Policy/administration
- Other (please specify):

3. Please state your current function or role:

Please select one or more answers.

- Director
- Staff member
- Professional not working in a team
- Lecturer, academic
- Researcher
- Volunteer
- Palliative care, pain management or harm reduction advocate
- Other (please specify):

4. What is your current workplace/affiliation?

Please select one or more answers.

- Ministry of Health
- Other Ministry
- Hospice or palliative care service
- Hospital
- Nursing home
- General practitioner / physician in own practice
- NGO
- Other (please specify):

5. How many years of professional (working) experience (in general) do you have?

- < 1 year
- 1-5 years
- 6-10 years
- 11-20 years
- >20 years

6. Please state your age group:

- < 21
- 21 – 30
- 31 – 40
- 41 – 50
- 51 – 60
- > 60

7. Please state your gender:

- Male
- Female

We kindly thank you for completing this questionnaire.

If you have any questions please contact:

- Saskia Jünger (Saskia.Juenger@ukb.uni-bonn.de) or
- Marjolein Vranken (m.j.m.vranken@uu.nl)

Annex 2. Proportion of respondents reporting issues as major barriers or as having major impact (n=199). Significant differences indicated as follows: *

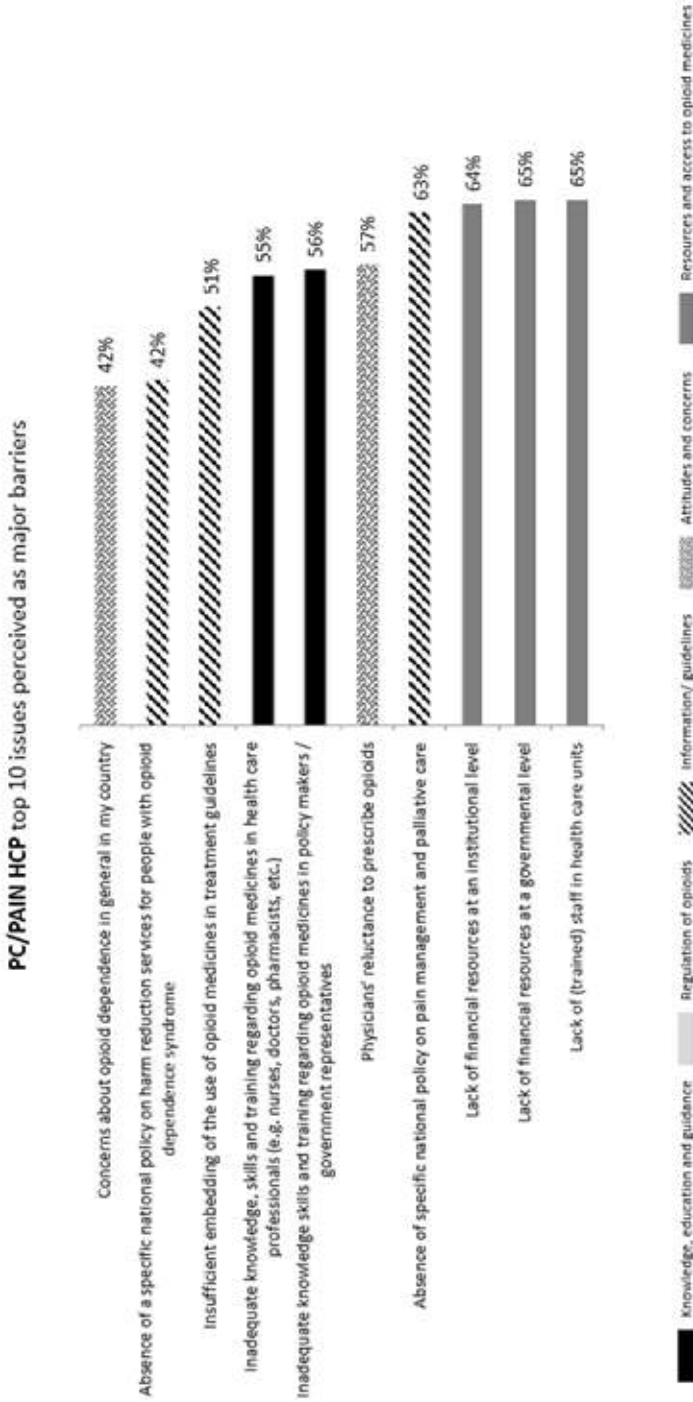
POTENTIAL BARRIER	PC / Pain	HR HCP	HCP (other)	PM	Other	Overall	p
Lack of (the availability of) consultation by a pain specialist for other healthcare providers (barrier)*	28%	48%	35%	23%	27%	30%	0.0010
Lack of (the availability of) consultation by a pain specialist for other healthcare providers (impact)	55%	57%	44%	45%	44%	49%	0.2930
Inadequate knowledge, skills and training regarding opioid medicines in healthcare professionals (barrier)	55%	52%	44%	35%	46%	47%	0.6790
Inadequate knowledge, skills and training regarding opioid medicines in healthcare professionals (impact)	74%	71%	58%	51%	65%	65%	0.6880
Inadequate knowledge skills and training regarding opioid medicines in policy makers/government representatives (barrier)	56%	76%	53%	36%	69%	55%	0.2120
Inadequate knowledge skills and training regarding opioid medicines in policy makers/government representatives (impact)*	74%	81%	70%	48%	88%	70%	0.0020
Excessive regulation / bureaucracy of opioids (barrier)*	31%	57%	36%	23%	48%	36%	0.0500
Excessive regulation / bureaucracy of opioids (impact)	32%	67%	36%	25%	56%	38%	0.0050
Excessive regulation / bureaucracy of opioids in pharmacy (barrier)	28%	38%	20%	20%	31%	26%	0.2080
Excessive regulation / bureaucracy of opioids in pharmacy (impact)	28%	38%	30%	20%	27%	28%	0.4710
Excessive regulation / bureaucracy of opioids for prescribing procedures (barrier)*	37%	52%	45%	23%	38%	38%	0.0270
Excessive regulation / bureaucracy of opioids for prescribing procedures (impact)*	44%	57%	57%	20%	46%	44%	0.0020
Complicated international requirements (barrier)	7%	19%	5%	15%	23%	12%	0.8490
Complicated international requirements (impact)	8%	29%	7%	18%	38%	16%	0.4530
Disproportional sanctions for unintended violations in medical or pharmaceutical practice (barrier)*	28%	33%	32%	20%	19%	27%	0.0010
Disproportional sanctions for unintended violations in medical or pharmaceutical practice (impact)*	34%	43%	27%	18%	44%	31%	0.0060
Administrative burden for regulators, physicians, nurses, or pharmacists (barrier)	34%	48%	43%	20%	31%	34%	0.1160
Administrative burden for regulators, physicians, nurses, or pharmacists (impact)*	40%	48%	36%	18%	50%	37%	0.0240

Insufficient embedding of the use of opioid medicines in treatment guidelines (barrier)	51%	38%	30%	23%	35%	37%	0.9250
Insufficient embedding of the use of opioid medicines in treatment guidelines (impact)	68%	55%	36%	23%	44%	47%	0.7140
Absence of specific national policy on pain management and palliative care (barrier)	63%	43%	45%	44%	54%	52%	0.1880
Absence of specific national policy on pain management and palliative care (impact)	65%	52%	44%	51%	65%	56%	0.4030
Absence of a specific national policy on harm reduction services for people with opioid dependence syndrome (barrier)	42%	57%	47%	28%	35%	41%	0.5200
Absence of a specific national policy on harm reduction services for people with opioid dependence syndrome (impact)	42%	71%	50%	34%	50%	47%	0.8710
Lack of acknowledged treatment guidelines on pain management and palliative care (barrier)*	31%	24%	30%	21%	35%	29%	0.0070
Lack of acknowledged treatment guidelines on pain management and palliative care (impact)*	35%	38%	33%	32%	48%	36%	0.0020
Lack of acknowledged treatment guidelines on harm reduction services for people with opioid dependence syndrome (barrier)	35%	38%	34%	16%	23%	30%	0.3460
Lack of acknowledged treatment guidelines on harm reduction services for people with opioid dependence syndrome (impact)	37%	62%	33%	24%	32%	36%	0.3040
Insufficient embedding of opioid medicines in acknowledged treatment guidelines (barrier)	38%	33%	34%	18%	38%	33%	0.7040
Insufficient embedding of opioid medicines in acknowledged treatment guidelines (impact)	48%	38%	35%	18%	54%	39%	0.5710
Physicians' reluctance to prescribe opioids (barrier)*	57%	62%	57%	32%	48%	51%	0.0230
Physicians' reluctance to prescribe opioids (impact)*	72%	76%	57%	39%	59%	61%	0.0170
Patients' reluctance to take opioids (barrier)	34%	14%	30%	26%	4%	26%	0.2420
Patients' reluctance to take opioids (impact)*	46%	29%	32%	32%	38%	37%	0.0320
Patients' relatives' reluctance to permit patients to take opioids (barrier)*	41%	24%	36%	26%	20%	33%	0.0010
Patients' relatives' reluctance to permit patients to take opioids (impact)*	54%	38%	37%	26%	33%	41%	0.0010
Nursing staff reluctance to administer opioids (barrier)*	26%	24%	30%	16%	24%	24%	0.0020
Nursing staff reluctance to administer opioids (impact)*	27%	29%	33%	18%	29%	27%	0.0010
Patients' reluctance to report pain (barrier)*	15%	19%	20%	24%	25%	19%	0.0090

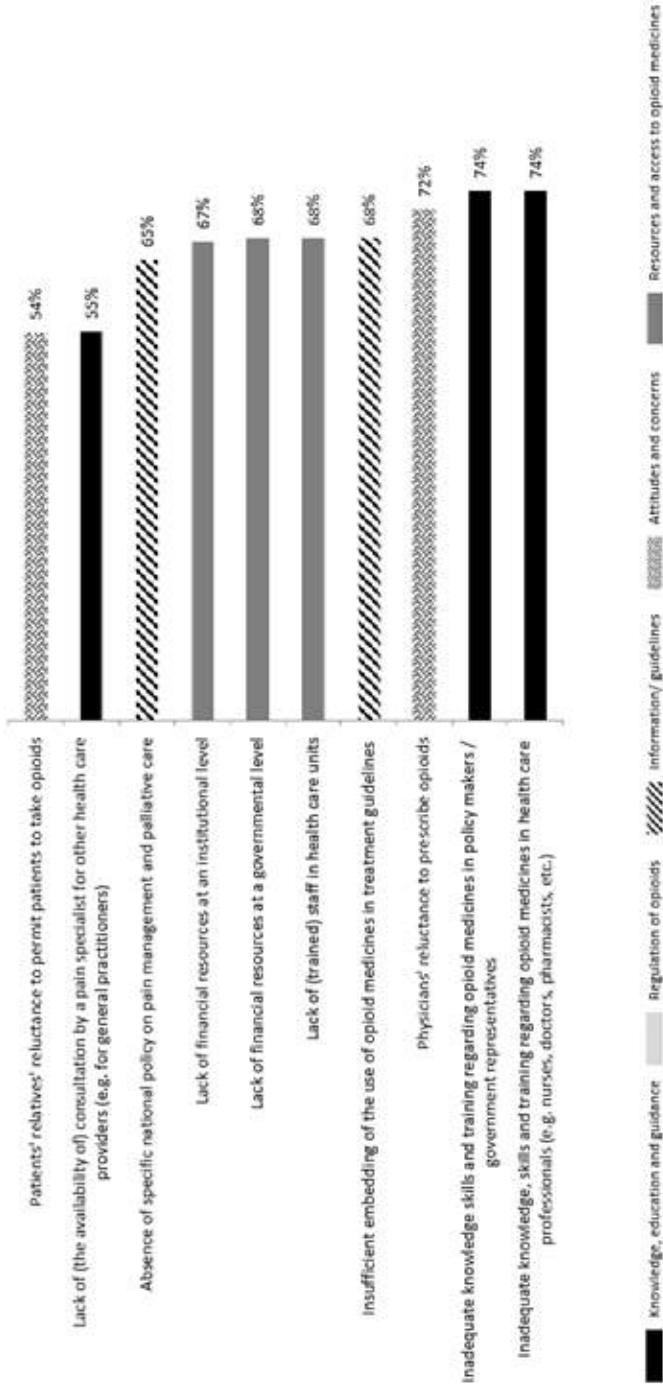
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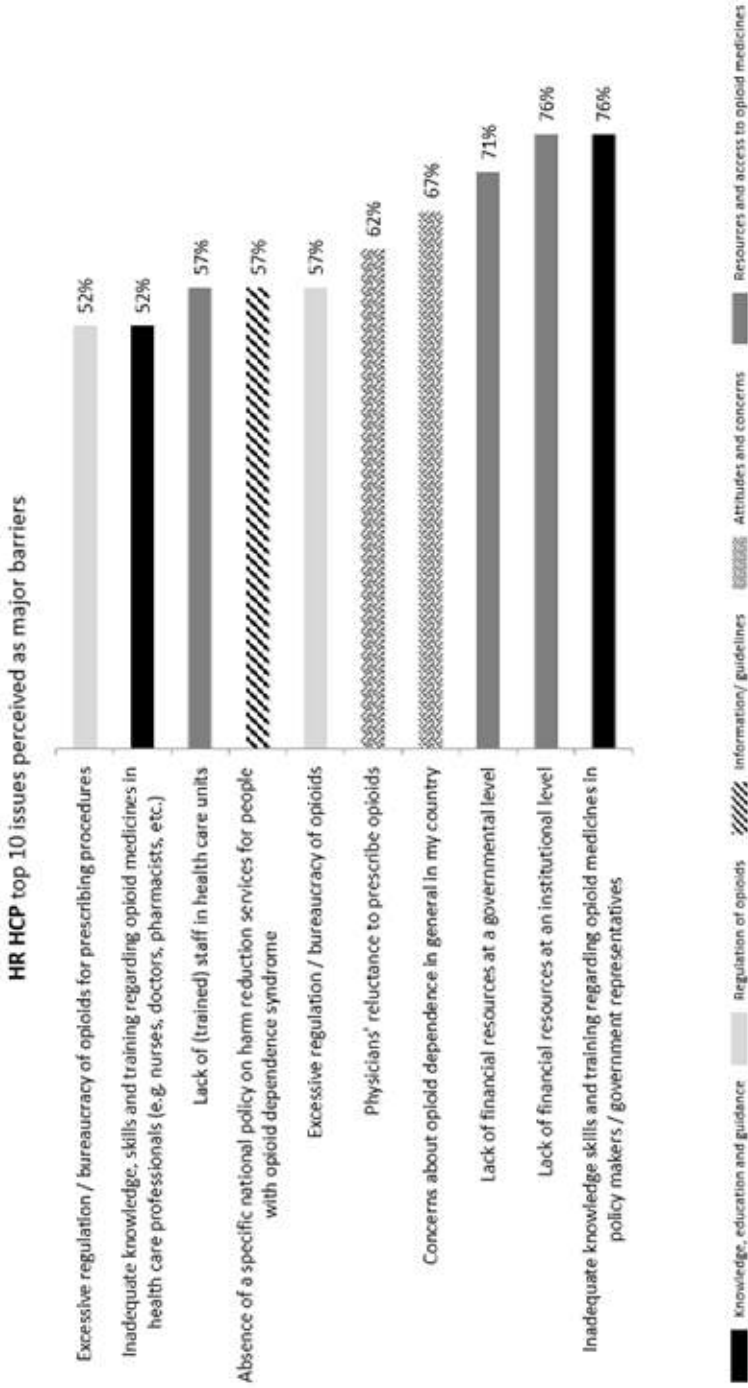
Patients' reluctance to report pain (impact)*	13%	19%	26%	32%	30%	22%	0.0350
Concerns about opioid dependence in general in my country (barrier)	42%	67%	50%	37%	50%	46%	0.1170
Concerns about opioid dependence in general in my country (impact)*	52%	71%	44%	32%	61%	49%	0.0110
Lack of equipment, e.g. medical devices used in pain management and palliative care (barrier)*	28%	5%	16%	28%	35%	24%	0.0000
Lack of equipment, e.g. medical devices used in pain management and palliative care (impact)*	36%	10%	21%	26%	50%	30%	0.0000
Lack of equipment, e.g. medical devices used in harm reduction (barrier)	28%	33%	23%	26%	27%	27%	0.1140
Lack of equipment, e.g. medical devices used in harm reduction (impact)	27%	43%	28%	26%	52%	32%	0.4920
Lack of (trained) staff in healthcare units (barrier)*	65%	57%	40%	43%	31%	49%	0.0160
Lack of (trained) staff in healthcare units (impact)*	68%	62%	41%	43%	50%	54%	0.0080
Lack of staff at a governmental level (barrier)	40%	38%	36%	38%	46%	39%	0.5660
Lack of staff at a governmental level (impact)*	48%	48%	34%	30%	65%	43%	0.0440
Lack of financial resources at a governmental level (barrier)	65%	71%	57%	58%	68%	63%	0.8890
Lack of financial resources at a governmental level (impact)	68%	71%	61%	55%	81%	66%	0.7820
Lack of financial resources at an institutional level (barrier)	64%	76%	61%	65%	73%	66%	0.9360
Lack of financial resources at an institutional level (impact)	67%	76%	68%	64%	85%	70%	0.7250
Lack of access to a wide range of dosage forms of opioids and to a variety of substances (barrier)*	34%	48%	26%	40%	58%	38%	0.0000
Lack of access to a wide range of dosage forms of opioids and to a variety of substances (impact)*	41%	48%	28%	38%	62%	41%	0.0000
Difficulties in supply or distribution (barrier)*	22%	10%	26%	23%	27%	22%	0.0460
Difficulties in supply or distribution (impact)*	24%	10%	24%	26%	38%	25%	0.0150
Overall (barrier)	39%	42%	36%	29%	37%	36%	
Overall (impact)	46%	50%	39%	32%	51%	43%	

Annex 3. Top 10 issues perceived as major barriers or as having major impact on professional practice per stakeholder group

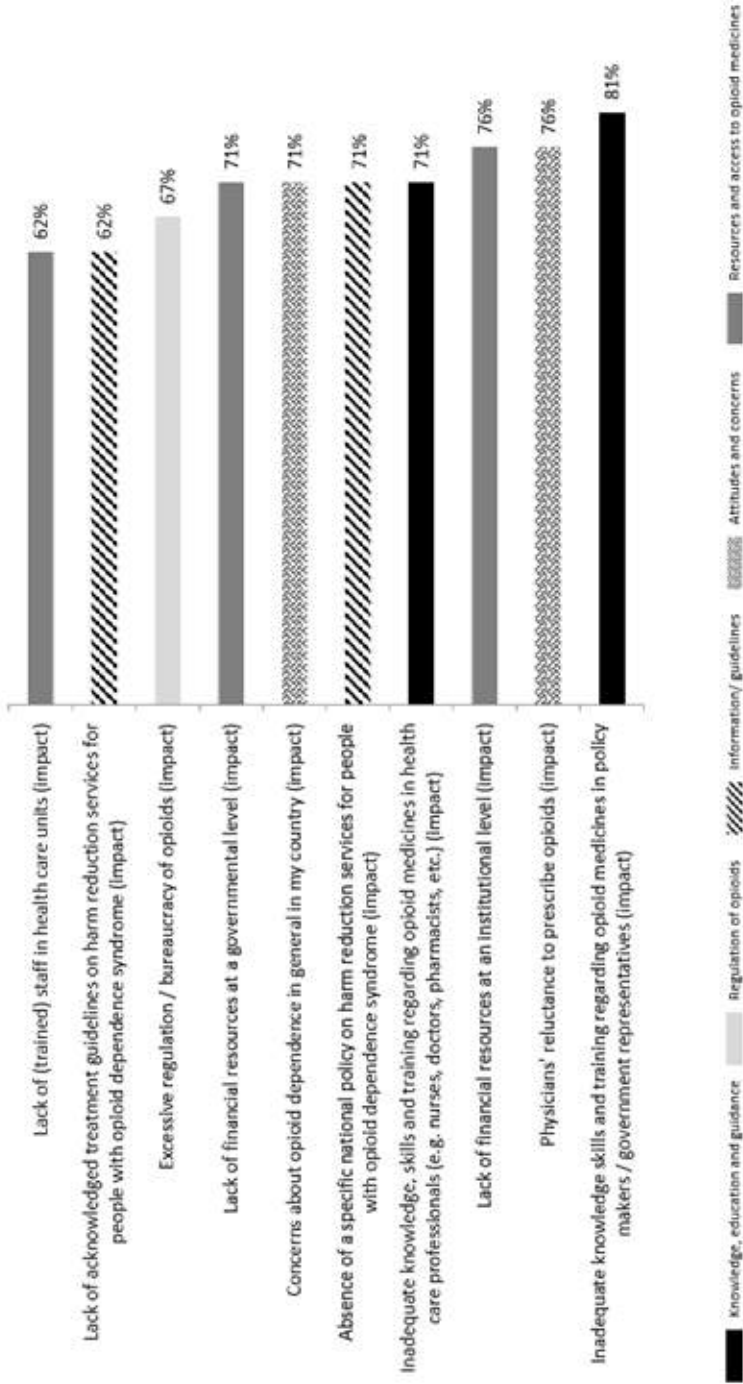


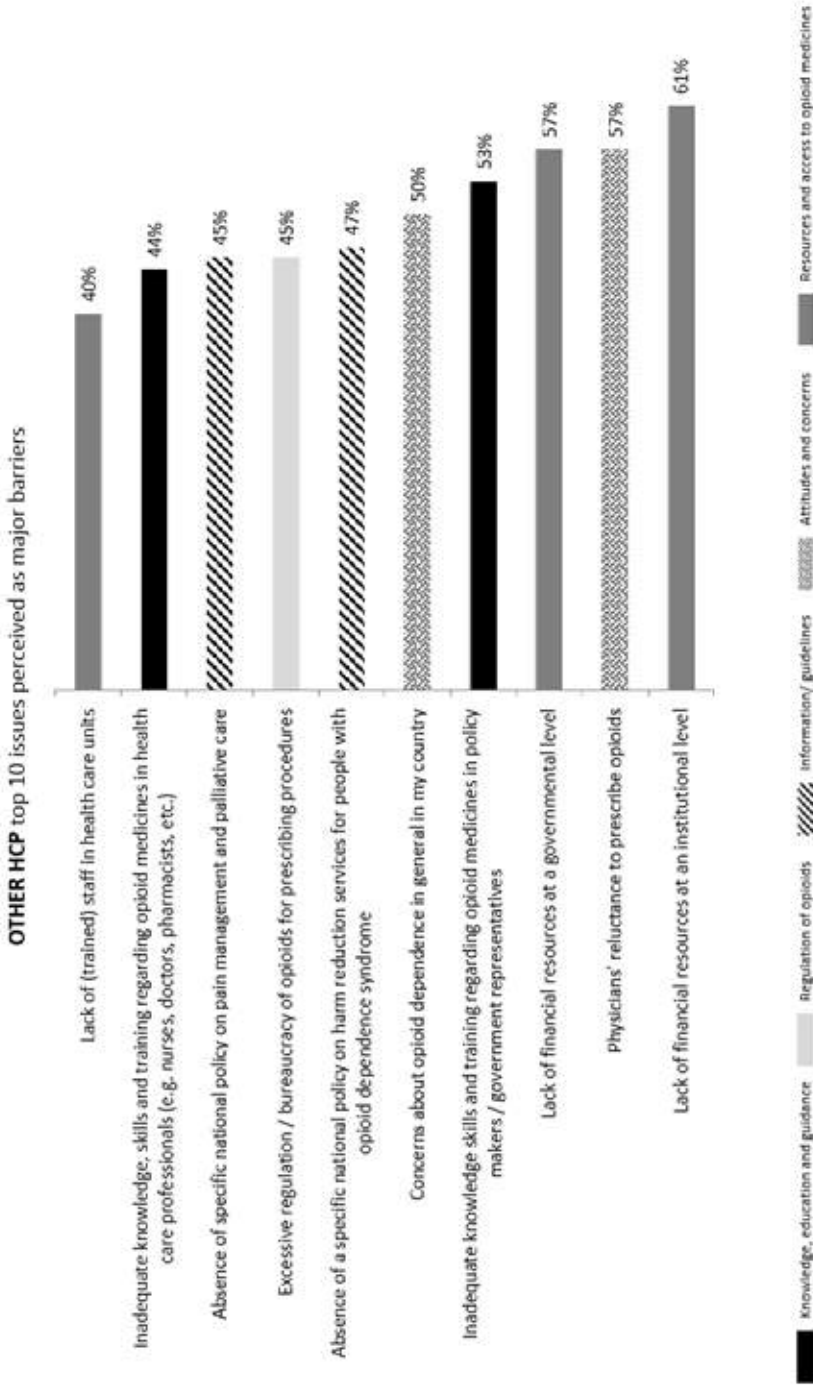
PC/PAIN HCP top 10 issues perceived as having major impact



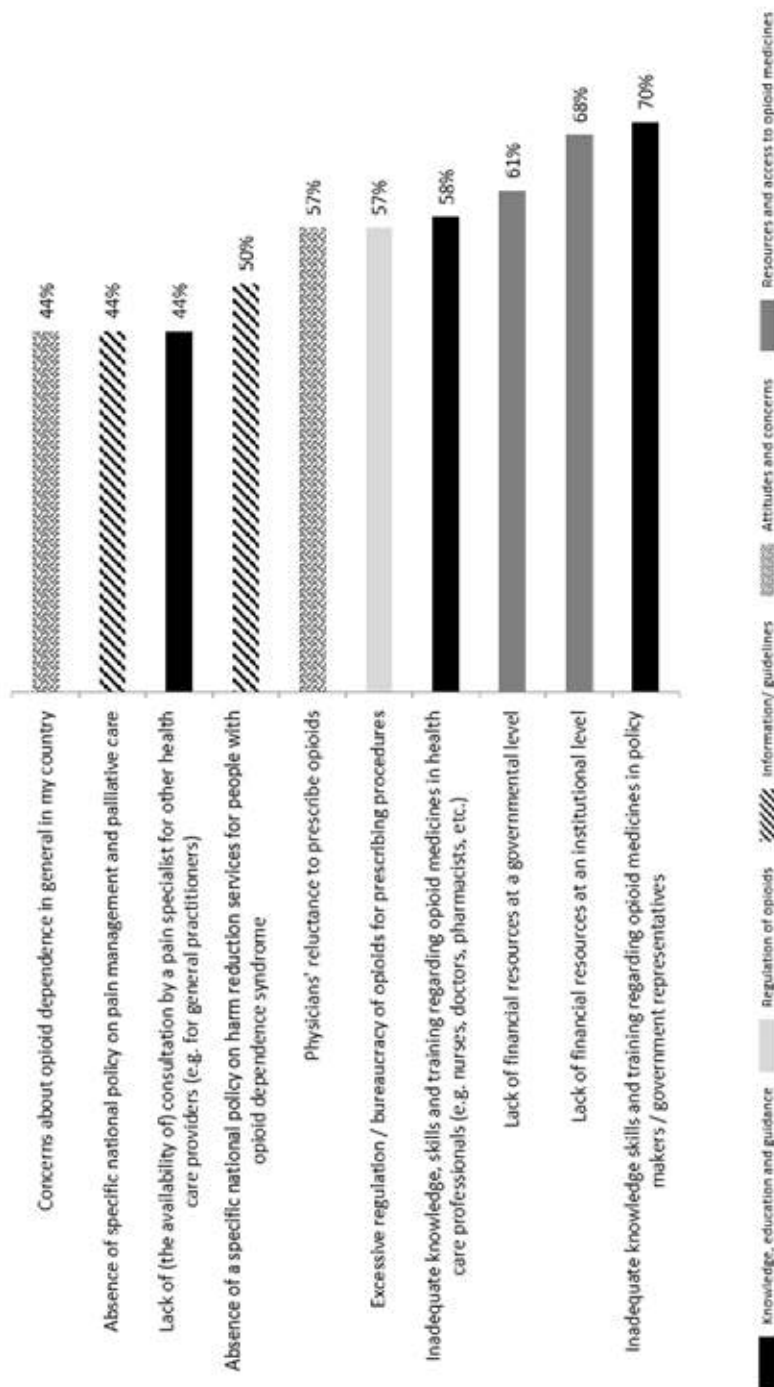


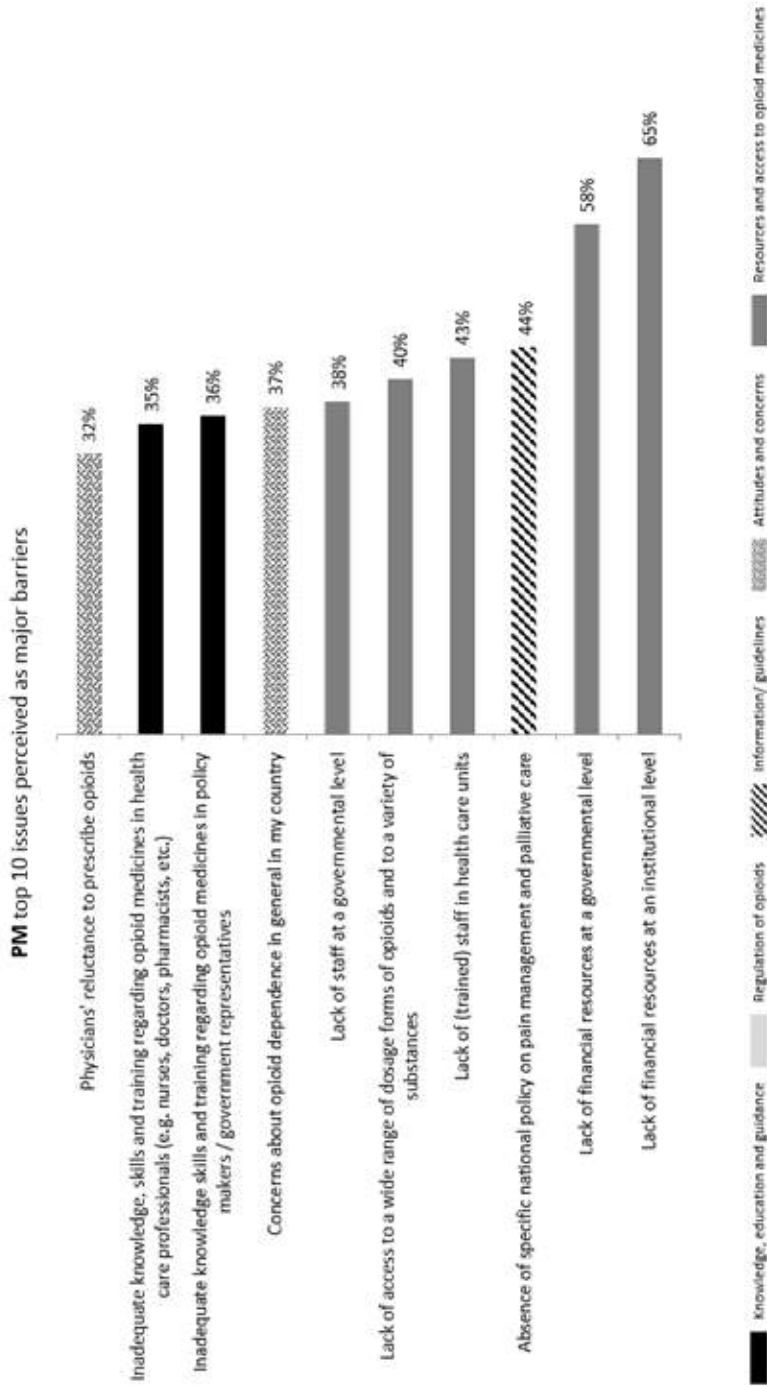
HR HCP top 10 issues perceived as having major impact





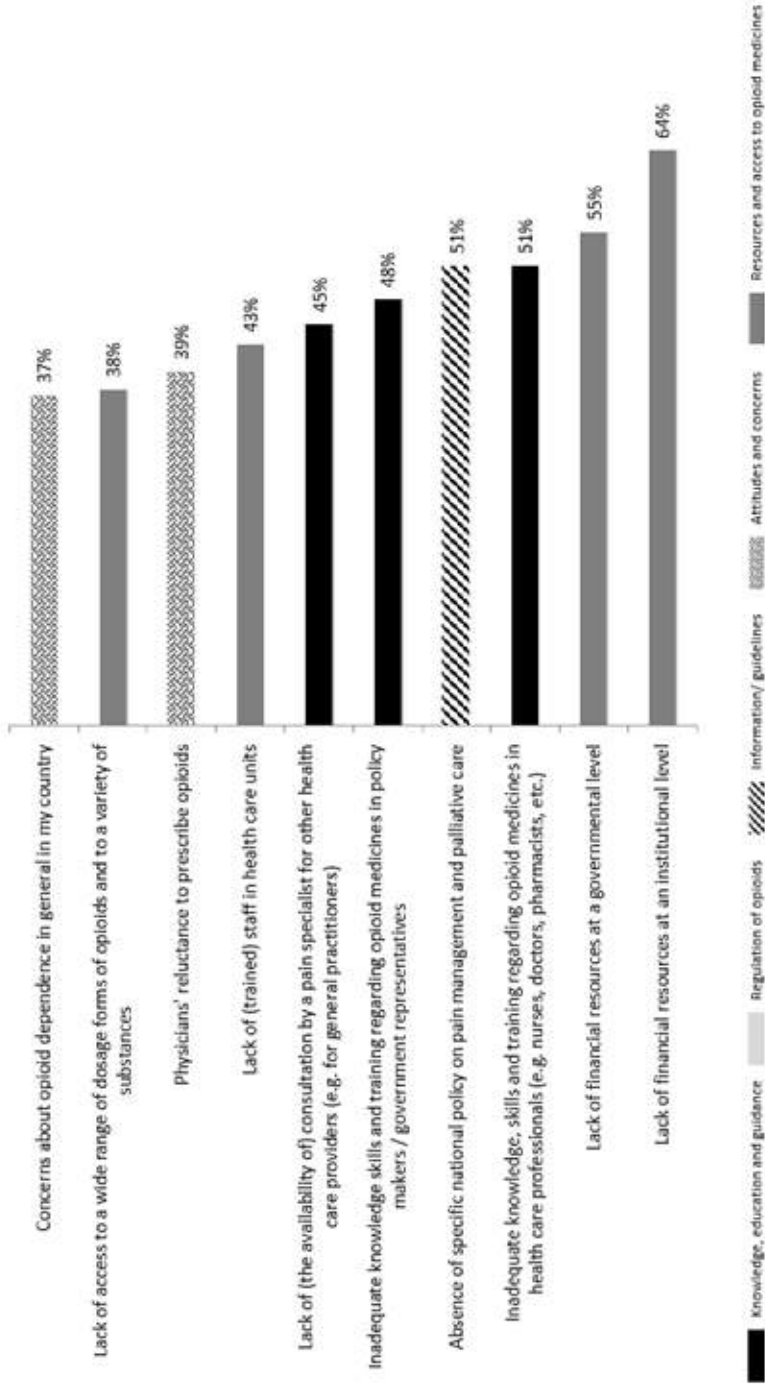
OTHER HCP top 10 issues perceived as having major impact



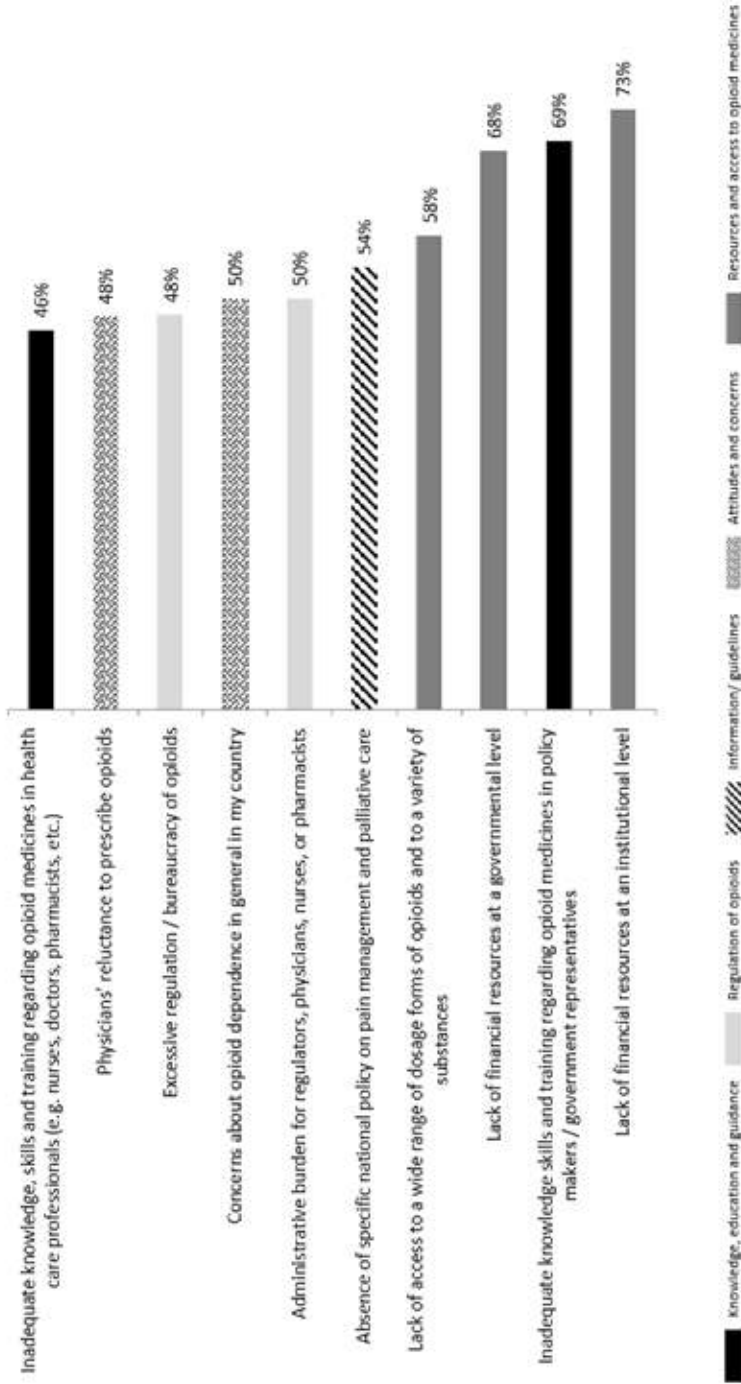


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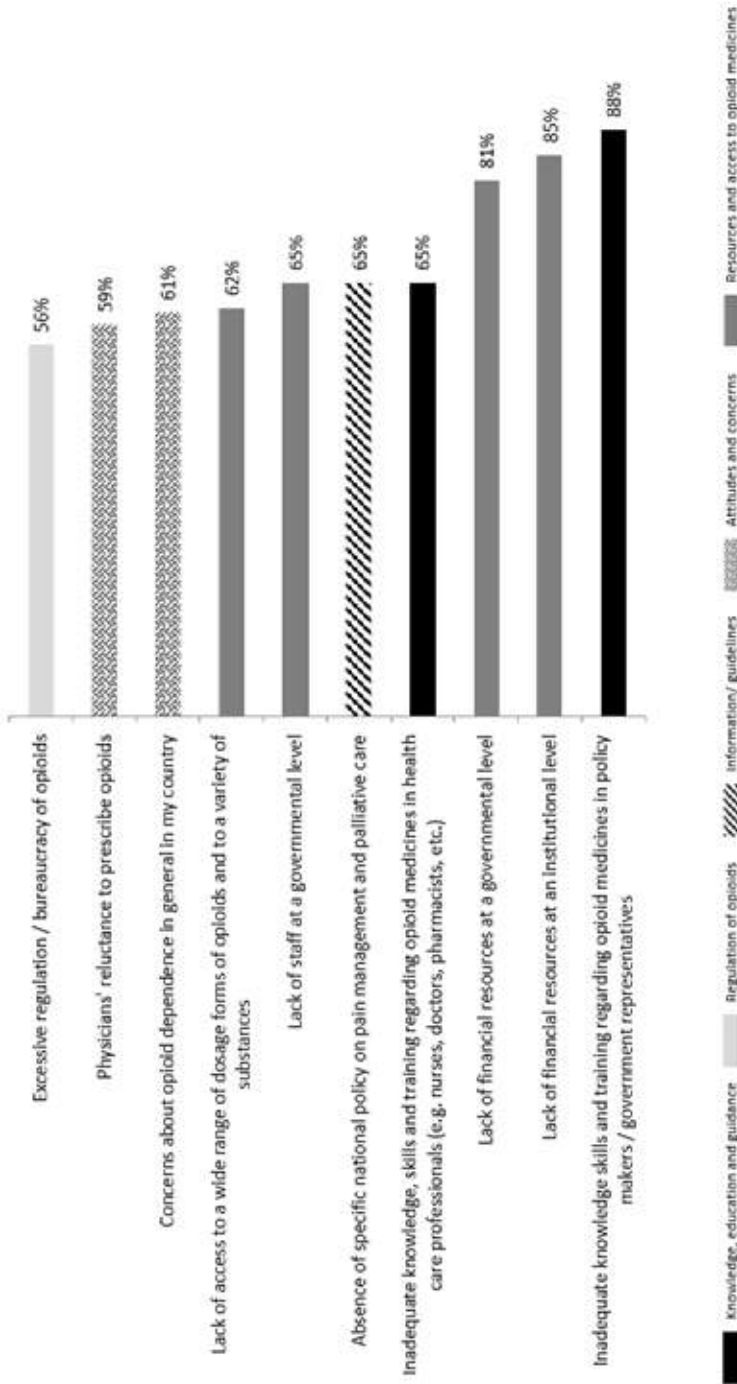
PM top 10 issues perceived as having major impact



OTHER top 10 issues perceived as major barriers



OTHER top 10 issues perceived as having major impact





CHAPTER 3.3

THE DOUBLE OPIOID CRISIS: A CALL FOR BALANCE

Marjolein J.M. Vranken, Marie-Hélène D. B. Schutjens, Aukje K. Mantel-Teeuwisse

Pharmacoepidemiol Drug Saf, 2019; 28(1): 1-3



INTRODUCTION

In this issue of *Pharmacoepidemiology and Drug Safety*, several research papers address the safe and appropriate use of opioids. This is important, given the critical situation on opioid use in the United States (US). According to preliminary data from the Centers for Disease Control and Prevention (CDC), more than 72 000 people in the United States died because of drug overdose in 2017 with over two-thirds involving opioids.¹ This situation has been declared a “national public health emergency.”² To address the so-called opioid epidemic, the House and Senate recently passed new legislation that aims to increase access to opioid dependence treatment and to prevent illicit opioids from entering the market, and supports research on other treatment options for pain besides opioids.^{3,4} Experts and activists are skeptical whether this agreement will solve the opioid crisis, at least in part because of limited funding.³

THE DOUBLE CRISIS: NONMEDICAL USE AND UNCONTROLLED PAIN

We acknowledge that abuse and diversion of opioids constitute a serious threat to public health. But it is also important to recognize that there is another side of the coin: opioids are an indispensable pharmaceutical treatment option for patients in pain, and many patients in medical need have inadequate access. Data from the International Narcotics Control Board (INCB) show that 95.7% of the global consumption of opioid analgesics in 2011 to 2013 took place in regions representing only 15% of the global population.⁵ In the light of these observed inequities, the opioid crisis can also be seen as two separate crises or a dual epidemic, both requiring our attention: the crisis of nonmedical use of opioids and the crisis of uncontrolled pain.⁶ The latter—the undertreatment of pain—is not a new problem originating from the nonmedical use crisis, but a long-standing problem for a major part of the global population. Although both crises are important, in discussions, the nonmedical use of opioids tends to be prioritized over the undertreatment of pain. How can we ensure that both are adequately addressed, and in particular, how can we prevent collateral damage in the crisis of uncontrolled pain?

CLINICAL GUIDELINES TO SUPPORT THE SAFE AND APPROPRIATE USE OF OPIOIDS

In recent years, there has been a large increase in the number of scientific studies reporting on the nonmedical use of opioids. Despite this scientific focus, there is still a lack of evidence-based guidance on the safe prescribing of opioid medicines and on the pathways from opioid dependence to opioid overdosing. Several studies have identified medication-related and patient-related factors associated with the risk of opioid overdose. Medication-related

factors include the use of long-acting or extended release formulations (especially within the first 2 weeks of initiation of therapy), combined use with benzodiazepines, high daily doses, and long-term opioid use.⁷ The latter two factors are also associated with the risk of opioid dependence.⁷ Patient-related factors associated with opioid dependence include a history of substance use disorder. Most of these risk factors are reflected in the CDC guidelines on opioid prescribing for chronic non-cancer pain, which were published⁸ in 2016. As opioid overdoses in the United States appear increasingly to be associated with heroin use (potentially mixed with illicit fentanyl) rather than the use of prescription opioids, there is also a high need for evidence on different pathways to opioid overdose, taking into account complex longitudinal patterns of prescribed and nonprescribed opioids.⁹

Prescribing guidelines are important to guide clinicians in the safe and appropriate prescribing of opioids. However, the CDC guidelines are also criticized for making some recommendations that are not supported by current scientific evidence, which is also acknowledged by the guidelines themselves.^{8, 10} Although the CDC guidelines categorize the evidence used by study design and limitations, Ranapurwala et al revealed several internal and external validity concerns in the opioid safety studies.¹¹ It can be argued that the CDC guidelines are a work in progress, and having recommendations based on some level of evidence is better than having no recommendations at all. However, it can be questioned whether recommendations that are crucial for safe and appropriate pain treatment should be based on limited evidence. Ranapurwala et al provide recommendations to overcome concerns related to validity in future research, so that a refined version of the guidelines can have a stronger evidence base.¹¹

COMPLIANCE WITH CLINICAL GUIDELINES

Aside from the level of evidence, it is useful to know to what extent these guidelines are followed in practice. In the current issue of *Pharmacoepidemiology and Drug Safety*, two papers have assessed compliance with CDC recommendations.^{12, 13} Hunnicutt et al have studied opioid prescribing in nursing homes in the United States in light of the recommendations to use immediate-release opioids when starting treatment.¹² Between 2011 and 2013, the initiation of opioid therapy in more than 182 000 long-stay nursing home residents was largely aligned with the CDC prescribing guidelines, with only 2% of patients receiving long-acting opioids at the start of therapy.¹² Young et al studied the recommendation to prescribe the lowest effective dosage when initiating opioid therapy, while avoiding an increase in dosages of extended release and long-acting (ER/LA) opioids to 90 morphine milligram equivalents (MME) or more per day, in combination with the label recommendation to establish opioid

tolerance before initiation of higher dose ER/LA opioids.¹³ A large database covering over 147 million inhabitants in the United States with employer-based insurance was used to identify adult patients initiating ER/LA opioids greater than or equal to 90MME. The results showed that 38% of the 372 038 initiators did not have evidence that opioid tolerance was established prior to initiation of greater than or equal to 90 MME of ER/LA opioids, which is not in line with label recommendations.¹³ It is unclear whether prior use of opioids paid in cash—and therefore unobserved in the database—may have contributed to the lack of evidence on established opioid tolerance. Young et al also found that nontolerant patients had a 37% increased risk of diagnosis with opioid poisoning after initiation. This increased risk was limited to the first 7 days after initiation.¹³

Compliance with clinical guidelines is an essential prerequisite for the functioning of health systems. But clinical guidelines are typically based on the average patient; there may be certain patients with individual circumstances that justify deviating from guidelines. For example, there may be patients that require treatment with an extended release formulation, or with a higher dose than 90 MME at onset of their treatment. This also applies to patients with a history or high susceptibility of opioid dependence; this group represents a particularly disadvantaged and challenging population. Providing these patients with opioids in a balanced fashion remains critical. Since this is a high-risk population, close clinical monitoring, management of abuse risk, and adequate access to opioid dependence treatment are crucial when opioid analgesics are justifiably used for pain management.

POTENTIAL IMPACT ON THE CRISIS OF UNCONTROLLED PAIN

Although the focus on appropriate prescribing and dispensing is understandable given the current opioid abuse and misuse crisis, there is a striking absence on research related to the other crisis, ie, the lack of equal access to medically justified opioids. A review of 46 articles published between 2007 and 2013 showed that 31.8% of the patients with cancer did not receive adequate pain relief.¹⁴ Current national drug control systems are thought to contribute to unequal access to opioid medicines, in addition to other factors such as a lack of knowledge and education, societal attitudes, and economic issues.¹⁵ We need to reflect on the question whether our efforts to combat the opioid epidemic (nonmedical use crisis) have a negative impact on the crisis of uncontrolled pain.

Societal attitudes regarding the medical use of opioid analgesics may have changed because of the opioid epidemic. In discussions addressing this crisis, people may not always distinguish between overdose, misuse or illegal diversion of prescribed opioids, and use of illicit opioids.

This confusion may result in a disproportionate generalized fear of opioids, limiting access for patients in medical need. Some experts believe that most patients with opioid dependence are recreational drug users who become dependent, rather than patients with pain becoming patients with opioid dependence.¹⁰ National drug control measures implemented to combat the crisis of nonmedical use may also potentially impact access to opioids for patients in legitimate medical need, although there is lack of solid evidence to support this theory. Likewise, it is still unclear whether the recently implemented opioid prescribing policies and prescription drug monitoring programs have a significant impact on the levels of nonmedical use of opioids in practice. Additionally, there is a need for research investigating other unintended consequences of policy measures and regulatory actions, such as the transitioning from prescription opioids to illicit opioids, including heroin. There is also a broader need for evidence to address data gaps on safety and the long-term effectiveness of different types of pain management treatments for different types of pain, including treatment with opioid analgesics. Future research could for example focus on the magnitude of the opioid-induced hyperalgesia effect for different kinds of patients and treatments, and critical success factors for effective long-term opioid treatment in managing different types of pain.

Although it is beyond any doubt that nonmedical use and diversion of opioids should be battled, this should not go at the expense of balanced strategies to ensure access to medicines that are legitimately on the market for patients in need of essential pain relief. The issue is how to monitor and minimize potential unintended consequences for these patients. The Access to Opioid Medication in Europe (ATOME) project—aimed at the increase of access to opioid medicines in 12 countries with statistical evidence of low opioid consumption — signalled clearly the importance of sustained investments in public health and education, and improved legal and regulatory systems to ensure safe and appropriate treatment of pain.¹⁶ Perhaps, one of the solutions for both crises lies in better education of health care professionals, patients and policy makers, in parallel with a more balanced view presented in the media.

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CHAPTER 4

ACCESS TO OPIOID MEDICINES IN CLINICAL PRACTICE





CHAPTER 4.1

VARIATION IN PRESCRIBING PRACTICES OF STRONG OPIOID ANALGESICS IN PRIMARY CARE IN THE NETHERLANDS

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ABSTRACT

BACKGROUND: Opioid analgesic prescribing increased in the period 2005-2015 in the Netherlands, which was mainly attributable to an increase in non-cancer pain.

OBJECTIVE: This study aimed to explore variation in prescribing patterns across general practices in primary care. Additionally, this study aimed to evaluate the correlation between the level of strong opioid analgesic prescribing and its prescribing for non-cancer pain.

METHODS: Data were derived from the Nivel Primary Care Database, containing information on prescriptions from 1 622 459 unique inhabitants in 2015. Variation in the prescribing of strong opioid analgesics, oxycodone, fentanyl and morphine was assessed using Defined Daily Doses (DDD) per 1 000 inhabitants for the year 2015. Regional variation in the prescribing was assessed comparing the median DDD/1 000 prescribed between the 12 Dutch provinces. The inter-practice variability in the prescribing across the 12 provinces was assessed by comparing the 25th and 75th percentile. The DDD/1 000 prescribed and the relative prescribing for non-cancer pain were contrasted to evaluate their correlation. A linear correlation was evaluated using a squared linear correlation coefficient.

RESULTS: In total, 146 016 prescriptions of strong opioid analgesics (406 practices) were included. We found a 2.2 to 4.6-fold variation in the median amount prescribed per practice across the 12 provinces and a 3.3 to 6.8-fold difference between high- and low prescribing practices. General practices in Limburg prescribed the highest amount of strong opioid analgesics, while the largest variation between general practices was seen in Groningen. The low R^2 value (1.6% variance explained) indicates that there is no correlation between the DDD/1 000 strong opioid analgesics prescribed and the % of volume prescribed for patients with non-cancer pain in the general practices evaluated.

CONCLUSIONS: We did find substantial variation in the prescribing of strong opioid analgesics in primary care. However, we did not observe that practices with high volumes of opioid prescriptions also had more preferential use for non-cancer pain. The variation observed and the lack of correlation between volume and use for non-cancer pain may be explained by population and practice characteristics, which need to be assessed in future analyses.

INTRODUCTION

Increasing attention is paid to the use of strong opioid analgesics, mostly from a perspective of inappropriate use. Discussions also focus on the rapid increase of strong opioid analgesics prescribing for the long-term treatment of non-cancer pain. Given the lack of solid and conclusive evidence supporting their use for this patient group, there are concerns on the appropriateness of opioid analgesics for chronic non-cancer pain.¹⁻⁴ A 2017 systematic review for example concluded that there is currently no reliable information about how well high-dose opioids work and how safe they are when used on a long-term basis for chronic non-cancer pain.³ Despite this lack of evidence, there are data showing that certain subgroups of patients with chronic non-cancer pain experience substantial benefits from their treatment with opioids.^{2,5,6} The Netherlands is considered a liberal country when it comes to its drug policy, but is regarded relatively conservative when it comes to the prescribing of certain groups of medicines, for example antibiotics and opioids for refractory dyspnoea in COPD.^{7,8} Despite this reserve, an increase was seen in opioid analgesic prescribing in the period 2005-2015.⁹ A report published in 2017 focusing on general practices showed that this increase was primarily related to an increased prescribing for patients with non-cancer pain.⁹ Although the opioid prescribing levels plateaued after 2017, the Dutch Minister for Medical Care recently announced measures to ensure a potential further increase would be curbed.¹⁰ These measures include the standardization of medical treatment guidelines. Within this context, the Minister called upon the professional organization of general practitioners to look into the factors driving increased prescribing in primary care, and to take the required actions to reduce unnecessary opioid use. Data on the increased prescribing of opioid analgesics in the Netherlands have been reported on a national level only; it is unclear whether there is a large variation across general practices and between regions. Other studies examining prescribing practices in a primary-care setting in the Netherlands have found considerable variation, for example in the prevalence of polypharmacy among patients aged 55 years and older or in the prescribing of antibiotics for pediatric respiratory tract infections.^{11,12} It is also unclear whether general practices with a high level of opioid prescribing have a relatively high level of opioid prescribing for non-cancer pain. This would be particularly interesting to know, given the fact that recent data show an increase in the prescribing of opioids in several countries worldwide, with the majority of prescriptions for non-cancer pain.¹³⁻¹⁵ This study aimed to explore variation in prescribing patterns across regions and general practices in primary care. Additionally, this study aimed to evaluate the correlation between the level of strong opioid analgesic prescribing and its relative prescribing for patients with non-cancer pain.

METHODS

Data sources

Primary care practice data regarding opioid prescriptions were retrospectively extracted from the Nivel Primary Care Database (Nivel-PCD). The Nivel-PCD contains anonymized data that are routinely recorded from a representative sample of the Dutch population. This database includes information on General Practitioner (GP) prescriptions, clinical diagnosis, patient gender and year of birth. Practices with at least 500 patients and sufficient data quality (≥ 46 weeks of contact data and a registered Anatomical Therapeutic Chemical (ATC) code in $\geq 85\%$ of the prescriptions) were included in the study on a per-year basis. Our study population consisted of all persons registered in these practices in 2015. Within this study population, prescription data were extracted from patients that had a database history of at least one prescription of a medicinal product starting with the ATC codes N02A, N01AH and N07BC. Information on clinical diagnosis was categorized into the following five groups based on patient morbidity data or a recorded indication linked to the prescription, using the International Classification of Primary Care (ICPC) codes: 1. cancer, 2. back pain, 3. drug dependence, 4. other clinical diagnosis and 5. unknown/not registered.

Dutch legislation allows the use of extracts of electronic health records for research purposes under certain conditions. According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for this kind of observational studies containing no directly identifiable data. This study has been approved by the applicable governance bodies of Nivel Primary Care Database under number NZR00316.045.

Strong opioid analgesics

A selection was made within the prescription data records to include strong opioid analgesics only, starting with ATC code N02A, excluding weak opioid analgesics (e.g. codeine and tramadol), opioids that are mainly used as anesthetic or for the treatment of cough and diarrhea (see Annex 1). Additionally, opioids starting with ATC code N07BC were included, unless they were prescribed in combination with the ICPC code related to drug dependence (see Annex 1).

Variables and data analysis

The amount prescribed, expressed as daily defined doses (DDD) as defined by the World Health Organization¹⁶ per 1 000 persons for the year 2015 was calculated to indicate the level of opioid use. This was done for the group strong opioid analgesics as a whole and for the three most frequently prescribed strong opioid analgesics. The DDD/1 000 was calculated on

a general practice level and on a regional level based on the number of patients registered in each of the general practices. The start dates (prescription date) and the end dates of the prescription records were used to calculate the total number of DDDs prescribed. In case no total number of DDDs could be calculated, the average DDD of all prescription data within the said ATC code was used. The four-digit postal code of each general practice was used to link prescription data to one of the regions (the 12 Dutch provinces). Prescription data were stratified into cancer pain (ICPC code related to cancer, see Table 1) and non-cancer pain groups (ICPC codes related to back pain and other clinical indications, see Table 1). When stratifying between cancer and non-cancer pain groups, prescriptions relating to drug dependence and prescriptions without information on clinical diagnosis were excluded.

Statistical analysis

Data analysis included descriptive statistics (percentages, mean and median values). The inter-practice variability in the prescribing of strong opioid analgesics was assessed by comparing the 25th and 75th percentile for each of the regions. Absolute variation between high and low-prescribing general practices was indicated by the difference between 25th and 75th percentile. The relative degree of variation between general practices was indicated by the ratio between both percentiles.

The correlation between the total amount strong opioid analgesics prescribed and the relative use of strong opioid analgesics in non-cancer pain was assessed by contrasting the DDD/1 000 prescribed by the individual general practices against their relative use for patients with non-cancer pain. A squared linear correlation coefficient (R^2) was obtained which provides an index of the degree to which the paired measures co-vary. As a sensitivity analysis, we restricted the analysis to general practices that recorded a clinical diagnosis in at least 80% of their prescriptions based on the volume strong opioid analgesics prescribed.

Analyses were conducted using SAS Enterprise Guide 7.1.

RESULTS

Data were collected from 406 general practices (n=1 622 459 patients). In total, 146 016 prescriptions for strong opioid analgesics were recorded and 2.1% of the patients (n=34 089 patients) were prescribed at least one dose of a strong opioid analgesic in 2015, see Table 1. Oxycodone was by far the most frequently prescribed strong opioid analgesic (57.5%), followed by fentanyl (28.9%) and morphine (10.6%), see Table 1. The majority of prescriptions were for non-cancer pain: 8.1% of the prescriptions were for cancer pain, 14.5% for back pain, 0.1% for drug dependence, 36.0% for other clinical diagnosis and 41.3% were not recorded/unknown.

Table 1. Characteristics of the study population in numbers (percentages) in 2015

No. PRACTICES	406
No. PATIENTS	1 622 459
PATIENTS WITH ≥ 1 PRESCRIPTION STRONG OPIOID ANALGESICS IN 2015	34 089
WOMEN	20 358 (59.7%)
MEN	13 731 (40.3%)
No. PRESCRIPTIONS	
TOTAL	146 016
MORPHINE (N02AA01)	15 478 (10.6%)
OXYCODONE (N02AA05)	83 916 (57.5%)
FENTANYL (N02AB03)	42 244 (28.9%)
OTHER	4 378 (3.0%)
CLINICAL DIAGNOSIS / RECORDED INDICATION (No. PRESCRIPTIONS)*	
CANCER	11 869 (8.1%)
BACK PAIN	21 162 (14.5%)
DRUG DEPENDENCE	206 (0.1%)
OTHER	52 511 (36.0%)
NOT RECORDED/UNKNOWN	268 (41.3%)

*ICPC codes related to cancer include A79, B72-74, D74-77, L17.01, N74, R84, R85, S77, T71, U75-77, W72, X75-77, Y77 and Y78. ICPC codes related to back pain include L02, L03 and L86. ICPC codes related to drug dependence include P19.

Regional variation in the prescribing of strong opioid analgesics

Overall, the median amount strong opioid analgesics prescribed per practice varied 2.2-fold between the provinces, ranging from 1327 DDD/1 000 in Noord-Holland to 2 903 DDD/1 000 in Limburg, see Figure 1. For oxycodone and fentanyl, also a 2.2-fold variation was seen, with the lowest median amounts prescribed in Zuid-Holland/Noord-Holland (oxycodone; 222.4 DDD/1 000) and Noord-Holland (fentanyl; 936 DDD/1 000) and the highest amounts prescribed in Flevoland (oxycodone; 488 DDD/1 000) and Limburg (fentanyl; 2065 DDD/1 000). A 4.6-fold variation was seen for morphine, with 45 DDD/1 000 in Utrecht and 204 DDD/1 000 in Groningen, see Figure 1. Comparing regions, oxycodone accounted for 13.2-31.4% of the amount of strong opioid analgesics prescribed, with the lowest relative use in Zeeland and the highest in Flevoland. Fentanyl accounted for 51.4% (Utrecht) to 82.1% (Groningen) of the volume prescribed, and the relative use of morphine varied from 2.3% in Utrecht to 8.8% in Groningen, see Figure 1.

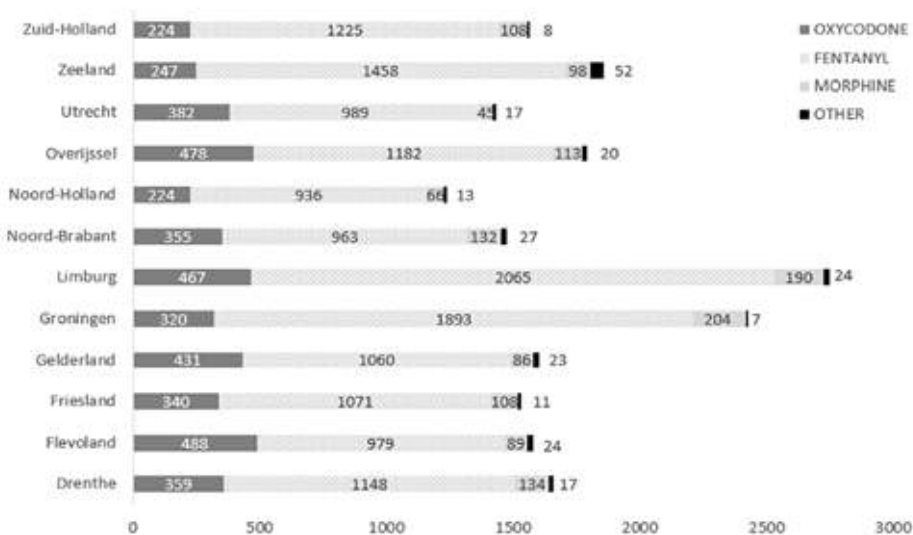


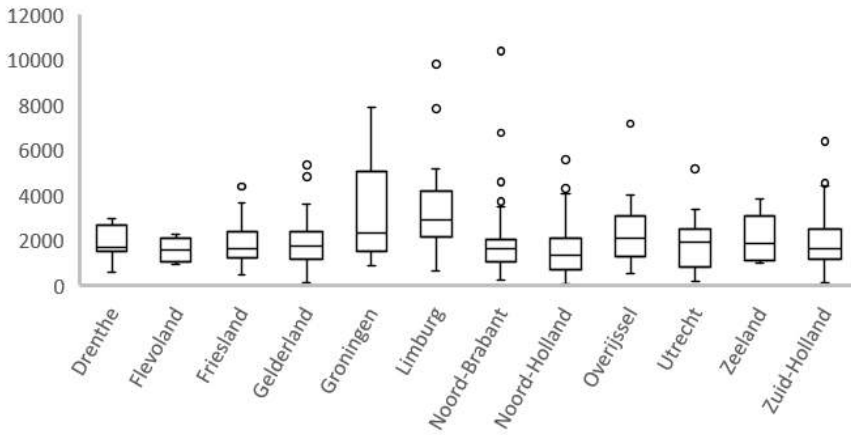
Figure 1. Median number of DDD/1 000 persons prescribed per general practice in primary care for oxycodone, fentanyl, morphine and other strong opioid analgesics for the twelve provinces in the Netherlands in 2015

Variation in the amount prescribed across general practices

Figures 2a-d and Table 2 show the variation in strong opioid analgesic prescribing between general practices for strong opioid analgesics as a group and for oxycodone, fentanyl and morphine separately. The largest absolute variation was seen in Groningen with a gap between

general practices (difference between the 75th and 25th percentile) of 3 490 DDD/1 000 for strong opioid analgesics, 3 320 DDD/1 000 for fentanyl and 232 DDD/1 000 for morphine, see Figures 2a, 2c-d and Table 2. For oxycodone, the largest variation between practices was seen in Limburg, with an absolute difference between high and low prescribing practices of 458 DDD/1 000, see Figure 2b and Table 2.

The largest relative variation for the group strong opioid analgesics as a whole and for fentanyl and morphine was seen in Groningen, with a 3.3-fold difference between the 75th percentile (highest prescribing practices) and the 25th percentile of values (lowest prescribing practices) for strong opioid analgesics, a 4.3-fold difference for fentanyl and a 6.8-fold differences for morphine. The highest relative variation for oxycodone was in Noord-Holland with a 3.0-fold difference between the 75th and 25th percentile of values, see Figure 2b and Table 2.



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Figure 2a. DDD/1000 strong opioid analgesics prescribed across general practices for the twelve provinces in the Netherlands (2015 data)

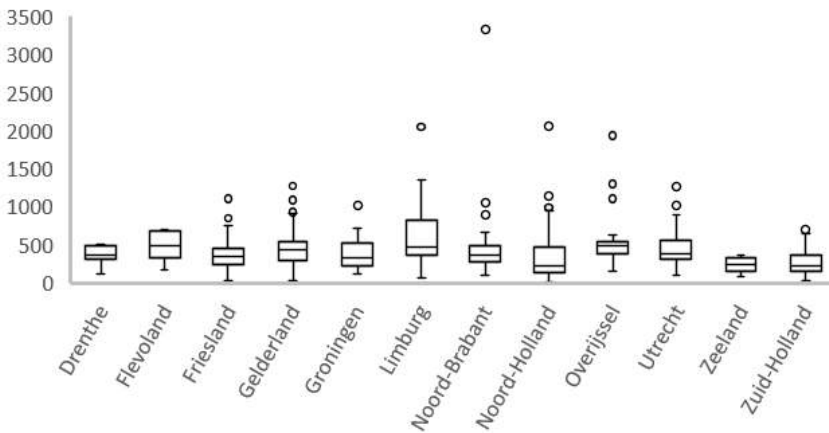


Figure 2b. DDD/1000 oxycodone prescribed across general practices for the twelve provinces in the Netherlands (2015 data)

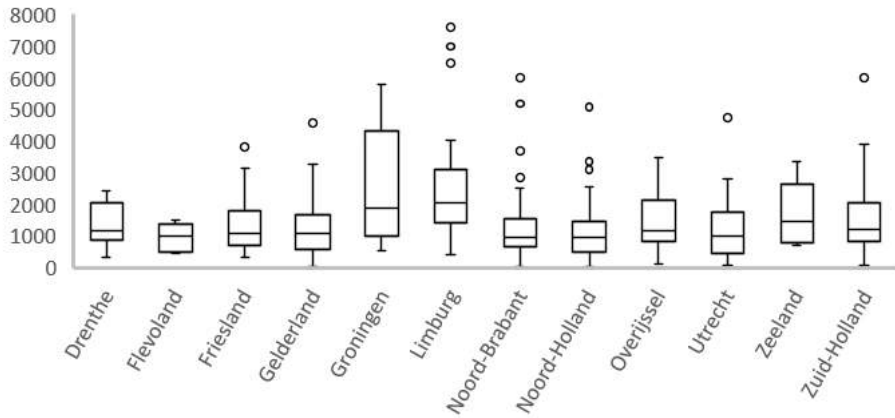


Figure 2c. DDD/1000 fentanyl prescribed across general practices for the 12 provinces in the Netherlands (2015 data)

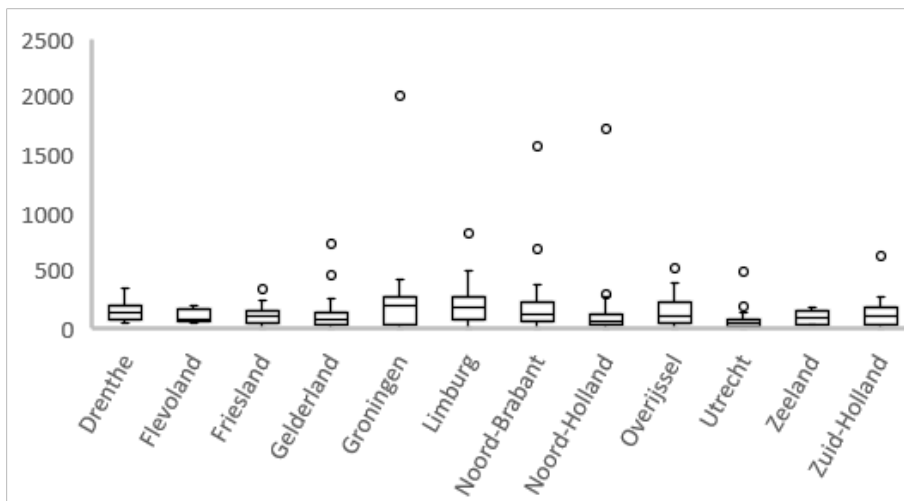


Figure 2d. DDD/1000 morphine prescribed across general practices for the 12 provinces in the Netherlands (2015 data)

Table 2. Variation in the prescribing of strong opioid analgesics across general practices for the twelve provinces in the Netherlands in 2015

AMOUNT PRESCRIBED PER PROVINCE, DDD/1 000 (No. GENERAL PRACTICES)		MEAN (SD)	25 th PERCENTILE	75 th PERCENTILE	MEDIAN	ABSOLUTE VARIATION	RELATIVE VARIATION
DRENTHE (n=12)	OPIOID ANALGESICS	1905.1 (711.8)	1529.4	2658.4	1682.7	1129.0	1.7
	OXYCODONE	363.3 (117.7)	316.4	478.7	359.0	162.3	1.5
	FENTANYL	1360.2 (662.3)	863.1	2054.0	1147.9	1190.9	2.4
	MORPHINE	158.0 (99.4)	79.7	207.6	134.1	127.9	2.6
FLEVOLAND (n=5)	OPIOID ANALGESICS	1573.0 (544.2)	1060.5	2094.9	1553.9	1034.4	2.0
	OXYCODONE	496.4 (209.9)	321.9	675.4	487.5	353.5	2.1
	FENTANYL	942.7 (462.4)	481.2	1386.2	978.7	905.0	2.9
	MORPHINE	112.6 (59.3)	68.0	169.2	88.7	101.2	2.5
FRIESLAND (n=26)	OPIOID ANALGESICS	1885.0 (992.1)	1201.4	2363.8	1639.6	1162.4	2.0
	OXYCODONE	379.0 (241.7)	231.5	443.3	340.3	211.8	1.9
	FENTANYL	1361.8 (884.6)	680.6	1780.9	1071.2	1100.3	2.6
	MORPHINE	123.4 (90.2)	55.1	153.4	108.1	98.3	2.8
GELDERLAND (n=62)	OPIOID ANALGESICS	1892.9 (1084.0)	1140.2	2375.6	1723.8	1235.4	2.1
	OXYCODONE	481.5 (271.2)	293.8	547.3	431.2	253.5	1.9
	FENTANYL	1246.2 (919.7)	593.5	1685.3	1060.0	1091.8	2.8
	MORPHINE	121.3 (129.1)	39.3	140.4	86.5	101.0	3.6
GRONINGEN (n=12)	OPIOID ANALGESICS	3219.8 (2380.4)	1545.4	5035.1	2304.7	3489.7	3.3
	OXYCODONE	405.5 (252.2)	224.5	524.7	319.8	300.2	2.3
	FENTANYL	2477.6 (1927.2)	1011.2	4330.9	1892.6	3319.7	4.3
	MORPHINE	315.6 (547.3)	39.9	271.8	203.6	231.9	6.8
LIMBURG (n=29)	OPIOID ANALGESICS	3401.9 (2136.5)	2172.7	4163.6	2902.9	1990.9	1.9
	OXYCODONE	620.4 (427.6)	365.9	823.5	467.5	457.6	2.3
	FENTANYL	2507.0 (1794.8)	1413.8	3083.5	2064.9	1669.8	2.2

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	MORPHINE	215.0 (172.3)	84.5	270.0	190.1	185.5	3.2
NOORD-BRABANT (n=42)	OPIOID ANALGESICS	2022.4 (1832.5)	1046.4	2028.7	1609.2	982.2	1.9
	OXYCODONE	447.6 (495.7)	270.8	481.6	355.1	210.9	1.8
	FENTANYL	1334.6 (1256.8)	660.3	1533.6	962.8	873.3	2.3
	MORPHINE	187.3 (252.0)	66.1	237.2	132.1	171.0	3.6
NOORD-HOLLAND (n=92)	OPIOID ANALGESICS	1554.0 (1031.8)	707.6	2110.4	1327.2	1402.8	3.0
	OXYCODONE	330.5 (313.7)	134.0	463.4	224.4	329.4	3.5
	FENTANYL	1080.3 (831.5)	489.6	1460.7	936.2	971.1	3.0
	MORPHINE	103.8 (189.0)	29.8	127.3	66.1	97.5	4.3
OVERIJSEL (n=32)	OPIOID ANALGESICS	2324.2 (1306.6)	1275.5	3105.5	2106.6	1830.0	2.4
	OXYCODONE	549.2 (357.2)	378.6	545.9	477.7	167.3	1.4
	FENTANYL	1544.4 (1058.0)	823.2	2122.0	1181.6	1298.8	2.6
	MORPHINE	152.1 (128.5)	45.7	232.4	112.9	186.8	5.1
UTRECHT (n=33)	OPIOID ANALGESICS	1788.9 (1110.2)	841.8	2504.1	1926.3	1662.3	3.0
	OXYCODONE	474.3 (287.8)	308.5	552.3	382.2	243.8	1.8
	FENTANYL	1191.7 (961.8)	463.0	1766.2	989.3	1303.2	3.8
	MORPHINE	75.9 (95.2)	22.0	86.5	44.7	64.6	3.9
ZEELAND (n=5)	OPIOID ANALGESICS	2060.0 (1108.1)	1139.2	3072.6	1876.2	1933.4	2.7
	OXYCODONE	239.6 (102.0)	146.1	329.2	247.3	183.0	2.3
	FENTANYL	1672.6 (1062.2)	796.0	2656.3	1458.4	1860.2	3.3
	MORPHINE	99.6 (61.5)	42.9	157.1	98.0	114.2	3.7
ZUID-HOLLAND (n=56)	OPIOID ANALGESICS	1941.2 (1223.5)	1185.5	2492.0	1627.1	1306.4	2.1
	OXYCODONE	277.8 (181.7)	143.2	355.7	223.6	212.5	2.5
	FENTANYL	1521.3 (1104.1)	808.4	2063.8	1224.6	1255.4	2.6
	MORPHINE	120.0 (105.4)	40.0	181.9	107.8	141.9	4.6

Correlation between the level of strong opioid analgesic prescribing and non-cancer pain use

Table 1 shows that strong opioid analgesics were primarily prescribed for the treatment of non-cancer pain in comparison to cancer pain. For each general practice, the DDD/1 000 strong opioid analgesics prescribed and the percentage prescribed for non-cancer pain are contrasted in Figure 3. The results show that most general practices are clustered in the upper left corner, with a relatively high use in non-cancer pain vs non-cancer pain and a relatively low level of strong opioid analgesic prescribing.

Evaluation of the correlation between the total amount of strong opioid analgesics prescribed (DDD/1 000) and the percentage prescribed for patients with non-cancer pain yielded a R^2 value of 0.0159 and a correlation plot trend line gradient of $2E-05$ indicating no correlation (formula: $y = 2E-05x + 0.7772$). Similar results were obtained when the analysis was restricted to general practices that had a high level of recorded clinical diagnosis based on the volume strong opioid analgesics prescribed, R^2 value of 0.0569 (formula: $y = -3E-05x + 0.7293$).

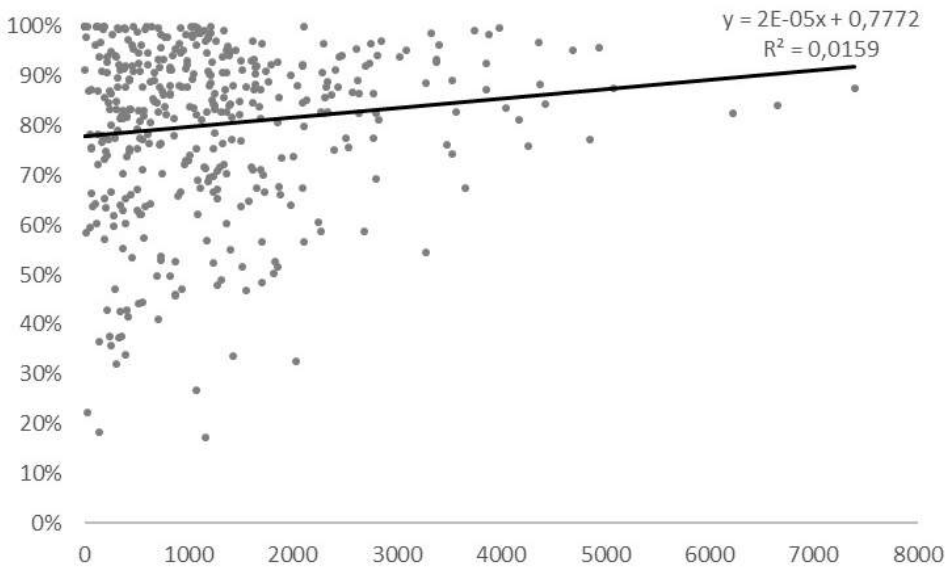


Figure 3. Non-correlation between the percentage prescribed for non-cancer pain and the number of DDD/1 000 persons strong opioid analgesics prescribed in general practices (n=406)

DISCUSSION

This study aimed to explore variation in prescribing patterns across regions and between general practices. We found a 2.2 to 4.6-fold variation in the median amount prescribed per practice across the twelve provinces in the Netherlands. Additionally, we found substantial inter-practice variation in the prescribing of strong opioid analgesics, with a 3.3 to 6.8-fold difference between high and low-prescribing general practices. Comparing the twelve regions, general practices in Limburg prescribed the highest amount of strong opioid analgesics, while the largest variation between general practices was seen in Groningen. We also assessed the correlation between the level of strong opioid analgesics prescribing and the relative prescribing for patients with non-cancer pain in general practices. The low R^2 value (1.6% variance explained) indicates that there is no linear correlation between the DDD/1 000 strong opioid analgesics prescribed and the % of volume prescribed for patients with non-cancer pain in the general practices evaluated.

Our results showed a variation in prescribing practices which was also reported- to a greater or lesser degree - by other studies examining regional or inter-practice variation in opioid prescribing. Douglas et al. found substantial geographic variation in the US in 2008, with the top quarter of counties using 7.1 times as much oxycodone and 3.8 times as much opioids as the lowest quarter.¹⁷ A more recent study in the United States by Schieber et al. found a smaller variation among states, with a 2.2-fold difference in the amount of opioids supplied in 2017, calculated as the ratio between the 90th and the 10th percentile of values.¹⁸ The variation we observed was in line with these studies. Variation in the prescribing was also observed in several European countries. A study conducted in England showed an almost eight-fold difference in the total amount prescribed by clinical commissioning groups in 2018.¹⁹ Another study in England found a north-south gradient in opioid prescribing, with nine out of ten of the highest prescribing areas located in the north of the country.²⁰ In Switzerland, a marked geographical variation in the use of strong opioids was observed in different cantons.²¹

In the current study, we found that general practices in Limburg prescribed the highest amount of strong opioid analgesics. A recent study examining the opioid use in primary care in the Netherlands between 2010 and 2017 using claims data found a relatively high prevalence of long-term opioid users in a number of border areas in the north and south of the Netherlands.²² However, as further details on this finding are lacking we do not know whether these border areas (also or exclusively) include Limburg. A possible explanation for the higher opioid prescribing in Limburg may be found in the demographic features of the

population. Prescription-related data reported by the information system of the National Health Care Institute show that the prevalence of opioid analgesic users (ATC code N02A) in the Netherlands is highest in the age group 45-64, with a higher prevalence in women than in men.²³ Looking at the distribution of the population by age groups in Limburg, the largest group (31.2%) is between 45 and 65 years of age, which is higher than any of the other regions that show a variation of 26.6% in Utrecht to 30.1% in Groningen.²⁴ A large survey in 15 European countries and Israel among 46 394 adults showed that respondents in the age group 41-60 years appeared to suffer more from chronic pain than other age groups.²⁵ A study conducted in Denmark showed that a higher prevalence of chronic non-cancer pain was related to increasing age, the female gender, short education, non-Western background, obesity and being widowed, separated or divorced.²⁶ Differences between the Dutch provinces regarding these aspects could (partly) explain the variation found in the current study.

Another interesting finding is the markedly higher use of morphine in Groningen, which accounted for 8.8% of the total amount opioid analgesics prescribed (vs 6.1% average), while the relative amount oxycodone prescribed was only 13.9% (vs 19.7% average). Other authors looking for an explanation for a strong rise in oxycodone consumption in their country have suggested that marketing activities by pharmaceutical companies may have played a role.^{27,28} There is no evidence that this is the case in the Netherlands. Groningen is also the region with the largest variation between general practices. As the aim of this study was to explore regional and inter-practice variation in the prescribing of strong opioid analgesics, we did not perform multivariate logistic regression analysis to identify factors associated with strong opioid analgesic prescribing. Yet, it would be interesting to look into the factors that explain the variation found in this study. These factors could include characteristics on a general practice and on a patient level, including demographic, clinical aspects and attitudes towards treatment with opioid analgesics. This could also inform the Dutch Minister for Medical Care in understanding the current prescribing dynamics and variation across general practices, and identifying potential opportunities for improvement. In addition to understanding variation, future research could also focus on the increased prescribing of opioid analgesics for patients with non-cancer pain, both from a perspective of undertreatment and overuse. This is particularly important given the growing concern on the appropriateness of their use for non-cancer pain. For example, studies could evaluate changes in the health-related quality of life of patients with non-cancer pain following long-term treatment with opioid analgesics. In this study, a first small step was made in understanding the increased prescribing in non-cancer pain. Although we expected to find a more preferential use for non-cancer pain

in general practices with high volumes of opioid prescriptions, this was not the case. The majority of general practices included in this study showed a relatively high use in non-cancer pain despite a low volume of opioid prescribing. As far as we know, there are no recent studies that evaluated this correlation in other countries, or that examined the increased prescribing of strong opioid analgesics in primary care in the Netherlands. Future research in this field would therefore be valuable in understanding the current prescribing practices.

Several limitations of the current study should be addressed. First, we did not control for population characteristics, which may provide an explanation for the variation found. Secondly, 32% of the prescription records lacked details on the frequency of use, and for these prescription records the average DDD was used as the actual DDD could not be calculated. A third limitation of this study is the relatively low number of practices included in this study for the provinces Flevoland and Zeeland, which may have caused an under- or overestimation in the amount prescribed and in the variance across practices. We also cannot exclude the possibility that patients with a diagnosis of cancer have been prescribed opioids for the relief of non-cancer pain and vice versa. Similarly, the large number of prescriptions without registration of a diagnostic code may have caused a bias in the distribution of the prescribing for cancer-pain versus non-cancer pain. However, as similar results were obtained when restricting the analysis to general practices with a high level of recorded diagnostic codes, this potential bias may be small. A strength of the current study is that we used prescription data routinely recorded at an individual patient level from a large national database representative of the general Dutch population (the Nivel primary care database).

In conclusion, this explorative study indicates that there may be substantial variation in the prescribing of strong opioid analgesics across general practices in the twelve provinces of the Netherlands. We did not observe that general practices with high volumes of opioid prescriptions also had more preferential use for non-cancer pain. However, the variation observed and the lack of correlation may be explained by population and practice characteristics, which need to be assessed in future analyses. Evaluating and understanding inter-practice and regional variation in prescribing is an important step to identify potential opportunities for improving strong opioid analgesic prescribing in primary care, both from a perspective of undertreatment and inappropriate use.

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Annex 1. Overview of opioids included and excluded in data analysis.

OPIOIDS INCLUDED		
ATC CODE	NAME	RATIONALE
N02AA01	morphine	Strong opioid analgesic
N02AA03	hydromorphone	Strong opioid analgesic
N02AA04	nicomorphine	Strong opioid analgesic
N02AA05	oxycodone	Strong opioid analgesic
N02AA55	oxycodone and naloxone	Strong opioid analgesic
N02AB02	pethidine	Strong opioid analgesic
N02AB03	fentanyl	Strong opioid analgesic
N02AC01	dextromoramide	Strong opioid analgesic
N02AC03	piritramide	Strong opioid analgesic
N02AD01	pentazocine	Strong opioid analgesic
N02AE01	buprenorphine	Strong opioid analgesic
N02AF02	nalbuphine	Strong opioid analgesic
N02AX06	tapentadol	Strong opioid analgesic
N07BC01	buprenorphine	Strong opioid analgesic
N07BC02	methadone	Strong opioid analgesic
OPIOIDS EXCLUDED		
ATC CODE	NAME	RATIONALE
N02AA02	opium	Treatment of diarrhoea
N02AA08	dihydrocodeine	Weak opioid analgesic / treatment of cough
N02AA10	papavaretum	Not available in The Netherlands
N02AA51	morphine combinations	Not available in The Netherlands
N02AA53	hydromorphone and naloxone	Not available in The Netherlands
N02AA56	oxycodone and naltrexone	Not available in The Netherlands
N02AA58	dihydrocodeine combinations	Not available in The Netherlands
N02AA59	codeine combinations excl. psycholeptics	Not available in The Netherlands
N02AA79	codeine combinations with psycholeptics	Not available in The Netherlands
N02AB01	ketobemidone	Not available in The Netherlands

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N02AB52	pethidine combinations excl. psycholeptics	Not available in The Netherlands
N02AB72	pethidine combinations with psycholeptics	Not available in The Netherlands
N02AC04	dextropropoxyphene	Not available in The Netherlands
N02AC05	bezitramide	Not available in The Netherlands
N02AC52	methadone combinations excl. Psycholeptics	Not available in The Netherlands
N02AC54	dextropropoxyphene combinations excl. psycholeptics	Not available in The Netherlands
N02AC74	dextropropoxyphene combinations with psycholeptics	Not available in The Netherlands
N02AD02	phenazocine	Not available in The Netherlands
N02AF01	butorphanol	Not available in The Netherlands
N02AG01	morphine and antispasmodics	Not available in The Netherlands
N02AG02	ketobemidone and antispasmodics	Not available in The Netherlands
N02AG03	pethidine and antispasmodics	Not available in The Netherlands
N02AG04	hydromorphone and antispasmodics	Not available in The Netherlands
N02AJ01	dihydrocodeine and paracetamol	Not available in The Netherlands
N02AJ02	dihydrocodeine and acetylsalicylic acid	Not available in The Netherlands
N02AJ03	dihydrocodeine and other non-opioid analgesics	Not available in The Netherlands
N02AJ06	codeine and paracetamol	Weak opioid analgesic
N02AJ07	codeine and acetylsalicylic acid	Not available in The Netherlands
N02AJ08	codeine and ibuprofen	Not available in The Netherlands
N02AJ09	codeine and other non-opioid analgesics	Not available in The Netherlands
N02AJ13	tramadol and paracetamol	Weak opioid analgesic
N02AJ14	tramadol and dextetoprofen	Weak opioid analgesic
N02AJ15	tramadol and other non-opioid analgesics	Not available in The Netherlands
N02AJ17	oxycodone and paracetamol	Not available in The Netherlands
N02AJ18	oxycodone and acetylsalicylic acid	Not available in The Netherlands
N02AJ19	oxycodone and ibuprofen	Not available in The Netherlands

N02AX01	tilidine	Not available in The Netherlands
N02AX02	tramadol	Weak opioid analgesic
N02AX03	dezocine	Not available in The Netherlands
N02AX05	meptazinol	Not available in The Netherlands
N07BC03	levacethylmethadol	Not available in The Netherlands
N07BC04	lofexidine	Not available in The Netherlands
N07BC05	levomethadone	Not available in The Netherlands
N07BC06	diamorphine	Opioid dependence treatment
N07BC51	buprenorphine combinations	Opioid dependence treatment



CHAPTER 4.2

IMPACT OF MEDIA COVERAGE FOLLOWING A MORPHINE RELATED TRAGEDY ON THE PRESCRIBING OF STRONG OPIOIDS: AN INTERRUPTED TIME SERIES ANALYSIS

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Submitted for publication



ABSTRACT

BACKGROUND: In 2013, an event took place in a palliative care setting in the Netherlands involving morphine, which attracted substantial media attention.

OBJECTIVE: This study aimed to examine how a period of intense media coverage affected the prescribing of strong opioid analgesics in primary care.

DESIGN: Changes in prescribing of strong opioid analgesics were assessed using monthly data on three prescription outcome measures: 1. Defined daily doses (DDD) per 100 000 inhabitants per day (HTID), 2. Number of prescriptions per HTID (P/HTID) and 3. DDD per prescription (DDD/P). Interrupted time series (ITS) models were used to assess changes in the trend and level after the event related media attention, both nationally and regionally.

SETTING/SUBJECTS: Data were derived from the Nivel Primary Care Database, containing information on prescriptions from 2 136 401 unique inhabitants over the period 2012-2015.

RESULTS: In total, 438 201 prescriptions of strong opioid analgesics (444 practices) were included. In the Netherlands, a gradual increase was seen in the DDD/HTID opioid analgesics over time before the intervention which continued in the period after, with a non-significant trend change of -0.24 DDD/HTID ($p=0.86$). In the region, a decrease was seen in the DDD/HTID opioid analgesics, which plateaued after the intervention period, yielding a non-significant trend change of -0.27 DDD/HTID per month ($p=0.94$).

CONCLUSIONS: There is no evidence that the morphine event and related media attention resulted in more reluctant prescribing practices for strong opioid analgesics in the Netherlands, and more specific, in the region around the village where the event driving the media coverage occurred.

BACKGROUND

Opioid analgesics are indispensable for the relief of moderate to severe cancer pain.¹ The World Health Organization (WHO) has recognized this medical necessity by adding several opioid analgesics to its essential medicines list, including morphine, fentanyl and codeine.² Although there is broad consensus on the medical need of opioid medicines for cancer pain, serious concerns exist on the harm that is associated with non-medical use of opioid substances. In the United States (US) and to a lesser extent also in Canada, high rates of opioid overdose and misuse induced death have been reported.³⁻⁵ While the situation in the US has been declared a “public health emergency”⁶, concerns also exist whether the actions taken to prevent harm have a negative impact on access for patients in legitimate medical need of these medicines.⁷⁻⁹

In August 2013 a tragedy took place in a small village in the Netherlands, with extensive media attention in the period thereafter. A terminally ill patient receiving palliative sedation therapy passed away 30 minutes after receiving 1 000 mg morphine and 350 mg midazolam from his general practitioner (GP). The situation gave rise to an investigation by the Dutch Health Care Inspectorate.¹⁰ The public and professional debate peaked when the GP involved committed suicide in October 2013, see Box 1 for a short overview of this tragic event. Particularly within the communities of prescribing physicians and professional organizations of GPs, this tragedy, both of the terminally ill patient and of the GP involved, resulted in an intense debate and outcry on professional responsibility and autonomy in the context of palliative care. This tragedy and the aftermath may have particularly affected the colleagues in the close region, for example as a result of a relatively high regional media coverage in addition to national media attention or due to personal involvement.

In the aftermath of this event we wanted to investigate the impact of the wide media coverage of the above reported tragedy on prescribing practices of strong opioids across the Netherlands and in the region. Media coverage on health-related issues is known to induce changes in health services utilization.¹¹ Our hypothesis is that the unplanned media coverage following the tragedy may have led to a decrease in the prescribing of strong opioid analgesics, in the Netherlands as a whole, and specifically in the region around the village.

Box 1. Short overview of the tragic event*

On August 19 2013, a general practitioner (GP) and his intern visit a patients who is terminally ill and at the end-stage of his life. The situation is critical, the patient has severe respiratory problems and is suffering unbearably. The GP administers 1 000 mg morphine and 350 mg midazolam to alleviate the suffering and sedate the patient. Shortly after administering the medication, the patient passes away.

On the next day the intern notifies her supervisor of the actions of the GP, who in turn notifies the Dutch Health Care Inspectorate on August 22nd without first consulting the GP. As a consequence, the GP who has had 22 years of professional experience was not given the opportunity to explain his actions to the intern and the supervisor.

On August 26th, both the private premises and the general practice of the GP are searched by The Ministry of Justice and Security. One week later, the GP is notified that he is a murder suspect and that a criminal investigation by the Public Prosecution Service will be initiated. The GP is severely affected by the situation; he feels that nobody is interested in his side of the story. He is depressed, has suicidal thoughts and is voluntarily admitted to a psychiatric clinic. During his stay in the clinic he is interrogated on two occasions by The Ministry of Justice and Security.

On the 27th of September 2013, the Health Care Inspectorate announces that the GP is (temporarily) suspended pending the criminal investigation and is hence not allowed to work as a GP. The suspension (including the name of the GP) is made public on the website of the Health Care Inspectorate on October 4 2013. The GP commits suicide three days later.

*This information is available in the public domain (various sources)

METHODS

Prescription data

Prescription data of opioid analgesics were retrospectively extracted from the Nivel Primary Care Database (Nivel-PCD). The Nivel-PCD contains anonymized primary care data routinely recorded from a representative sample of the Dutch population. This database includes information on GP prescriptions, clinical diagnosis, patient gender and year of birth. Practices were included in the study on a per-year basis if at least 500 patients were registered. Our study population consisted of all inhabitants registered in these practices in the years 2012-2015. Within this study population, prescription data were extracted from patients that had a database history of at least one prescription of a medicinal product starting with the Anatomical Therapeutic Chemical (ATC) codes N02A, N01AH and N07BC in the same period. Prescription data were converted into three different monthly prescription outcome measures: 1. daily defined doses (DDD) as defined by the World Health Organization¹² per 100 000 inhabitants per day (DDD/HTID), 2. Number of prescriptions per 100 000 inhabitants per day (P/HTID) and 3. DDD per prescription (DDD/P). The start and end dates of the prescription records were used to calculate the total number of DDDs prescribed. In case no total number of DDDs could be calculated, the average DDD of all prescription data within the said ATC code was used. Prescriptions were quantified for the group strong opioid analgesics and for morphine for three regions: 1. the Netherlands as a whole, 2. the region around the village where the event occurred (region that includes postal code area's starting with the numbers 14, 16, 17 and 18 and is hereinafter also referred to as "the region"), and 3. the rest of the Netherlands (for comparison purposes).

The group strong opioid analgesics included all opioid analgesics that are available in the Netherlands starting with ATC code N02A, excluding weak opioid analgesics (e.g. codeine and tramadol), opioids that are mainly used as anesthetic, for the treatment of cough or diarrhea (see Annex 1). Additionally, opioids starting with ATC code N07BC were included if prescribed in combination with the clinical diagnosis cancer or back pain based on International Classification of Primary Care (ICPC) codes (see Annex 1).

The unplanned media coverage following the event

A period of high media coverage was seen from October 2013 until December 2013, and is referred to as the methodological intervention period. The start date and end date of this period was selected by carrying out a LexisNexis and a Google Trends search, using the name of the village as a search term in combination with "morphine" to track the frequency of these search term in newspapers and other (online) media over time. Both searches showed peaks in October, November and December 2013, see Figure 1.

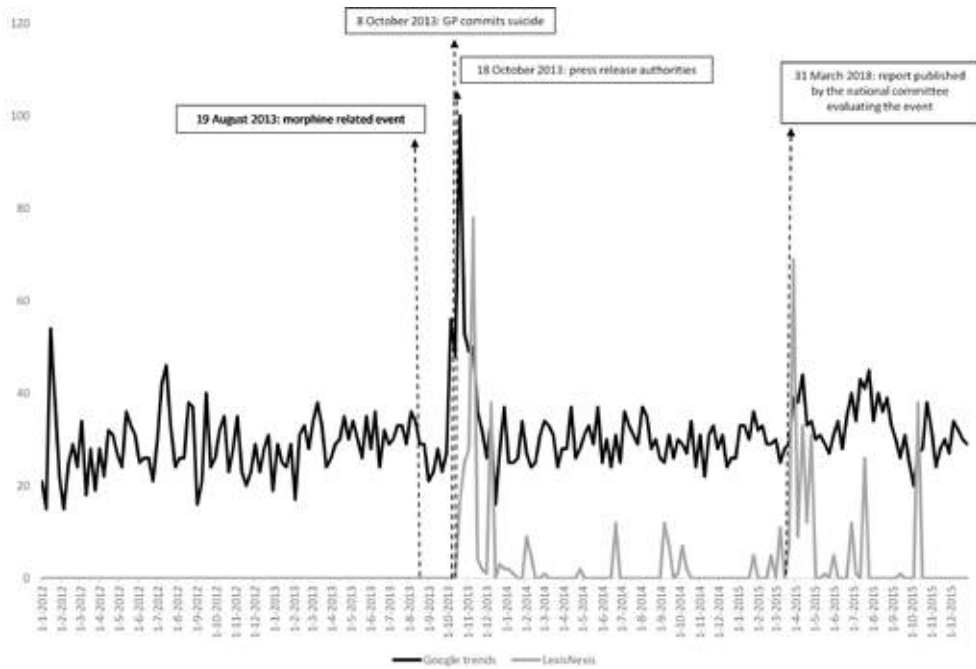


Figure 1. Timeline highlighting events concerning the morphine incident and related media coverage, including the number of searches (Google Trends) and number of (online) news media publications (LexisNexis) using the name of the village as search term in combination with “morphine” within the period January 2012 – December 2015.

Data analysis

To measure the impact of the media coverage on the prescribing of strong opioid analgesics and morphine alone separately, an interrupted-time series analysis was conducted, using a segmented-regression model.¹³ A direct effect was determined by assessing level changes, and changes in long term prescribing patterns were assessed by looking at slope changes. A least-square regression line was fitted in each segment, assuming a linear correlation between the various outcome measures (DDD/HTID, P/HTID and DDD/P) and time. The Durbin-Watson test was used to test the residuals of the models for first-order autocorrelation, and an autoregressive term was introduced in the model if necessary. An indicator variable was used to estimate whether there was a change in the prescribing outcomes before and after the intervention period.

Analyses were conducted using IBM SPSS Statistics 25.0. A p-value ≤ 0.05 was considered statistically significant. Dutch legislation allows the use of extracts of electronic health records for research purposes under certain conditions. According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for this kind of observational studies containing no directly identifiable data. This study has been approved by the applicable governance bodies of Nivel Primary Care Database under number NZR00316.045.

RESULTS

Data were collected from 444 general practices (n=1 802 094 patients), varying from 297 general practices (n=1 188 384 patients) in 2012 to 406 general practices (n=1 622 459 patients) in 2015, see Table 1. The region around the village consisted of 25 general practices (n =76 415 patients). In total, 438 201 prescriptions for strong opioids were recorded and 4.1% of the patients (n =74 014 patients) were prescribed at least one dose of a strong opioid analgesic throughout the duration of this study (see Table 1). Within the group strong opioid analgesics, oxycodone was most prescribed (52.3%), followed by fentanyl (31.9%).

Table 1. Characteristics from the study population in numbers (percentages) for two regions: the Netherlands and for the region around the village where the event occurred.

		STUDY POPULATION	
		NETHERLANDS	REGION
No. PRACTICES	TOTAL	444	25
	2012	297	14
	2013	370	22
	2014	371	21
	2015	406	24
No. PATIENTS	TOTAL	1 802 094	76 415
PATIENTS WITH ≥ 1 PRESCRIPTION	STRONG OPIOID ANALGESICS	74 014	3 524
	WOMEN	43 231 (58.4%)	2 081 (59.1%)
	MEN	30 782 (41.6%)	1 443 (40.9%)
	UNKNOWN	1	0
No. PRESCRIPTIONS	TOTAL	438 201	20 296
	MORPHINE (N02AA01)	56 982 (13.0%)	2 578 (12.7%)
	HYDROMORPHONE (N02AA03)	1 098 (0.3%)	73 (0.4%)
	NICOMORPHINE (N02AA04)	366 (0.1%)	0 (0.0%)
	OXYCODONE (N02AA05)	228 996 (52.3%)	10 541 (51.9%)
	OXYCODONE AND NALOXONE (N02AA55)	117 (0.0%)	11 (0.1%)
	PETHIDINE (N02AB02)	609 (0.1%)	1 (0.0%)
	FENTANYL (N02AB03)	139 549 (31.9%)	6 762 (33.3%)
	DEXTROMORAMIDE (N02AC01)	260 (0.1%)	0 (0.0%)
	PIRITRAMIDE (N02AC03)	256 (0.1%)	3 (0.0%)
	PENTAZOCINE (N02AD01)	359 (0.1%)	0 (0.0%)
	BUPRENORPHINE (N02AE01)	8 106 (1.9%)	249 (1.2%)
	NALBUPHINE (N02AF02)	0 (0.0%)	0 (0.0%)
	TAPENTADOL (N02AX06)	634 (0.1%)	36 (0.2%)
	BUPRENORPHINE (N07BC01)*	4 (0.0%)	1 (0.0%)
	METHADONE (N07BC02)*	865 (0.2%)	41 (0.2%)

*Only used in case the prescription was recorded in combination with the clinical diagnosis cancer or back pain based on ICD codes.

Time trends – The Netherlands

The results of the interrupted time series analysis showed a gradual increase in the total volume of strong opioid analgesics prescribed (DDD/HTID) and the prescribing rate (P/HTID) over time in the Netherlands in the period before the intervention. This positive trend continued after the intervention period, see Figure 2. The number DDD/P slowly decreased over time, which also continued after the intervention period. For all prescription outcome measures, no significant trend or level effect was observed, see Table 2.

When restricting the analysis to morphine alone, a small increase over time was seen in the prescribing of morphine for all outcome measures (DDD/HTID, P/HTID, DDD/P) in the Netherlands before the intervention period. After the intervention period, the prescribing of morphine remained fairly stable (DDD/HTID, DDD/P) or slightly decreased (P/HTID). This change in trend was statistically significant for the number of DDDs prescribed (change in slope: -0.49, p=0.00) and for the prescribing rate of morphine (change in slope: -0.02, p=0.00), see Table 2. No statically significant changes were seen in the number of DDDs per prescription.

a.

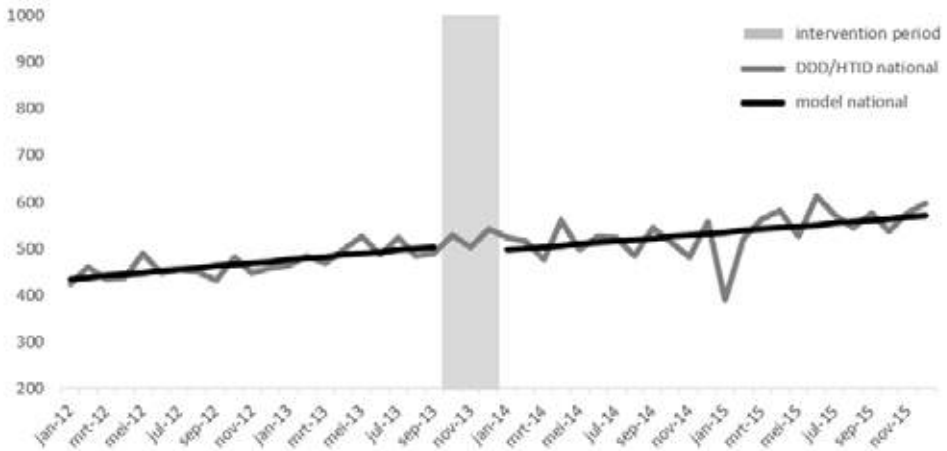


Figure 2. Average amount of opioid analgesics prescribed (DDD/HTID) displayed per month, stratified per postcode area indicating changes between the period before and after the intervention (2013 morphine incident related media coverage) in a. the Netherlands and b. the region around the village where the incident occurred vs the remaining part of the Netherlands. The grey period illustrates the period of media coverage.

b.

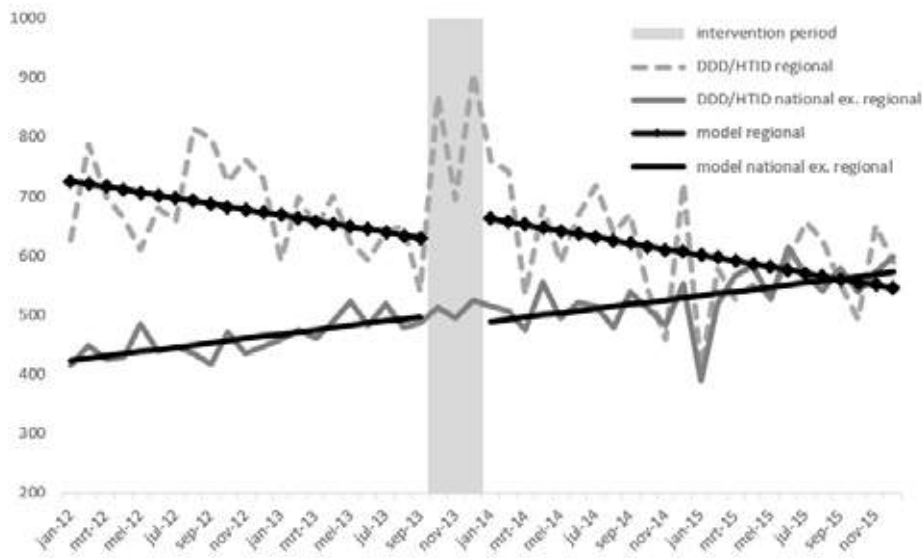


Figure 2. Average amount of opioid analgesics prescribed (DDD/HTID) displayed per month, stratified per postcode area indicating changes between the period before and after the intervention (2013 morphine incident related media coverage) in a. the Netherlands and b. the region around the village where the incident occurred vs the remaining part of the Netherlands. The grey period illustrates the period of media coverage.

Time trends – region around the village

In the region around the village, a decrease was seen in the prescribing of strong opioid analgesics (DDD/HTID) and in the number of DDDs per prescription (DDD/P) over time in the period before the intervention. This trend continued after the intervention period. An increase was seen in the prescribing rate (P/HTID) of strong opioid analgesics over time, which also continued after the intervention period. There was no evidence of a significant level or trend effect for any of the prescription outcome measures, see Table 2.

When restricting the analysis to morphine alone, a decrease was seen in the number of DDDs morphine prescribed (DDD/HTID) and in the number of DDDs per prescription (DDD/P) in the period before the incident related media coverage, which continued after this intervention period without significant changes in level or slope. The prescribing rate (P/HTID) for morphine slightly increased over time before the intervention period, and decreased in the period after the intervention. This change in trend was statistically significant (change in slope: -0.06, p=0.00), see Table 2.

Table 2. Results of ITS analysis for the group strong opioid analgesics and for morphine for three regions: 1. The Netherlands, 2. the region around the village where the event occurred and 3. The Netherlands excluding this region.

		LEVEL EFFECT	P VALUE	CHANGE IN SLOPE	P VALUE
STRONG OPIOID ANALGESICS*					
DDD/ 100 000/day**	The Netherlands	-11.56	0.52	-0.24	0.86
	Region around the village	32.83	0.46	-0.27	0.94
	The Netherlands ex. the region	-12.87	0.48	-0.14	0.92
Prescriptions/ 100 000/day**	The Netherlands	0.13	0.84	0.07	0.14
	Region around the village	-0.55	0.40	0.10	0.06
	The Netherlands ex. the region	0.16	0.80	0.07	0.15
DDD/prescription**	The Netherlands	-0.83	0.13	0.01	0.82
	Region around the village	2.15	0.22	-0.01	0.93
	The Netherlands ex. the region	-0.96	0.09	0.01	0.82
MORPHINE*					
DDD/ 100 000/day	The Netherlands	0.41	0.75	-0.49	0.00
	Region around the village	-2.17	0.77	-0.47	0.41
	The Netherlands ex. the region	0.62	0.61	-0.48	0.00
Prescriptions/ 100 000/day	The Netherlands	0.06	0.50	-0.02	0.00
	Region around the village	-0.17	0.51	-0.06	0.00
	The Netherlands ex. the region	0.07	0.46	-0.02	0.01
DDD/prescription	The Netherlands	-0.09	0.84	-0.06	0.09
	Region around the village	1.37	0.65	0.23	0.34
	The Netherlands ex. the region	-0.10	0.83	-0.07	0.07

* See Table 1 for ATC codes. Statistically significant results highlighted in bold.

** DDD/HTID = daily defined doses per 100 000 inhabitants per day; P/HTID = number of prescriptions per 100 000 inhabitants per day; DDD/P = daily defined doses per prescription.

DISCUSSION

This study aimed to examine a potential association between a critical event, i.e. a strong opioid related tragedy and the media outcry in the aftermath, and the prescribing of strong opioid analgesics. Our hypothesis that this media exposure may have interrupted underlying trends in the prescribing of strong opioid analgesics and may have caused more reluctant prescribing behavior could not be confirmed, not in the Netherlands as a whole, nor in the region close to the critical event. Although a decrease was seen in the total amount of strong opioid analgesics prescribed in the region around the village where the event occurred when looking at the amount prescribed over time (Figure 2b), the results of the interrupted time series analysis showed that this downward trend already started before the tragedy occurred. While no association was found for strong opioid analgesics, we did observe a small and statistically significant decrease in prescribing rate (P/HTID) trends for morphine in all three comparison groups studied. Additionally, a statistically significant change was observed in the total amount of morphine prescribed in the Netherlands. However, these changes did not result in a statistically significant change in the overall prescribing of strong opioid analgesics. These results are in line with the outcomes of a survey among 866 Dutch GPs in which the large majority of physicians reported that their attitudes and behavior towards palliative sedation therapy was not affected by the morphine related incident.¹⁴

While we did not observe an effect of the media coverage in this study, most other studies published that assessed a (potential) association between media coverage and prescribing or usage patterns of medicines did.^{11,15-21} This effect was often immediate but temporal, with the duration of the effect varying from less than a year to several years.¹⁶⁻²⁰ A possible explanation for the inconsistency of our findings with other studies may be found in the specific topic that was covered by the media. In the majority of studies published, the risks (in relation to the benefits) of certain types of medication were topic of discussion following a scientific publication^{15,20} or regulatory interventions¹⁶⁻¹⁸. In the current study, the media attention did not focus on the risks of opioid medicine use but focused on the suicide of the GP and the role of the intern and the Health Care Inspectorate, reflecting the intense discussions on professional responsibility and autonomy in the context of palliative care. Another possible explanation for the inconsistency of our findings with other studies is the subject of our study; as this study looks at the prescribing of strong opioid analgesics in general, different results may have been observed when focusing on medicines prescribed in a palliative care setting. Finally, we did not assess the duration and intensity of the media attention in the current study in relation to other studies published, which may be a possible

explanation for the differences in findings.

It remains unclear why the average level of every prescription outcome measure in the period before the intervention was substantially higher in the region around the village in comparison to the average levels observed nationally (excluding the region). The data indicated that the higher level of prescription outcome measures in the region could not be attributed to one practice; all practices included in the region showed levels above the average national level. Agreements made on a regional level concerning the prescribing of strong opioid analgesics or the treatment of moderate to severe pain may provide an explanation for the higher outcome levels. As this study did not evaluate separate indications, we could not assess if GPs have become more restrictive in using opioid analgesics in end of life care.

A strength of this study is that we used prescription data routinely recorded at an individual patient level from a large national database representative of the general Dutch population, the Nivel primary care database. However, some prescription records lacked details on the frequency of use, and for some prescription records the average DDD was used as the actual DDD could not be calculated. The proportion of prescriptions with unclear or undefined use or without DDD was between 41.3% (region) and 34.5% (the Netherlands), which may have caused a bias in the results. Furthermore, changes in the prescribing behavior were evaluated in a separate region around the village where the incident occurred. This region may be considered small. However, when selecting a larger region, it will be less likely that changes can be linked to the geographical location of general practices in the proximity of the village where the incident occurred. In addition, the number of DDDs prescribed was calculated by using the start dates (prescription date) and the end date generated by the information system used by the practice based on prescribing information. Incorrectly generated end dates may have caused an under- or overestimation of the volume prescribed. However, a manual check of several prescriptions records showed that the chances of incorrect calculation of the number of DDDs prescribed is relatively low. Finally, the intervention period was selected based on a LexisNexis and a Google Trends search. Although the LexisNexis search showed a second and smaller peak in January 2015 that was not visible in the Google Trends search, a visual inspection of the data showed no changes in trend and/or level of the prescription outcome measures.

As this study evaluates changes in prescribing practices of strong opioid analgesics in general and did not focus on a palliative care setting, future research could look at changes in prescribing trends of medicines that alleviate suffering in end-of-life care.

CONCLUSION

There is no evidence that the morphine incident and related media attention resulted in more reluctant prescribing practices for strong opioid analgesics in the Netherlands, and more specific, in the region around the village where the critical event driving the media coverage occurred.

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Annex 1. Overview of opioids included and excluded in data analysis.

OPIOIDS INCLUDED		
ATC CODE	NAME	RATIONALE
N02AA01	morphine	Strong opioid analgesic
N02AA03	hydromorphone	Strong opioid analgesic
N02AA04	nicomorphine	Strong opioid analgesic
N02AA05	oxycodone	Strong opioid analgesic
N02AA55	oxycodone and naloxone	Strong opioid analgesic
N02AB02	pethidine	Strong opioid analgesic
N02AB03	fentanyl	Strong opioid analgesic
N02AC01	dextromoramide	Strong opioid analgesic
N02AC03	piritramide	Strong opioid analgesic
N02AD01	pentazocine	Strong opioid analgesic
N02AE01	buprenorphine	Strong opioid analgesic
N02AF02	nalbuphine	Strong opioid analgesic
N02AX06	tapentadol	Strong opioid analgesic
N07BC01	buprenorphine	Strong opioid analgesic
N07BC02	methadone	Strong opioid analgesic
OPIOIDS EXCLUDED		
ATC CODE	NAME	RATIONALE
N02AA02	opium	Treatment of diarrhoea
N02AA08	dihydrocodeine	Weak opioid analgesic / treatment of cough
N02AA10	papavaretum	Not available in The Netherlands
N02AA51	morphine combinations	Not available in The Netherlands
N02AA53	hydromorphone and naloxone	Not available in The Netherlands
N02AA56	oxycodone and naltrexone	Not available in The Netherlands
N02AA58	dihydrocodeine combinations	Not available in The Netherlands
N02AA59	codeine combinations excl. psycholeptics	Not available in The Netherlands
N02AA79	codeine combinations with psycholeptics	Not available in The Netherlands
N02AB01	ketobemidone	Not available in The Netherlands
N02AB52	pethidine combinations excl. psycholeptics	Not available in The Netherlands
N02AB72	pethidine combinations with psycholeptics	Not available in The Netherlands
N02AC04	dextropropoxyphene	Not available in The Netherlands
N02AC05	bezitramide	Not available in The Netherlands

N02AC52	methadone combinations excl. Psycholeptics	Not available in The Netherlands
N02AC54	dextropropoxyphene combinations excl. psycholeptics	Not available in The Netherlands
N02AC74	dextropropoxyphene combinations with psycholeptics	Not available in The Netherlands
N02AD02	phenazocine	Not available in The Netherlands
N02AF01	butorphanol	Not available in The Netherlands
N02AG01	morphine and antispasmodics	Not available in The Netherlands
N02AG02	ketobemidone and antispasmodics	Not available in The Netherlands
N02AG03	pethidine and antispasmodics	Not available in The Netherlands
N02AG04	hydromorphone and antispasmodics	Not available in The Netherlands
N02AJ01	dihydrocodeine and paracetamol	Not available in The Netherlands
N02AJ02	dihydrocodeine and acetylsalicylic acid	Not available in The Netherlands
N02AJ03	dihydrocodeine and other non-opioid analgesics	Not available in The Netherlands
N02AJ06	codeine and paracetamol	Weak opioid analgesic
N02AJ07	codeine and acetylsalicylic acid	Not available in The Netherlands
N02AJ08	codeine and ibuprofen	Not available in The Netherlands
N02AJ09	codeine and other non-opioid analgesics	Not available in The Netherlands
N02AJ13	tramadol and paracetamol	Weak opioid analgesic
N02AJ14	tramadol and dextetoprofen	Weak opioid analgesic
N02AJ15	tramadol and other non-opioid analgesics	Not available in The Netherlands
N02AJ17	oxycodone and paracetamol	Not available in The Netherlands
N02AJ18	oxycodone and acetylsalicylic acid	Not available in The Netherlands
N02AJ19	oxycodone and ibuprofen	Not available in The Netherlands
N02AX01	tilidine	Not available in The Netherlands
N02AX02	tramadol	Weak opioid analgesic
N02AX03	dezocine	Not available in The Netherlands
N02AX05	meptazinol	Not available in The Netherlands
N07BC03	levacetylmethadol	Not available in The Netherlands
N07BC04	lofexidine	Not available in The Netherlands
N07BC05	levomethadone	Not available in The Netherlands
N07BC06	diamorphine	Opioid dependence treatment
N07BC51	buprenorphine combinations	Opioid dependence treatment



CHAPTER 4.3

ACCESS TO STRONG OPIOID ANALGESICS IN THE CONTEXT OF LEGAL AND REGULATORY BARRIERS IN ELEVEN CENTRAL AND EASTERN EUROPEAN COUNTRIES

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ABSTRACT

BACKGROUND: In 2011-2013, over 95% of the global opioid analgesics consumption occurred in three regions, accounting for 15% of the world population. Despite abundant literature on barriers to access, little is known on the correlation between actual access to opioid analgesics and barriers to access, including legal and regulatory barriers.

OBJECTIVE: This study aimed to evaluate the correlation between access to strong opioid analgesics and barriers to access in national legislation and regulations in 11 central and eastern European countries that participated in the Access to Opioid Medication in Europe (ATOME) project.

DESIGN: Two variables were contrasted to assess their correlation: the country level of access to strong opioid analgesics indicated by the Adequacy of Consumption Measure (ACM) and the number of potential legal and regulatory barriers identified by an external review of legislation and regulations.

MEASUREMENTS: A linear correlation was evaluated using a squared linear correlation coefficient.

RESULTS: Evaluation of the correlation between the ACM and the number of potential barriers produces a R^2 value of 0,023 and a correlation plot trend line gradient of -0,075, indicating no correlation between access to strong opioid analgesics and the number of potential barriers in national legislation and regulations in the countries studied.

CONCLUSIONS: No correlation was found, which indicates that other factors besides potential legal and regulatory barriers play a critical role in withholding prescribers and patients essential pain medication in the studied countries. More research is needed towards better understanding of the complex interplay of factors that determine access to strong opioid analgesics.

INTRODUCTION

Inadequate pain relief is associated with a decreased overall quality of life and impairments in physical, social and psychological functioning.^{1,2} Failure to provide adequate pain relief may result in worsening of the pain and suffering and high healthcare costs due to more frequent hospital admissions and absence from work.^{1,2} Although various treatment options currently exist, data indicate that these treatment options are not always available or accessible. A survey in 16 countries in 2003 showed that moderate to severe chronic pain occurred in 19% of the 46 394 respondents, of which one third were not treated for their pain.³ Similar results were seen in cancer pain: a review of 46 articles published between 2007 and 2013 showed that 31.8% of the patients with cancer did not receive adequate pain relief.⁴ In 2013, a total number of 422 542 patients in Italy received chronic opioid therapy for their chronic pain, which represents only 4% of the estimated requirements for opioid analgesics based on prevalence data.⁵

These data- representing a high prevalence of inadequately treated pain- are in line with global consumption data of opioid analgesics.³⁻⁶ Recently published data from the International Narcotics Control Board (INCB)⁶ show that a major part of the world population still lacks access to opioid analgesics, even though several international treatment guidelines recognize that these medicines are indispensable for the relief of moderate to severe (cancer) pain.⁷⁻¹⁰ In 2011-2013, 95.7% of the global consumption of opioid analgesics occurred in three regions, accounting for only 15% of the global population.⁶ Even though progress in opioid analgesic use was seen, this growth was mainly accountable to high-income countries and minimal improvement was seen in low and middle-income countries.⁶

To improve access to opioid analgesics it is paramount to identify factors that are associated with inadequate access. According to policy guidelines of the World Health Organization (WHO) these factors can be classified into four different categories: (1) economic or financial circumstances, (2) factors relating to societal attitudes, (3) knowledge and educational issues, and (4) policies or regulations.¹¹ Despite abundant literature on factors that are perceived to interfere with access to opioid medicines, little is known on the correlation between individual factors and access in clinical practice. In the category of factors relating to economic circumstances, the Human Development Index (HDI) and the Gross Domestic Product (GDP) have been shown to be predictive variables for a country's opioid consumption level.^{6, 12-14} But little evidence exists for other determinants of access to opioid analgesics, including issues relating to drug control systems which have frequently been reported to impede access to opioid medicines in a way that is disproportional to their benefit for the prevention of non-medical use.^{10, 15-21}

This study therefore aimed to evaluate the correlation between access to strong opioid analgesics and potential legal and regulatory barriers in 11 central and eastern European countries that participated in the Access To Opioid Medication in Europe (ATOME) project.

MATERIALS AND METHODS

Data collection

In this study, the level of consumption of strong opioid analgesics was calculated using a modified version of the Adequacy of Consumption Measure (ACM). The ACM is based on consumption data of opioid analgesics that are mandatory reported to the INCB.¹² It was first developed by Seya et al. using data from 2006 and recalculated by Duthey and Scholten for 2010.^{12, 22} For this paper, author WS calculated the modified ACM (hereinafter also referred to as ACM) excluding the morbidity correction and the opioid medicine pethidine, which is considered obsolete.

First, the per capita consumption of the four main opioid full-agonist analgesics (fentanyl, hydromorphone, morphine and oxycodone) was calculated for each of the countries in this study: Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Serbia, Slovakia, Slovenia and Turkey. Consumption data were used for 2013 for all countries with the exception of Greece; for Greece, data from 2010 were used as data from 2013 were not available. As a second step, equipotent quantities were calculated using the WHO Defined Daily Dose as a conversion factor²³, expressed as “mg Morphine Equivalents”. As a third step, the average per capita consumption of the top 20 most developed countries worldwide (according to HDI) was calculated and set as a benchmark (defined as 100%), being considered an adequate level of consumption. As a final step, the ACM was calculated as a proportion of this benchmark, based on the per capita consumption of opioid analgesics and expressed as a fraction of the benchmark. For example, a country consuming 60% of the average of the 20 most developed countries has an ACM of 60%. Since this study focuses on European countries, for further comparison, the ACM was also calculated for the three European countries ranking highest in the HDI (Norway, Switzerland, and Denmark) (see Table 1).

The number of potential barriers was identified in an external review of national legislation and regulations in each of the 11 countries which was conducted as part of the ATOME project.²⁴ This analysis used eight predefined categories to group the potential barriers that were identified: prescribing, dispensing, usage, affordability, manufacturing, trade and distribution, penalties and other.²⁴ The total number of potential barriers for all eight categories was calculated for each country (see Table 2).

Table 1. Build-up of the adequacy of consumption measure for the countries in this study

COUNTRY/REGION	FENTANYL		HYDROMORPHONE		MORPHINE		OXYCODONE		ALL FOUR SUBSTANCES	
	Per capita consumption	Contribution to ACM, %	Per capita consumption	Contribution to ACM, %	Per capita consumption	Contribution to ACM, %	Per capita consumption	Contribution to ACM, %	Per capita consumption	Contribution to ACM, %
ATOME countries										
Bulgaria	5.0	2	-	-	5.3	2	3.3	1	13.6	5
Cyprus	2.5	1	-	-	1.7	1	6.0	2	10.2	4
Estonia	7.1	3	-	-	3.5	1	5.3	2	16.0	6
Greece	92.1	46	-	-	0.4	0	-	-	92.4	46
Hungary	87.7	34	2.1	1	0.7	0	1.0	0	91.5	36
Latvia	27.0	11	-	-	1.8	1	-	-	28.8	11
Lithuania	28.4	11	-	-	3.0	1	-	-	31.4	12
Serbia	33.5	13	1.0	0	1.0	0	-	-	35.6	14
Slovakia	63.2	25	3.0	1	1.8	1	6.1	2	74.0	29
Slovenia	100.8	40	1.6	1	30.1	12	13.3	5	145.8	57
Turkey	16.8	7	0.1	0	0.2	0	0.0	0	17.0	7
Average of top 20 most developed countries worldwide (considered adequate level)										
European average										
Average of the top 3 most developed countries in Europe										
Norway									254.8	100
Switzerland									127.0	50
Denmark									323.2	127
									223.9	88
									263.4	103
									482.3	189

Per capita consumption expressed in milligram morphine equivalents. Data for 2013 (Greece: data for 2010).

*Owing to rounding errors, the sum in this column may slightly deviate from total of the columns "Contribution to ACM, %" ACM, Adequacy of Consumption Measure; ATOME, Access To Opioid Medication in Europe.

Table 2. Potential legal and regulatory barriers of 11 central and eastern European Countries

	Bulgaria	Cyprus	Estonia	Greece	Hungary	Latvia	Lithuania	Serbia	Slovakia	Slovenia	Turkey
No of potential barriers in legislation and regulation	77	22	102	83	97	115	128	35	48	29	42
No of potential barriers in legislation and regulation in two categories (prescribing + dispensing)	49	6	55	53	51	76	75	15	20	23	25
No of potential barriers in legislation and regulation excluding no of barriers to access to opioid medicines used in the treatment of opioid dependence	57	15	102	72	91	84	82	32	40	27	32

Analysis

Both variables (ACM and number of potential barriers, see Tables 1 and 2) were contrasted to assess the correlation between the ACM and the number of potential barriers identified in national legislation and regulations. Closeness of fit was assessed by plotting the reported number of potential barriers of individual countries against the ACM in these countries. A squared linear correlation coefficient (R^2) was obtained which provides an index of the degree to which the paired measures co-vary. As a secondary examination, we restricted the analysis to potential barriers in the categories prescribing and dispensing as it may be assumed that these types of barriers are more likely to influence access than others. Finally, we did an additional sensitivity analysis excluding potential barriers to access to opioid medicines that specifically focused on the treatment of opioid dependence.

RESULTS

The ACM for each country, the benchmark (an ACM of 100%), and European consumption levels (top 3 HDI and European average) are presented in Figure 1 and more in detail in Table 1. The results show a wide variation between study countries in their ACM, ranging from 4% of the global benchmark (Cyprus) to 57% of the global benchmark (Slovenia), indicating an opioid analgesic consumption level that is very low to moderate. Additionally, for each country the total number of potential barriers in national legislation and regulations is presented in Table 2. When contrasting the ACM and the total number of barriers, a wide spread between individual countries was observed (see Figure 2).

Looking at the results in Figure 2, we can identify three distinct clusters of countries based on distance from the centre and positioning on both axes. In the upper right quadrant there is a cluster of two countries (Greece and Hungary) with a relatively high level of access to strong opioid analgesics despite a relatively high number of potential barriers. The cluster of countries in the lower left quadrant (Cyprus, Serbia and Turkey) shows the contrary: access to strong opioid analgesics is (very) low despite a relatively low number of potential barriers. A third cluster of countries in the lower-right quadrant shows a pattern that is more in line with expectations: four countries with low ($10\% \leq \text{ACM} < 30\%$: Latvia and Lithuania) to very low ($3\% \leq \text{ACM} < 10\%$: Bulgaria and Estonia) access to strong opioid analgesics and a relatively high number of potential barriers in national legislation and legislation.

Evaluation of the correlation between the ACM and the number of potential barriers produces a R^2 value of 0,023 and a correlation plot trend line gradient of -0,075 indicating no correlation (formula: $y = -0,0745x + 25,903$). Similar results were obtained in case the

analysis was restricted to two separate categories of potential barriers (prescribing and dispensing), R^2 value of 0,007 (formula: $y = -0,062x + 23,162$), and when excluding potential barriers to access to opioid medicines for the treatment of opioid dependence, R^2 value of 0,002 (formula: $y = -0,029x + 22,306$).

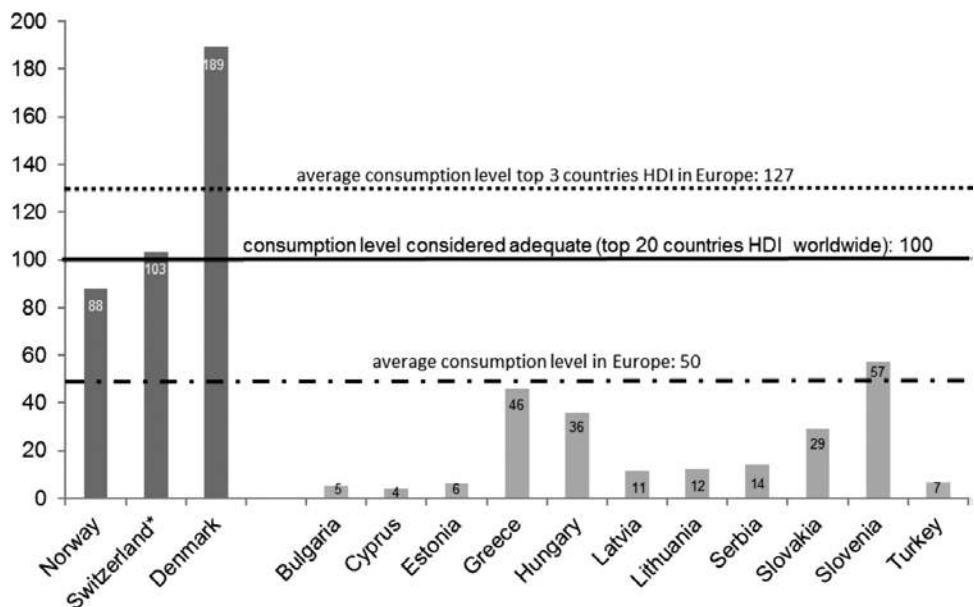


Figure 1. The ACM calculated based on the per capita consumption of the four main opioid analgesics in 2013 (Greece: data for 2010). Per capita consumption expressed in milligram morphine equivalents for the 11 central and eastern European countries in this study and the top 3 countries in the HDI. **including Liechtenstein. ACM, Adequacy of Consumption Measure; HDI, human development index.

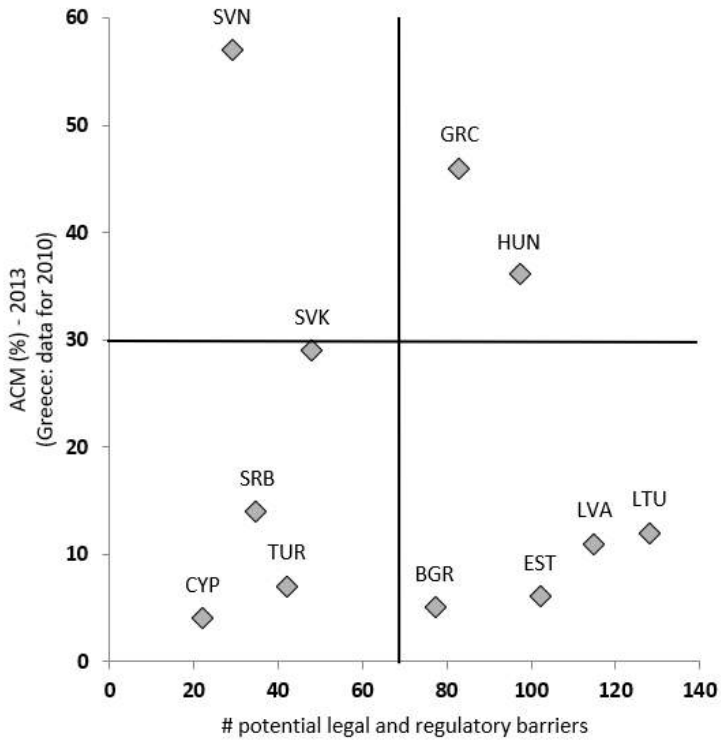


Figure 2. Noncorrelation between access to opioid analgesics (ACM) and the number of potential legal and regulatory barriers in 11 central and eastern European countries: Bulgaria (BGR), Cyprus (CYP), Estonia (EST), Greece (GRC), Hungary (HUN), Latvia (LVA), Lithuania (LTU), Serbia (SRB), Slovakia (SVK), Slovenia (SVN), and Turkey (TUR).

DISCUSSION

In this study, we aimed to evaluate the correlation between the level of access to strong opioid analgesics indicated by the ACM and the number of potential barriers in national legislation and regulations in 11 central and eastern European countries. The low R^2 value (2% variance explained) indicates that there is no correlation between ACM and the number of potential barriers in legislation and regulations in the countries studied. Our findings suggest that other factors play a role in explaining variation in access to strong opioid analgesics. For example, one of the findings of the ATOME project was that pain treatment education in the medical curriculum falls short in many countries.²⁵ Later, similar conclusions were drawn from the Advancing the Provision of Pain Education and Learning (APPEAL) study.²⁶ Unfortunately, there are no studies examining a possible correlation between the ACM and the level of treatment education.

We would expect to find a decrease in the ACM as the number of potential barriers in national legislation and regulation increases and vice versa. However, looking at the results in Figure 2 there are two clusters of countries that show a pattern that is not in line with these expectations. Two countries in the upper right quadrant (Greece and Hungary) have a relatively high level of access to strong opioid analgesics compared to the other countries in this study despite a relatively high number of potential barriers. A possible explanation could be that some of the overly strict rules that are set out in law (*de jure*) in these countries are not always followed in practice (*de facto*). For example, a workaround has been found to bypass certain barriers or violation of rules may be tolerated to a certain level. A prime example can be found within the field of harm reduction where a country may choose not to prosecute drugs possession for personal use based on discretionary powers although it remains an act against the law.²⁷ In the same manner potential barriers that were identified in national legislation and regulations in these countries may not constitute actual barriers in practice.

The cluster of countries in the lower left quadrant shows the contrary: access to strong opioid analgesics is low (Serbia) to very low (Cyprus and Turkey) despite a relatively low number of potential barriers. In these countries other factors may play a more significant role in impeding access to opioid analgesics such as issues concerning the affordability of opioid analgesics or fear for opioid analgesic use. For Cyprus, the relatively low number of potential barriers may possibly be related to the fact that Cyprus is a former British colony.²⁸ It is not unlikely that influences from British colonial times are still visible in legislation. However,

there are no (scientific) data available to support this theory. Serbia underwent a legislation review process as a part of an International Pain Policy Fellowship to improve the availability and accessibility of opioids for cancer pain. As a result, a new law on psychoactive controlled substances was enacted in 2011 which is likely to have contributed to the relatively low number of potential barriers.²⁹ The impact of this revision may not yet have resulted in a (substantially) higher level of opioid consumption. A similar initiative in Vietnam that started earlier appeared to have supported the reduction of barriers to access, with a year-on-year increase in morphine consumption per capita since the start of the project in 2005 until 2010.³⁰ However, as this project comprised a broad set of actions and no research has been conducted to examine the correlation between the different interventions and morphine consumption, it remains difficult to highlight indicators for success. In a study that evaluated the effectiveness of a series of workshops aimed at improving access to opioids in 13 Latin American countries, no significant differences were seen between countries that had one, two or no workshops and the outcome measures, being (changes in) opioid consumption and formulations available.¹⁴ The authors discussed that it may take several years before results can be observed.¹⁴ For Cyprus, Serbia and Turkey, key challenges to access to opioids were identified in aspects concerning education and training, societal attitudes and financial issues in addition to legal and regulatory issues.²⁵ In all three countries fear of opioid medicines and misconceptions around their medical use (for example the misconception that prescribing of opioid medicines automatically results in opioid dependence or hastened death) were considered a major barrier to access.^{25, 29} More (financial support for) education and training in pain management and palliative care were considered a necessity to improve the current situation. In addition, more financial resources are needed to support the treatment of pain, palliative care or harm reduction. In Cyprus for example, due to lack of governmental funding, the provision of palliative care mostly relies on charity funds.²⁵

We also see countries showing a pattern that is more in line with expectations. In the lower-right quadrant there is a cluster of countries (n=4) with low (Latvia and Lithuania) to very low (Bulgaria and Estonia) access to strong opioid analgesics and a relatively high number of potential barriers in national legislation and regulation. In the upper-left corner we see one country (Slovenia) with moderate access to strong opioid analgesics and a relatively low number of potential barriers. Although we describe countries that have a relatively high level of opioid analgesic consumption, it should be noted that the level of opioid analgesic consumption is considered inadequate in all 11 countries studied and even below the European average in 10 of the 11 countries.

Besides GDP and HDI there is little evidence for determinants of access to opioid analgesics. A recent study by Berterame et al. assessed the correlation between actual consumption data of opioid analgesics and impediments to access to opioid analgesics.⁶ Information on the number of impediments was collected by sending a survey on various impediments to 214 national authorities, which included the impediment ‘onerous regulations’. The authors found that the frequency of the reported impediment ‘onerous regulations’ decreased substantially since 1995. Moreover, they found that after adjustment for GDP and country-level development, the total number of reported impediments (including onerous regulations) was no longer associated with use of opioid analgesics. Governments of countries with a low GDP and/or HDI may have difficulties in ensuring the availability and affordability of opioid medicines due to limited resources and infrastructure, as indicated by the significant relation between GDP, HDI and use.⁶ A potential limitation of the study by Berterame et al. is that other important stakeholders such as healthcare professionals and patient representatives involved in pain management were not included in the surveys. As different stakeholders may perceive different types of barriers, limiting the group of respondents to national authorities may have caused underreporting of the number and nature of impediments.³¹ A strength of our study is that we used data on potential barriers that were identified by an external review of legislation and were disseminated to the ATOME country teams for validation.³² These ATOME country teams included various stakeholders, among which healthcare professionals, patient representatives and national authorities. An additional study has been undertaken by the ATOME working group to assess differences in the perception of barriers to access to opioid medicines among key stakeholders; a publication is currently in preparation.

Several limitations of the current study should be considered when interpreting the results. First, the limited sample size may have caused the study to be underpowered to identify significant differences between countries. Secondly, as data from 2013 were not available for Greece, we used data from 2010. Changes in opioid analgesic consumption may have taken place in the period between 2010 and 2013, resulting in underestimation or overestimation of the ACM for Greece. However, in the ten other countries only small changes were seen between 2010 and 2013 (average change -1%; range -7% to +3%). Thirdly, this study evaluated potential barriers to access to opioid medicines in relation to opioid analgesic consumption data. These opioid analgesic consumption data did not include opioid agonists such as methadone. However, similar results were found when excluding potential barriers to access to opioid medicines used for the treatment of opioid dependence. Possible future steps may include validation of this updated method to calculate the level of opioid consumption on a wider scale.

CONCLUSIONS

In conclusion, our hypothesis that countries with a heavier burden of legal and regulatory barriers to control strong opioid analgesics would have even less access to these essential medicines for patients in medical need could not be confirmed. This is an important result in the context of finding solutions for improving access to opioid analgesics for patients in need for effective and safe pain medication. Obviously, there are other factors that play a critical role in withholding prescribers and patients essential pain medication. More research is needed towards better understanding of the complex interplay of factors that determine access to opioid analgesics.

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CHAPTER 5

GENERAL DISCUSSION



INTRODUCTION

Ensuring appropriate access to opioid medicines is currently a widely debated issue. Opioid medicines are an essential pharmaceutical treatment option for – amongst other – patients in pain and for the treatment of opioid dependence.¹ This medical necessity has been recognized by the World Health Organization (WHO) by adding several opioids to its list of “essential medicines”.² As such, opioid medicines should be available and accessible for patients in medical need at an affordable price. At the same time, opioid use may potentially lead to the development of opioid dependence, which can be harmful for individuals and public health. For this reason, the use of opioids is highly regulated on an (inter)national level. Within this context, governments and policy makers have a dual obligation: ensuring access for patients in medical need while preventing harm associated with non-medical use and diversion.¹

Although this dual obligation exists, it is difficult to reach equilibrium when it comes to achieving maximum health outcomes. Reaching equilibrium is only possible if a system of control does not create unintended barriers for the availability of opioids for medical and scientific purposes, and does not interfere with the legitimate medical use for patients.¹ While the current aim is to achieve balance in drug control policies, historically the focus of the international drug control system has moved from a public-health oriented system to a criminal-law based system.³ In the 1990s, the public-health focus regained importance as the undertreatment of pain received interest from a broad international audience, including the WHO and the American Pain Society.⁴ Several projects and initiatives were launched in the following decades to improve the treatment of pain and access to opioids. One of these initiatives was the Access To Opioid Medication in Europe (ATOME) project, which started in 2009 as a five-year project funded under the European Union’s 7th Framework Programme, with the aim to improve access to opioids in 12 central and eastern European countries. Recently, a shift in focus is seen towards concerns about inappropriate use rather than concerns about undertreatment as a result of the “opioid epidemic” in the United States (US).

It is clear that the challenge for governments to achieve maximum public health outcomes as a result of finding the right balance has not reached its optimum yet. To date, various actions are taken in the US to address the “opioid epidemic”, which claimed more than 42 000 lives in 2016.⁴ At the same time, there is still a high level of inequity when it comes to access to opioids for patients in legitimate medical need: data from the International Narcotics Control Board (INCB) show that in 2015, 81.6% of the world population lived in countries

with an inadequate consumption level.⁵ Although the inequity is most prominent in low- and middle-income countries (LMICs)⁶, there are also reports of patients being undertreated in countries with higher consumption levels, including the US.⁷ Finding the right balance is a complex task; measures implemented by governments to increase access for patients in medical need may unintentionally interfere with their task to prevent the non-medical use and diversion of opioids. Vice versa, control measures taken to prevent non-medical use and diversion may have a negative impact on access for patients in medical need.

The challenge to ensure appropriate access is – as highlighted above – not new and is also not unique for opioid medicines. Many situations exist where access to medicines may be compromised by necessary control measures, for example to prevent harm or to control the costs of healthcare. As an example, tension may exist between ensuring access to antibiotics to treat bacterial infections and managing antibiotic resistance, which increases treatment costs and mortality.⁸ Additionally, access to high-priced medical treatments such as orphan drugs may be hampered by necessary measures to ensure the affordability of healthcare. Although various situations exist where access and control come together, the situation regarding opioid medicines may be considered different in the way that there is a higher level of control on an international level. As a consequence, barriers may occur at multiple levels of the healthcare system with a high level of interconnectedness.

This thesis aimed to study which factors may have a negative impact on appropriate access to opioid medicines, focusing on legal, regulatory and policy aspects. In this chapter, we will reflect on the most important findings from our research and we will put these learnings into a broader perspective. First, we focus on legal and regulatory aspects, and assess to what extent barriers can be identified in national drug control systems for patients in medical need of opioid medicines. Secondly, we assess the perception of different types of barriers to appropriate opioid use of several stakeholder groups, and assess whether differences in the perception of barriers exist depending on the stakeholder involved. Thirdly, we reflect on access to opioid medicines in clinical practice in the context of barriers. We also discuss challenges for governments, policy makers and health authorities to ensure essential opioid medicines can be available for patients in legitimate medical need, and provide suggestions for implementing effective solutions in order to ensure appropriate access to opioid medicines.

INTERNATIONAL AND NATIONAL DRUG CONTROL SYSTEMS: BARRIERS TO ACCESS?

Opioid medicines are controlled under the international conventions.^{9,10} States Parties to these conventions are required to undertake certain control measures to- in short- limit the

use of opioids to scientific and medical purposes.¹¹ At the same time, States Parties also have the freedom to adopt stricter control measures than required by the conventions if they believe these measures are necessary or desirable.¹² As a result, national drug control systems contain measures that may impede access to opioid medicines in a way that is not proportional to their impact on the prevention of non-medical use and diversion. The majority of studies and international organizations that reported on barriers to access used surveys focusing on a predefined subset of barriers.^{13–15} A disadvantage is that this method does not allow for the identification of every single potential barrier in every area, including those located in less obvious areas. Additionally, little is known about the existence of additional legal and regulatory barriers for specific groups of patients, such as patients with opioid dependence.

In chapters 2.1 to 2.3 we identified potential barriers to access to opioid medicines in 11 central and eastern European countries participating in the ATOME project: Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Serbia, Slovakia, Slovenia and Turkey. We looked at *potential* barriers as we did not assess the actual impact of barriers on access in clinical practice. In chapter 2.1, a quick-scan method was used to identify potential barriers. In chapter 2.2 we developed an assessment instrument for the systematic analysis of national legislation and regulations, and identified potential barriers using this instrument. In chapter 2.3 we built on the analyses in chapter 2.2 and identified specific potential barriers for patients with opioid dependence.

Although slightly different methods were used, chapters 2.1 to 2.3 all showed that the reviewed legislation and regulations contained many potential barriers to access. The majority of potential barriers concerned the prescribing and dispensing of opioid medicines, with individual differences between countries in the level of impediment. Comparing the quick-scan method (chapter 2.1) and the in-depth analysis (chapters 2.2 and 2.3), more potential barriers were identified using the in-depth analysis which can be explained by the higher number of legal and regulatory documents reviewed and by the more thorough review method used. A strength of the quick-scan method is that it can be used as a relatively simple method by any person with basic knowledge of the system in place to control opioid medicines. It not only gives insight into “quick wins” in terms of improvement but also provides a good basis for an in-depth analysis. Our in-depth analysis revealed a total number of 778 potential barriers across 11 countries, with the smallest number in Cyprus (n=22) and the largest number in Lithuania (n=128). The results found in chapters 2.2 and 2.3 are largely in line with other studies reporting on prescribing and dispensing limitations.

Differences between our findings and those of other studies may be associated with the high level of detail in our study, which is inherent to the systematic review method used and the large number of documents reviewed. In chapter 2.3 we found that patients with opioid dependence are likely to experience specific barriers to accessing opioid medicines in addition to those experienced by other patients, such as strict requirements for accessing opioid agonist treatment. Of the 778 potential barriers identified in chapter 2.2, a total of 144 barriers (19%) in 10 countries (all except Estonia) were considered potential barriers exclusively for patients with opioid dependence, with the smallest number in Slovenia (n=2, 7%) and the largest number in Lithuania (n=46, 36%). Results of previous studies that were similar to the results of the current study included age restrictions for accessing harm reduction services, strict admission criteria, treatment costs and strict exclusion criteria.^{16–20} Chapters 2.1 to 2.3 also showed that all countries assessed had disrespectful language in their legislation that contributed to the stigmatisation of the use of opioid medicines. This was in particular the case for the language used towards patients with opioid dependence, which was characterized by stigmatization and criminalization. Our results showed the use of stigmatizing language to a larger extent than reported in other studies, which may be the result of the detailed review method used in our study and the potential underreporting by the survey's respondents in other studies.^{13,21–24} For example, Cherny et al. found that out of 40 countries, only 12 reported the use of negative language in opioid regulations. Opioid analgesics were referred to as drugs of addiction by 11 countries, dangerous drugs by five countries and poisons by two countries.¹³ In contrast to our findings, Cherny et al. reported the use of neutral language in seven European countries that were deemed to have stigmatizing language in their legislation in our study which was based on WHO policy guidelines that give clear examples of what is considered non-stigmatizing terminology. This could indicate that there may be misconception or misunderstanding about what is considered neutral, negative or stigmatizing language.

Overall, chapters 2.1 to 2.3 have shown that national drug control systems may play a role in limiting access to opioid medicines for patients in medical need. Still, we don't know to what extent these potential barriers have an impact on access in clinical practice. For some provisions that have been identified as potential barriers it may be evident that they impede access for patients to the treatment they need. For example, legal restrictions on the maximum daily dose may interfere with adequate treatment in the situation that a patient may require a higher dose than allowed by law.²⁵ However, there is also the possibility that these legal provisions are not always followed in practice. This situation could for example occur if violation of certain control measures is tolerated by the authorities or if a workaround has been found

to bypass these measures. In this case, there is evidently no rationale for maintaining these potentially impeding provisions in legislation or regulations. So far, only anecdotal evidence exists showing a direct correlation between strict prescribing or dispensing requirements and patients being denied adequate treatment.^{25–27} Future research could study the effect of the respective provisions on opioid access in clinical practice, for example by undertaking a survey or conducting structured interviews among patients in medical need of opioid medicines and their healthcare providers in the European countries that participated in the ATOME project. This survey could focus upon the quality of their treatment provided, both from a patient and healthcare provider perspective and on barriers that were encountered that hampered adequate treatment. A strength of our studies focusing on legal and regulatory barriers is that we systematically reviewed legislation, taking into account all elements in the pharmaceutical supply chain by using an assessment instrument which we developed based on WHO policy guidelines that can be used by others in an universal matter. A systematic review of legislation and regulations and revision of unbalanced provisions is also recommended on a wider scale to improve access to opioid medicines for patients in medical need, and to remove language that contributes to the stigmatization of legitimate opioid use. Countries that are considering a review of their legislation could make use of the work that has been done by the Pain & Policy Studies Group²⁸ or by the ATOME project, which includes the studies presented in chapters 2.1 to 2.3. Countries that wish to improve existing policies could also make use of the WHO policy guidelines, which include a self-assessment checklist to identify and assess policy barriers.¹

OTHER BARRIERS AND THEIR IMPACT ON APPROPRIATE ACCESS

Besides barriers that can be linked directly to national drug control systems, other types of barriers have been reported in scientific literature that may hamper access to appropriate opioid use. A distinction can be made between barriers relating to economic aspects, knowledge and education, policy aspects, and societal attitudes.¹ Barriers can also be grouped into supply side barriers and demand side barriers.²⁹ Many studies report on barriers that are perceived by healthcare professionals (e.g. physicians, nurses and pharmacists) and patients.^{17,30–33} Yet, little is known on barriers perceived by stakeholder groups that are involved in drafting an implementing drug control policies.^{34,35} Limited information also exists on barriers perceived by healthcare professionals working with opioid medicines in different medical fields, such as pain management, palliative care and harm reduction. Chapters 3.1 and 3.2 focus on the perception of barriers to appropriate opioid use of several stakeholder groups in the countries that participated in the ATOME project, including representatives from governmental bodies and organizations, and these different medical fields.

In chapter 3.1 we studied key common challenges to the accessibility of opioid medicines in the ATOME countries. Common barriers were identified in breakout sessions by representatives (n=84) of the national Ministries of Health, national controlled substances authorities, experts representing regulatory and law enforcement authorities, leading health care professionals, and patient representatives. We found that lack of appropriate access to opioid medicines is multifactorial, with barriers existing on numerous levels which are interlinked and partially reinforced by each other. Common challenges identified were educational, regulatory, legislative, and training barriers that limit the ability of both physicians and nurses to provide adequate treatment with opioids to patients. Several suggestions were made to improve the situation in the countries, which included raising public awareness about the beneficial effects of opioids to reduce fear for prescribing opioids, the introduction of electronic prescription forms to overcome barriers related to excessive regulations, the development of policy guidelines and the improvement of education in the field of pain management, which also includes involving and educating regulatory authorities to underline that access to pain relief is a fundamental human right. A potential limitation of this study was the selection of experts and participants attending the workshops, as their views may not represent the situation in the countries concerned. In chapter 3.2 we assessed the perception of barriers on a larger scale by conducting surveys, and assessed whether different barriers were perceived depending on the stakeholder involved. In total, 199 (54%) participants from seven countries completed the questionnaire. We found that policy makers perceived issues less often as major problems compared to other stakeholders. For example, a high proportion of healthcare professionals (44-57%) reported that excessive regulation or bureaucracy of prescribing procedures had a major impact on accessing opioids, while this was seen as a major issue by only 20% of the policy makers. This regulatory burden was most prominent amongst harm reduction professionals. This specific finding is in line with the results of chapter 2.3, which showed that patients with opioid dependence may experience specific barriers to accessing opioids in addition to those experienced by non-dependent patients. Aspects that were most frequently perceived as major barriers included lack of training, lack of financial resources and physicians' reluctance to prescribe opioids. These aspects were also identified as key challenges in chapter 3.1. In chapter 3.3 we discussed the challenges for governments, health authorities and healthcare providers to ensure access to opioids for patients in legitimate medical need while implementing strategies that aim to prevent non-medical use of opioids. Although both objectives are important, in discussions the non-medical use of opioids tends to be prioritized over the undertreatment of pain. Close monitoring of national drug control measures that are being implemented to combat the non-medical use of opioids is considered crucial to minimize unintended consequences for

patients in legitimate medical need. This is in particular important for patients with (a history of) opioid dependence, as this group represents a particularly disadvantaged population.

ACCESS IN CLINICAL PRACTICE IN THE CONTEXT OF BARRIERS

Despite abundant literature on factors that are perceived to interfere with access to opioid medicines, very little is known on the correlation between individual factors and access in clinical practice. What we do know is that the Human Development Index (HDI) and the Gross Domestic Product (GDP) have shown to be predictive variables for a country's opioid consumption level.^{6,36,37} However, little evidence exists for other determinants of access to opioids, including issues relating to drug control systems or societal aspects. These data are important in the context of finding solutions for improving access to opioid analgesics for patients in medical need. In chapters 4.1 to 4.3 we positioned access to opioid medicines in clinical practice within the context of different types of barriers.

Chapter 4.1 focusses on variation in the prescribing of strong opioid analgesics between practices in the Netherlands. We evaluated differences in the amount prescribed (expressed in DDDs per 1 000 persons in 2015) for the main strong opioid analgesics, and assessed variation in the prescribing of strong opioids for non-cancer pain. The latter is currently being debated due to lack of solid and conclusive evidence supporting long term use of opioids in chronic non-cancer pain.³⁸ We found a 2.2-fold variation in the prescribing of oxycodone and fentanyl, with the lowest median amounts prescribed in Zuid-Holland/Noord-Holland (oxycodone) and Noord-Holland (fentanyl) and the highest amounts prescribed in Flevoland (oxycodone) and Limburg (fentanyl). A 4.6-fold variation was seen for morphine, with the lowest median amount prescribed in Utrecht and the highest in Groningen. The majority of general practices showed a relatively low volume of opioid prescribing, despite a relatively high use in non-cancer pain. As we did not find a linear correlation between the amount of strong opioid analgesics prescribed and the relative amount prescribed for non-cancer pain, there is no evidence that suggests that high volume prescribing might be exclusively driven by preferential use for non-cancer pain. An important limitation of our study is that we did not control for population characteristics, which may provide an explanation for the variation and the lack of correlation found. Future analyses could further evaluate variation, and look into the factors that explain potential variation found, taking into account characteristics on a general practice level and on a patient level. In chapter 4.2 we subsequently examined how a period of intense media attention following a strong opioid related tragedy affected the prescribing of strong opioid analgesics in primary care in the Netherlands. We found that the media attention did not result in more reluctant prescribing behavior among general

practitioners. This is not in line with previous research, showing a (potential) association between media coverage and prescribing or usage patterns of other types of medicines. A possible explanation for the differences observed may be found in the specific topic that was covered by the media; the media in the large majority of other studies reported on risks of certain types of medication while in the current study the conduct of the authorities were topic of discussion. Apparently, these discussions did not result in a widespread concern on the prescribing of strong opioid analgesics in a way that changed the prescribing behavior of general practitioners. As chapter 4.2 evaluates changes in prescribing practices of strong opioid analgesics in general and did not focus on a palliative care setting, future research could look specifically at changes in prescribing trends of medicines that alleviate suffering in end-of-life care.

In chapter 4.3 we evaluated the correlation between access to opioid analgesics and potential legal and regulatory barriers by contrasting two variables for 11 central and eastern European countries: the country level of access to opioid analgesics estimated by the Adequacy of Consumption Measure (ACM)³⁹ and the number of potential legal and regulatory barriers as identified in chapter 2.2. Although we expected to find a decrease in the country level of access to opioid analgesics with an increasing number of potential barriers in national legislation and regulation and vice versa, this possible correlation could not be confirmed. Apparently, other factors exist that may play a critical role in withholding patients essential pain medication. Several other barriers were reported in chapters 3.1 and 3.2, which may also play a role in determining actual access to opioid medicines. As mentioned before, there is a paucity of studies examining the correlation between actual access and barriers to access. Berterame et al. showed that after adjustment for GDP and country-level development, the total number of reported impediments (including onerous regulations) was no longer associated with use of opioid analgesics.⁶ Information on the number of barriers was collected by sending a survey to national authorities. A potential limitation of their study is that important stakeholders such as healthcare professionals and patient representatives involved in pain management were not included in the surveys. In chapter 3.2 we found that policy makers perceived issues less often as major problems compared to other stakeholders, which may have caused underreporting of the number and nature of impediments in the study by Berterame et al. Future research is needed to assess a possible correlation between actual access and different types of barriers on a larger scale as our limited sample size in chapter 4.3 may have caused the study to be underpowered to identify significant differences between countries.

UNDERSTANDING BARRIERS TO APPROPRIATE ACCESS

This thesis aimed to study which factors may have a negative impact on appropriate access to opioid medicines. The majority of the individual studies in this thesis focused on central and eastern European countries with statistical evidence of inadequate consumption of opioids per capita. What we learned from these individual studies is that (potential) barriers to access can be identified, either by an external review of legislation (chapters 2.1 to 3.2) or by examining barriers to access perceived by stakeholders (chapters 3.1 and 3.2). However, when positioning actual access in the context of regulatory barriers (chapter 4.3), a possible correlation between access and one specific type of regulatory barrier could not be confirmed. The question may be raised whether the potential barriers that were identified in our studies constitute actual barriers in clinical practice. However, the statistical evidence of inadequate opioid per capita consumption shows that actual barriers to access must exist. One of the factors that may contribute to the complexity of studying the impact of potential barriers in clinical practice is that numerous barriers to access exist that relate to different aspects of access in the pharmaceutical supply chain. This was also highlighted by the studies presented in chapters 3.1 and 3.2. The possibility that barriers are interlinked and may even be partially reinforced by each other increases the complexity faced while studying their impact. Adding additional complexity to studying the impact of barriers is the possibility that barriers are interlinked, and may even be partially reinforced by each other. For example, the misconceptions about opioids that were reported as a key common barrier in chapters 3.1 and 3.2 may contribute to the fear of prescribing or using opioid medicines in medical practice and hence could restrict access. Additionally, this fear might cause governments and policy makers to implement restrictive policies and legislation (chapter 2.1 to 2.3). Subsequently, these restrictive policies and legislation may create a sense of fear of using opioid medicines (chapters 2.1 to 2.3), particularly if severe sanctions are involved for unintended violations, which was found in chapters 2.2 and 2.3.

The complexity of improving access to medicines has been addressed from a wider health system perspective by Bigdeli et al.⁴⁰ Their findings suggest that approaches aimed at improving access to medicines in LMICs may not have worked as desired as they do not address the full complexity of barriers and their interconnectedness, but instead use vertical approaches focussing on supply barriers instead of demand. As many other system barriers hamper access, actions may only have a limited and temporal effect.⁴⁰ Bigdeli et al. conclude that a wider health system perspective on access to medicines, taking into account the dynamic relationship between medicines and other components of the health system may offer an opportunity for addressing access to medicines. The complexity of barriers and their interconnectedness as discussed by Bigdeli et al. is also shown by the studies presented

in chapters 3.1 and 3.2. However, when applying their concept of a wider health system perspective, positioning actual access in the context of regulatory barriers (chapter 4.3) can be classified as a vertical approach, not addressing the full complexity of barriers that determine actual opioid consumption. Our conclusion that other factors exist that may play a critical role in withholding patients essential pain medication is supported by the framework proposing a health system perspective on access to medicines.

When discussing opportunities for improving appropriate access, patients in pain would benefit from the discovery and development of a novel class of strong analgesics. The holy grail is a new class of medicines with properties that are similar to those of current opioid medicines in terms of effectiveness but with a much better benefit-risk profile. It is hopeful that studies with new therapeutic targets and agents are currently being conducted (including botulinum toxin conjugates⁴¹, the nuclear receptors REV-ERB α and REV-ERB β ⁴² and Nav1.7 inhibitors⁴³) which may potentially lead to the availability of a novel generation analgesics in the future. Hopefully, by that time, the illicit use of opioid substances will also be resolved, as the availability of a new class of strong analgesics may not necessarily prevent this.

Until then, a possible approach to improve appropriate access to opioids would be the development of tailormade action plans for countries or even for regions. As shown by chapter 3.2, it is paramount to develop this action plan together with all stakeholders involved. Government officials and policy makers should not be excluded as they play a key role in developing policies and legislation that aim to address both objectives: the prevention of abuse and diversion and ensuring access for patients in medical need. A dialogue with healthcare professionals and patient representatives is needed to learn which barriers are encountered in daily medical practices that need to be lifted in drug control policies and legislation. It is important to involve healthcare professionals from all relevant medical fields in which opioid treatment plays a pivotal role, including those working in the field of anaesthesiology, haematology, pulmonology, gynaecology, internal medicine and general medicine. Additionally, it is crucial to include representation from the medical field of harm reduction, as studies have shown that patients with opioid dependence may face additional challenges in accessing opioid medicines. Given that barriers may be partly reinforced by each other, these action plans should address all key barriers, instead of focussing on one barrier only. For example, the barrier “fear for prescribing or using opioid medicines” may not be lifted if this fear originates from severe punitive sanctions for unintended violations. Another reason for taking into account all factors that limit access while developing strategies is that a chain is only as strong as its weakest link; one single barrier may limit access to

essential medication. These studies could adopt the concept of access to medicines from a wider healthcare perspective, as suggested by Bidgdeli et al.⁴⁰

The ATOME project included a similar approach as described above: national action plans were developed by country teams to improve the situation in their country with regard to opioid accessibility. By the end of the project in November 2014, several of the countries were already in the process of revising legislation and policies, and implementing recommendations for improvement.⁴⁴ Some countries made changes to their legislation based on the findings of chapters 2.1 to 2.3. For example, in Lithuania, the total number of special prescription forms physicians are allowed to receive has been doubled from ten to 20. In Estonia, the requirement for pharmacies to obtain a special permit, which authorises them to dispense controlled medicines, was removed. Before the removal of this requirement, pharmacies were reluctant to apply for a licence with the result that patients had difficulties identifying a pharmacy that could dispense their opioid medicines. The impact of these revisions and other changes has not (yet) been studied. It is also unclear how long it will take before changes will translate into better access to opioids, and if changes can be observed when only one aspect is being addressed (vertical approach). For example, in Serbia an increase in opioid consumption was observed between 2006 and 2012, following a multifaceted approach as a part of the International Pain Policy Fellowship to improve the accessibility of opioids for cancer pain.²⁸ The approach included a review of legislation in 2006, which resulted in a new national law on psychoactive controlled substances in 2011.

APPROPRIATE ACCESS TO OPIOIDS CONTINUOUSLY UNDER PRESSURE?

As mentioned in the introduction, the recent developments in the US and to a lesser degree in other countries including Canada and Australia⁴⁵ have caused a shift in focus towards concerns about inappropriate use rather than concerns about undertreatment. There is no doubt that the crisis in the US constitutes a serious threat to public health, and that measures are needed to address this crisis. However, the situation in the US should not lead to a worldwide call for control measures that lead to the formation of new barriers that impede access for patients that urgently need these medicines. A lot of work has been done to address the stigmatization of opioid use and to address global inequities to access.^{1,7,46-48} Instead of going back towards a criminal-law focused drug control system, discussions should focus on how these medicines can be prescribed and used in a safe manner based on scientific evidence instead of emotion, while minimizing their potential for harm. There is still a long way to go when it comes to understanding the exact pathways from the onset of pain to opioid exposure and to potential negative consequences such as drug seeking related to the undertreatment of pain, opioid dependence and opioid overdose.⁴⁹ Additionally, it is also important to understand the role of

legally and illegally produced opioids, as there is increasing evidence that the opioid epidemic in the US is mainly driven by illegally manufactured fentanyl.^{5,50,51}

There is also much that can be done to reduce the potential development of opioid dependence. Several studies have identified factors associated with the risk of opioid overdose, including factors relating to the formulation (long-acting or extended release formulations), the exposure (high daily dose and long-term opioid use), the timing of exposure (first 2 weeks of initiation of therapy), and the use of co-medication (combined use with benzodiazepines).^{49,52} It is important that these risk factors are reflected in guidelines and policies that promote the safe and appropriate prescribing of opioids.

Although access to opioid medicines is strictly regulated in Europe in comparison to the US, many European countries are worried about the developments in the US and closely monitor their opioid consumption levels. The Netherlands is one of the countries with concerns about increased levels of opioid analgesic use.^{53,54} Recent data show that the number of patients using the strong opioid analgesics oxycodone, fentanyl, morphine and buprenorphine have increased between 2008 and 2017, and plateaued in 2018. In February 2019 the Dutch Minister for Medical Care announced measures to reduce the use of strong opioid analgesics, referring to the opioid epidemic in the US.⁵³ These measures include increasing the knowledge on the risks of opioids, standardizing clinical guidelines, conducting more scientific research and monitoring non-medical use. More scientific research is important as it remains unclear whether the increased use is an early sign of an evolving opioid epidemic, or the result of necessary progress made towards the adequate management of pain. As the prescribing of strong opioid medicines in the Netherlands is currently more topic of discussion than ever before, there is also increasing interest from the scientific community to study the recent developments. These studies will expectantly provide more insights into the factors that explain the increased prescribing of opioid analgesics for patients with non-cancer pain and potential variation between regions and general practices, both from a perspective of undertreatment and overuse. In either situation, patients and healthcare providers can benefit from more education on the safe and responsible prescribing and usage of opioid analgesics, as long as this information is provided in a balanced matter and does not contribute to the stigmatization of the medical use of opioids. In that context, it would be particularly interesting to evaluate the impact of the current media attention on the prescribing and usage of oxycodone in the Netherlands, as this media coverage has not always been balanced. While our research showed that general practitioners did not change their prescribing behaviour following a period of intense media attention, the current debates address a different topic (safety concerns involving strong opioids instead of the conducts of

health authorities), and may therefore have an impact on the prescribing of strong opioid analgesics in primary care. As the current perceptions regarding the use of opioids in the Netherlands may be changing as a result of the increased prescribing, the unbalanced media attention and the measures announced by the Minister for Medical Care, appropriate access to opioid medicines for patients in medical need may become under pressure in the near future.

CONCLUSION

Several barriers to appropriate access were identified in the individual studies presented in this thesis. From a legal and regulatory perspective, *potential* barriers were identified by an external review of legislation and *actual* barriers have been reported by various stakeholders. As there is no solid evidence that these (potential) barriers contribute to the prevention of non-medical use and diversion, there is a rationale for removing these barriers in the process of revising legislation and regulations. From a policy perspective, a variety of barriers has been reported by relevant stakeholders. These barriers occur at different levels, and very little is known on the complex interplay of these and other factors that determine appropriate access to opioids. Unless all individual factors limiting access are adequately addressed, approaches that aim to improve appropriate access to opioids may not have the desired impact. As a consequence, it remains difficult for governments and policy makers to develop effective and widely supported solutions to address both problems: the inappropriate use of opioids and the undertreatment of pain and opioid dependence with essential opioid medicines. With the recent shift in focus towards the prevention of non-medical use and diversion, the progress that has been made in the past to move towards more balance in national drug control systems is under pressure. It is therefore crucial to focus on how opioid medicines can be accessible for patients in a safe manner, without contributing to the stigmatization of legitimate opioid use for patients in medical need. We suggest an approach that includes removing obvious impediments to appropriate access in legal and regulatory documents that do not contribute to the prevention of non-medical use and diversion. In addition, we propose the implementation of medical treatment guidelines and policies that promote the safe and appropriate prescribing of opioids based on solid scientific evidence, reflecting risk factors associated with the development of opioid dependence. This should go in parallel with educating healthcare professionals, patients and policy makers to promote the safe and rationale use and equally important to avoid the stigmatization of legitimate opioid use. Finally, it is important that a more balanced view is presented in the media and in scientific literature. With this thesis we aimed to contribute to a better understanding on different types of barriers from on a legal and policy perspective, bringing patients in medical need one step closer towards appropriate access to opioid medicines.

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CHAPTER 6

SUMMARY AND SAMENVATTING





CHAPTER 6.1

ENGLISH SUMMARY



SUMMARY

Opioid medicines are an essential pharmaceutical treatment option for various types of pain and for the treatment of opioid dependence. Other medical uses include anesthesia, suppression of cough or diarrhea, dyspnoea, dyspnoea related anxiety and reversing opioid overdose. The World Health Organization (WHO) recognized this medical necessity by adding several opioids to its list of “essential medicines”. As such, opioid medicines should be available and accessible for patients in medical need at an affordable price. Examples of essential opioid medicines include fentanyl, morphine and methadone. In spite of international recognition of their high therapeutic value, concerns exist regarding their use. Opioid use may potentially lead to the development of opioid dependence, which can be harmful for individuals and public health. The use of opioids is therefore highly regulated on an (inter)national level. Within this context, governments and policymakers have a dual obligation: ensuring access for patients in medical need while preventing harm associated with non-medical use and diversion. This dual obligation is also referred to as the “central principle of balance”.

Although this dual obligation exists, it is difficult to reach equilibrium when it comes to achieving maximum health outcomes. In 2015, 81.6% of the world population lived in countries with an inadequate consumption level. The existing literature recognizes the role of drug control policies in limiting access to opioid medicines. Governments and policymakers may prioritize the need to prevent non-medical use and diversion over the need to ensure appropriate access to opioid medicines. Historically, this focus of drug-control systems has been dynamic moving from a public-health oriented system to a criminal-law based system and back to a more public-health focus in the 1990s. Recently, a shift in focus is seen towards concerns about inappropriate use rather than undertreatment due to the so-called opioid epidemic in especially the United States (US). Many other factors are considered to have an impact on access to opioid medicines besides drug control policies, including factors relating to economic aspects, knowledge and education, policy aspects, and societal attitudes.

Several initiatives have been undertaken to improve appropriate access to opioid medicines and to reduce harm associated with non-medical use of opioids, including the Access To Opioid Medication in Europe (ATOME) project. This project started in 2009 as a five-year project funded under the European Union’s 7th Framework Programme, with the aim to improve access to opioids in twelve central and eastern European countries with statistical evidence of inadequate consumption of opioids per capita: Bulgaria, Cyprus, Estonia, Greece, Hungary, Latvia, Lithuania, Poland, Serbia, Slovakia, Slovenia and Turkey. While several other initiatives have been launched to improve access, in the US a variety of actions has been taken focusing on the prevention of harm. These actions have been triggered by the four-fold increase in

the consumption of opioid analgesics between 1999 and 2010, which was paralleled by an increase in opioid overdose related deaths. Concerns about increased opioid analgesic use also exist in other high-developed countries, including the Netherlands.

This thesis aims to study which factors may have a negative impact on access to opioid medicines, focusing on legal, regulatory and policy aspects. These insights may provide directions for implementing effective solutions for lifting barriers, with the ultimate goal to ensure appropriate access to opioid medicines.

In **chapter 2**, we analyzed national drug control systems in central and eastern European countries participating in the ATOME project. As national drug control systems have frequently been reported to contain legislative and regulatory barriers to access, these results may help to locate obstacles to the legitimate medical use of opioid medicines. In chapter 2.1, we used a quick-scan method to identify potential barriers. An assessment instrument was developed in chapter 2.2, which we used for the systematic analysis of national legislation and regulations and identification of potential barriers. In chapter 2.3, we built on the analyses in chapter 2.2 and identified specific potential barriers for patients with opioid dependence. In all three studies many potential barriers to access were identified. The majority of these barriers concerned the prescribing and dispensing of opioid medicines, with variation in the level of impediment between individual countries. The quick-scan method in **chapter 2.1** showed to be a relatively simple method to identify potential barriers, giving insight into “quick wins” in terms of improvement and providing a good basis for an in-depth analysis. This in-depth analysis was conducted in **chapter 2.2**, which revealed a total number of 778 potential barriers across eleven countries varying from 22 potential barriers in Cyprus to 128 in Lithuania. Building on the in-depth analysis, we found in **chapter 2.3** that patients with opioid dependence are likely to experience specific barriers to accessing opioid medicines in addition to those experienced by other patients. Of the 778 potential barriers identified in chapter 2.2, a total of 144 barriers (19%) in 10 countries (all except Estonia) were considered to contain potential barriers exclusively for patients with opioid dependence, with the smallest number in Slovenia ($n = 2$, 7%) and the largest number in Lithuania ($n = 46$, 36%). These potential barriers include age restrictions for accessing harm reduction services, strict admission criteria, treatment costs and strict exclusion criteria. Chapters 2.1 to 2.3 also showed that all countries assessed had disrespectful and stigmatizing language in their legislation, which was in particular the case for the language used towards patients with opioid dependence. Future research could study the impact of the respective provisions on opioid access in clinical practice.

In **chapter 3**, we studied other types of barriers in addition to those that can be linked directly to national drug control systems. In **chapter 3.1** we studied common key challenges to the

accessibility of opioid medicines in the ATOME countries. Common barriers were identified in breakout sessions by representatives (n=84) of the national Ministries of Health, national controlled substances authorities, experts representing regulatory and law enforcement authorities, leading healthcare professionals, and patient representatives. We found that lack of appropriate access to opioid medicines is multifactorial, with barriers existing on numerous levels which are interlinked and partially reinforced by each other. Common challenges identified were educational, regulatory, legislative, and training barriers that limit the ability of both physicians and nurses to provide adequate treatment with opioids to patients. In **chapter 3.2** we assessed the perception of barriers on a larger scale by conducting surveys, and assessed whether different barriers were perceived depending on the stakeholder involved. In total, 199 (54%) participants from seven countries completed the survey. We found that policy makers perceived issues less often as major problems compared to other stakeholders. For example, a high proportion of healthcare professionals (44-57%) reported that excessive regulation or bureaucracy of prescribing procedures had a major impact on accessing opioids, while this was seen as a major issue by only 20% of the policy makers. This regulatory burden was most prominent amongst harm reduction professionals. In **chapter 3.3** we discussed the challenges for governments, health authorities and healthcare providers to ensure access to opioids for patients in legitimate medical need while implementing strategies that aim to prevent non-medical use of opioids. Although both objectives are important, in discussions the nonmedical use of opioids tends to be prioritized over the undertreatment of pain. We argued that close monitoring of national drug control measures that are being implemented to combat the nonmedical use of opioids is crucial to minimize unintended consequences for patients in legitimate medical need. This is in particular important for patients with (a history of) opioid dependence, as this group represents a particularly disadvantaged population. In **chapter 4**, we positioned access to opioid medicines in clinical practice within the context of different types of barriers. In **chapter 4.1**, we evaluated differences in the median amount prescribed (expressed in DDDs per 1 000 persons in 2015) per practice across the twelve provinces in the Netherlands for the main strong opioid analgesics, and assessed variation in the prescribing of strong opioids for non-cancer pain. We found a 2.2-fold variation in the median amount of oxycodone and fentanyl prescribed per practice between the provinces. A 4.6-fold variation was seen for morphine, with the lowest median amount prescribed in Utrecht and the highest in Groningen. The majority of general practices showed a relatively low volume of opioid prescribing, despite a relatively high use in non-cancer pain. As we did not find a linear correlation between the amount of strong opioid analgesics prescribed and the relative amount prescribed for non-cancer pain, there is no evidence that suggests that high volume prescribing might be exclusively driven by preferential use for non-cancer pain.

An important limitation of our study is that we did not control for population characteristics, which may provide an explanation for the variation and the lack of correlation found. Future analyses could further evaluate variation, and look into the factors that explain potential variation found, taking into account characteristics on a general practice level and on a patient level. In **chapter 4.2** we subsequently examined how a period of intense media attention following a strong opioid related tragedy affected the prescribing of strong opioid analgesics in primary care in the Netherlands. We found that the media attention did not result in more reluctant prescribing behavior among general practitioners. A possible explanation for this result may be found in the specific topic that was covered by the media; the media in the large majority of other studies reported on risks of certain types of medication while in the current study the conduct of the authorities were topic of discussion. As chapter 4.2 evaluated changes in prescribing practices of strong opioid analgesics in general and did not focus on a palliative care setting, future research could look specifically at changes in prescribing trends of medicines that alleviate suffering in end-of-life care. In **chapter 4.3** we evaluated the correlation between access to opioid analgesics and potential legal and regulatory barriers by contrasting two variables for eleven central and eastern European countries: the country level of access to opioid analgesics estimated by the Adequacy of Consumption Measure (ACM) and the number of potential legal and regulatory barriers as identified in chapter 2.2. Although we expected to find a decrease in the country level of access to opioid analgesics with an increasing number of potential barriers in national legislation and regulation and vice versa, this possible correlation could not be confirmed. Apparently, other factors exist that may play a critical role in withholding patients essential pain medication. Future research is needed to assess a possible correlation between actual access and different types of barriers on a larger scale as our limited sample size may have caused the study to be underpowered to identify significant differences between countries.

In **chapter 5**, the studies described above were placed in a broader perspective, providing policy recommendations for improving appropriate access to opioids. What we learned from the individual studies presented in this thesis is that several barriers to appropriate access were identified. From a legal and regulatory perspective, *potential* barriers were identified by an external review of legislation. From a policy perspective, a variety of *actual* barriers has been reported by relevant stakeholders. These barriers occur at different levels, and very little is known on the complex interplay of these and other factors that determine appropriate access to opioids. We discussed that, unless all individual factors limiting access are adequately addressed, approaches that aim to improve appropriate access to opioids may not have the desired impact. As a consequence, it remains difficult for governments and policymakers to develop effective and widely supported solutions to address both problems: the inappropriate

use of opioids and the undertreatment of pain and opioid dependence with essential opioid medicines. With the recent shift in focus towards the prevention of non-medical use and diversion, the progress that has been made in the past to move towards more balance in national drug control systems is under pressure. It is therefore crucial to focus on how opioid medicines can be accessible for patients in a safe manner, without contributing to the stigmatization of legitimate opioid use for patients in medical need. We suggest an approach that includes removing obvious impediments to appropriate access in legal and regulatory documents that do not contribute to the prevention of non-medical use and diversion. In addition, we propose the implementation of medical treatment guidelines and policies that promote the safe and appropriate prescribing of opioids based on solid scientific evidence, reflecting risk factors associated with the development of opioid dependence. This should go in parallel with educating healthcare professionals, patients and policy makers to promote the safe and rationale use and equally important to avoid the stigmatization of legitimate opioid use. Finally, it is important that a more balanced view is presented in the media and in scientific literature. With this thesis we aimed to contribute to a better understanding on different types of barriers from on a legal and policy perspective, bringing patients in medical need one step closer towards appropriate access to opioid medicines.



CHAPTER 6.2

NEDERLANDSE SAMENVATTING



SAMENVATTING

Opioïde geneesmiddelen zijn een essentiële farmaceutische behandeloptie voor verschillende soorten pijn en voor de behandeling van opioïdenafhankelijkheid. Daarnaast worden opioïden onder meer toegepast als anestheticum, bij hoest, diarree, dyspnoe, dyspnoe gerelateerde angst en als antidotum bij een overdosis opioïden. De Wereldgezondheidsorganisatie (WHO) heeft deze medische noodzaak erkend door verschillende opioïden toe te voegen aan de lijst met “essentiële geneesmiddelen”. In die context zouden opioïden beschikbaar en toegankelijk moeten zijn tegen een betaalbare prijs voor patiënten die deze geneesmiddelen medisch gezien nodig hebben. Voorbeelden van opioïden die op de lijst met “essentiële geneesmiddelen” staan zijn fentanyl, morfine en methadon.

Ondanks internationale erkenning van de hoge therapeutische waarde van opioïde geneesmiddelen bestaan er zorgen over hun gebruik. Het gebruik van opioïden kan mogelijk leiden tot de ontwikkeling van opioïdenafhankelijkheid, wat schadelijk kan zijn voor individuen en voor de volksgezondheid. Het gebruik van opioïden is daarom strikt gereguleerd op (inter)nationaal niveau. Binnen deze context hebben overheden en beleidsmakers een dubbele plicht: ervoor zorg dragen dat patiënten toegang hebben tot medisch noodzakelijke geneesmiddelen en tegelijkertijd schade voorkomen die verband houdt met niet-medisch gebruik en illegale handel. Het bewaren van het evenwicht tussen beide plichten wordt ook wel “the central principle of balance” genoemd.

Het balanceren tussen beide plichten blijkt lastig. In 2015 woonde 81.6% van de wereldbevolking in landen met een inadequaats consumptieniveau van opioïde analgetica. De wetenschappelijke literatuur bevat aanwijzingen dat het geneesmiddelen- en drugsbeleid een rol kan spelen bij het beperken van de toegang tot opioïde geneesmiddelen. Overheden en beleidsmakers verantwoordelijk voor dit beleid kunnen prioriteit geven aan het voorkomen van niet-medisch gebruik en illegale handel. Dit kan ten koste gaan van de plicht om te zorgen voor adequate toegang tot opioïde geneesmiddelen. Deze focus van het geneesmiddelen- en drugsbeleid is aan verandering onderhevig. In het verleden is de focus verschoven van een systeem dat gericht was op de volksgezondheid, naar een op strafrecht gebaseerd systeem. In de jaren negentig kwam er steeds meer aandacht voor pijnbestrijding, waardoor er een verschuiving in focus plaatsvond. Recentelijk lijkt er weer een verschuiving plaats te vinden; als gevolg van de zogenaamde opioïdenepidemie in de Verenigde Staten (VS) zijn de zorgen over inadequaats gebruik toegenomen. Naast het geneesmiddelen- en drugsbeleid kunnen vele andere factoren van invloed zijn op de toegang tot opioïde geneesmiddelen, waaronder factoren die betrekking hebben op economische aspecten, kennis en onderwijs, beleidsaspecten en de houding van de maatschappij ten opzichte van deze middelen.

Er zijn verschillende initiatieven genomen om de toegang tot opioïde geneesmiddelen te verbeteren en schade als gevolg van niet-medisch gebruik te voorkomen, waaronder het Access To Opioid Medication in Europe (ATOME) project. Dit project is in 2009 gestart als een vijfjarig project gefinancierd vanuit het 7^e kaderprogramma van de Europese Unie. Het doel van dit project was het verbeteren van de toegang tot opioïden in 12 Midden- en Oost-Europese landen met statistisch bewijs van ontoereikende consumptie van opioïden per hoofd van de bevolking: Bulgarije, Cyprus, Estland, Griekenland, Hongarije, Letland, Litouwen, Polen, Servië, Slowakije, Slovenië en Turkije. Hoewel er meerdere initiatieven zijn genomen om de toegang tot opioïde geneesmiddelen te verbeteren, zijn er in de VS ook verschillende acties ondernomen om schade door niet-medisch gebruik te voorkomen. Deze acties zijn een reactie op de viervoudige toename van het gebruik van opioïde analgetica tussen 1999 en 2010, die gepaard ging met een toename van sterfgevallen door opioïdenoverdosis. Bezorgdheid over toegenomen gebruik van opioïde analgetica bestaat ook in andere hoogontwikkelde landen, waaronder Nederland.

Het doel van dit proefschrift is te onderzoeken welke factoren een negatieve invloed kunnen hebben op de toegang tot opioïde geneesmiddelen, met de nadruk op juridische en beleidsaspecten. Deze inzichten kunnen aanwijzingen geven voor het implementeren van effectieve oplossingen voor het opheffen van belemmeringen, met als uiteindelijk doel de adequate toegang tot opioïde geneesmiddelen te waarborgen.

In **hoofdstuk 2** hebben we de nationale geneesmiddelen- en drugscontrolesystemen geanalyseerd van de Midden- en Oost-Europese landen die deelnamen aan het ATOME-project. Deze analyses kunnen helpen om belemmeringen in wet- en regelgeving te vinden voor het legitieme medische gebruik van opioïde geneesmiddelen. In hoofdstuk 2.1 hebben we een *quick-scan* methode gebruikt om mogelijke belemmeringen te identificeren. Vervolgens is in hoofdstuk 2.2 een beoordelingsinstrument ontwikkeld dat we hebben gebruikt voor de systematische analyse van nationale wet- en regelgeving en identificatie van potentiële belemmeringen. Voortbouwend op de analyses in hoofdstuk 2.2 identificeerden we in hoofdstuk 2.3 specifieke potentiële belemmeringen voor patiënten met opioïdenafhankelijkheid. De meeste van deze belemmeringen hebben betrekking op het voorschrijven en terhandstellen van opioïde geneesmiddelen, met verschillen in de mate van belemmering tussen individuele landen. De *quick-scan* methode in **hoofdstuk 2.1** bleek een relatief eenvoudige methode om potentiële belemmeringen te identificeren; er werd inzicht gegeven in "quick wins" voor verbetering en er werd een goede basis geboden voor een meer diepgaande analyse. Deze diepgaande analyse werd uitgevoerd in **hoofdstuk 2.2**, waarbij in totaal 778 potentiële belemmeringen werden geïdentificeerd in elf landen, variërend van 22 potentiële belemmeringen in Cyprus tot 128 in Litouwen.

Voortbouwend op de diepgaande analyse, vonden we in **hoofdstuk 2.3** dat patiënten met opioïdenafhankelijkheid waarschijnlijk specifieke belemmeringen ondervinden om toegang te krijgen tot opioïde geneesmiddelen bovenop de belemmeringen die andere patiënten ondervinden. Van de 778 potentiële belemmeringen die werden geïdentificeerd in hoofdstuk 2.2, werden in totaal 144 belemmeringen (19%) in 10 landen (alle landen behalve Estland) geacht potentiële belemmeringen te bevatten die uitsluitend van toepassing zijn op patiënten met opioïdenafhankelijkheid. Hierbij werd het kleinste aantal gezien in Slovenië (n = 2, 7%) en het grootste aantal in Litouwen (n = 46, 36%). Voorbeelden van potentiële belemmeringen zijn leeftijdsbeperkingen, strikte toelatingscriteria, behandelkosten en strikte uitsluitingscriteria voor toegang tot zorgverlening die zich richt op het beperken van schade bij drugsgebruik. Hoofdstukken 2.1 tot 2.3 lieten ook zien dat alle onderzochte landen respectloze en stigmatiserende taal in hun wetgeving hadden, wat met name het geval was voor de taal die wordt gebruikt richting patiënten met opioïdenafhankelijkheid. Toekomstig onderzoek zou de impact van de potentieel belemmerende bepalingen op de toegang tot opioïden in de klinische praktijk moeten bestuderen.

In **hoofdstuk 3** hebben we gekeken naar andere soorten belemmeringen, naast belemmeringen die verband houden met nationale drugscontrolesystemen. In **hoofdstuk 3.1** hebben we belangrijke gemeenschappelijke uitdagingen voor de toegankelijkheid van opioïde geneesmiddelen in de ATOME-landen bestudeerd. Gemeenschappelijke belemmeringen werden geïdentificeerd in breakout-sessies door vertegenwoordigers (n = 84) van de nationale ministeries van Volksgezondheid, autoriteiten van “controlled substances”, deskundigen die regelgevende en wetshandhavinginstanties vertegenwoordigen, vooraanstaande zorgverleners en patiëntvertegenwoordigers. We vonden dat vele factoren een rol spelen bij het beperken van de adequate toegang tot opioïde geneesmiddelen. Belemmeringen bestaan op verschillende niveaus, zijn met elkaar verbonden en kunnen elkaar (deels) versterken. Gemeenschappelijke uitdagingen waren belemmeringen op het gebied van onderwijs, regelgeving, wetgeving en opleiding, die het voor zowel artsen als verpleegkundigen moeilijk maken om patiënten adequaat te behandelen met opioïden. In **hoofdstuk 3.2** hebben we de perceptie van belemmeringen op grotere schaal onderzocht door middel van vragenlijstonderzoek. Hierbij hebben we gekeken of er verschillende belemmeringen werden waargenomen, afhankelijk van de betrokken belanghebbende. In totaal hebben 199 (54%) deelnemers uit zeven landen de vragenlijst ingevuld. We ontdekten dat beleidsmakers kwesties minder vaak als grote problemen zagen in vergelijking met andere belanghebbenden. Een groot deel van de zorgverleners (44-57%) meldde bijvoorbeeld dat excessieve regulering of bureaucratie van voorschrijfprocedures een grote invloed had op de toegang tot opioïden, terwijl dit door slechts 20% van de beleidsmakers als een belangrijk probleem werd gezien.

Zorgverleners die zich richten op het beperken van gezondheidsschade bij drugsgebruik hadden het meest last van de regelgeving. In **hoofdstuk 3.3** bespraken we de uitdagingen voor overheden, gezondheidsautoriteiten en zorgverleners om de toegang tot opioïden voor patiënten met een legitieme medische noodzaak te waarborgen en tevens strategieën te implementeren die gericht zijn op het voorkomen van niet-medisch gebruik van opioïden. Hoewel beide doelstellingen belangrijk zijn, lijkt het voorkomen van niet-medische gebruik van opioïden in discussies voorrang te krijgen boven het voorkomen van onderbehandeling van pijn. Nauwlettende monitoring van nationale drugscontrolemaatregelen, die worden ingevoerd om het niet-medisch gebruik van opioïden te bestrijden, lijkt cruciaal om de kans op onbedoelde gevolgen te minimaliseren voor patiënten die deze geneesmiddelen vanuit medisch oogpunt nodig hebben. Dit is met name belangrijk voor patiënten met (een geschiedenis van) opioïdenafhankelijkheid, aangezien deze groep een bijzonder kwetsbare populatie vertegenwoordigt.

In **hoofdstuk 4** werd de toegang tot opioïde geneesmiddelen in de klinische praktijk gepositioneerd in de context van verschillende soorten belemmeringen. In **hoofdstuk 4.1** zijn verschillen geëvalueerd in de mediane voorgeschreven hoeveelheid (uitgedrukt in DDD's per 1 000 personen in 2015) per praktijk in de twaalf provincies van Nederland voor de belangrijkste sterkwerkende opioïde analgetica. Daarnaast werd variatie in het voorschrijven van sterkwerkende opioïden voor niet-kankerpijn onderzocht. We vonden een 2,2-voudige variatie in de mediane voorgeschreven hoeveelheid oxycodon en fentanyl per praktijk tussen de provincies. Er werd een 4,6-voudige variatie waargenomen voor morfine, met de laagste mediane voorgeschreven hoeveelheid in Utrecht en de hoogste in Groningen. Het merendeel van de huisartspraktijken liet een relatief laag voorgeschreven volume opioïden zien, ondanks een relatief hoog gebruik bij niet-kankerpijn. We vonden geen lineaire correlatie tussen de hoeveelheid voorgeschreven sterkwerkende opioïde analgetica en de relatieve hoeveelheid die is voorgeschreven voor niet-kankerpijn. Daarmee is er geen bewijs dat suggereert dat het voorschrijven van hoge volumes opioïden uitsluitend zou worden bepaald door preferentieel gebruik van opioïden voor niet-kankerpijn. Een belangrijke beperking van onze studie is dat we niet hebben gecorrigeerd voor populatiekenmerken, wat een verklaring kan zijn voor de variatie en het gebrek aan correlatie. Toekomstige analyses kunnen variatie in het voorschrijven van opioïden verder evalueren, en factoren onderzoeken die de potentiële variatie verklaren. Hierbij dient rekening te worden gehouden met kenmerken op huisartsenpraktijkniveau en op patiëntniveau.

In **hoofdstuk 4.2** onderzochten we hoe een periode van intense media-aandacht na een opioïde gerelateerde tragedie invloed had op het voorschrijven van sterkwerkende opioïde analgetica in de eerste lijn in Nederland. We vonden dat de media-aandacht niet leidde tot

een meer terughoudend voorschrijfgedrag bij huisartsen. Een mogelijke verklaring voor dit resultaat is te vinden in het specifieke onderwerp dat door de media werd behandeld; in de overgrote meerderheid van andere studies rapporteerde de media over risico's van bepaalde soorten medicatie terwijl in het huidige onderzoek het gedrag van de autoriteiten onderwerp van discussie was. Aangezien in hoofdstuk 4.2 is gekeken naar veranderingen in het voorschrijfgedrag van sterkwerkende opioïde analgetica in het algemeen, en niet is gekeken naar het voorschrijfgedrag binnen de palliatieve zorg, zou toekomstig onderzoek specifiek gericht kunnen zijn op veranderingen in voorschrijftrends van geneesmiddelen die worden toegepast in de palliatieve zorg. In **hoofdstuk 4.3** evalueerden we de correlatie tussen toegang tot opioïde analgetica en potentiële belemmeringen in wet- en regelgeving door twee variabelen tegenover elkaar te stellen voor elf Midden- en Oost-Europese landen: het niveau van toegang tot opioïde analgetica geschat door de "Adequacy of Consumption Measure" (ACM) en het aantal potentiële belemmeringen in wet- en regelgeving zoals geïdentificeerd in hoofdstuk 2.2. Hoewel we hadden verwacht dat het niveau van toegang tot opioïde analgetica zou dalen naarmate het aantal potentiële belemmeringen in nationale wet- en regelgeving zou toenemen en vice versa, kon deze mogelijke correlatie niet worden bevestigd. Blijkbaar zijn er andere factoren die een cruciale rol kunnen spelen en patiënten de toegang tot essentiële pijnbestrijding kunnen onthouden. Toekomstig onderzoek is nodig om een mogelijke correlatie tussen daadwerkelijke toegang en verschillende soorten belemmeringen op grotere schaal te evalueren. De beperkte omvang van onze steekproefgrootte kan er namelijk toe hebben geleid dat het onderzoek onvoldoende power heeft om significante verschillen tussen landen te identificeren.

Hoofdstuk 5 plaatst de hierboven beschreven studies in een breder perspectief, waarbij beleidsaanbevelingen zijn gedaan ter verbetering van de adequate toegang tot opioïden. De individuele onderzoeken in dit proefschrift lieten zien dat verschillende belemmeringen bij de adequate toegang tot opioïden zijn geïdentificeerd. Vanuit een juridisch perspectief identificeerden we *potentiële* belemmeringen door middel van een analyse van wet- en regelgeving. Vanuit een beleidsperspectief werden verschillende belemmeringen *vanuit de praktijk* gerapporteerd door relevante belanghebbenden. Deze belemmeringen komen voor op verschillende niveaus, en er is heel weinig bekend over het complexe samenspel van deze en andere factoren die de adequate toegang tot opioïden bepalen. We stelden dat benaderingen, die gericht zijn op het verbeteren van de adequate toegang tot opioïden, mogelijk niet het gewenste effect hebben tenzij alle individuele factoren die de toegang beperken worden aangepakt. Als gevolg hiervan blijft het voor overheden en beleidsmakers moeilijk om effectieve en breed gedragen oplossingen te ontwikkelen om beide problemen tegelijkertijd aan te pakken: het inadequate gebruik van opioïden en de onderbehandeling

van pijn en opioïdenafhankelijkheid met essentiële opioïde geneesmiddelen. Met de recente verschuiving in aandacht voor de preventie van niet-medisch gebruik en de illegale handel, staat de vooruitgang die in het verleden is geboekt om te komen tot een betere balans in de nationale drugscontrolesystemen onder druk. Het is daarom cruciaal om te focussen op de vraag hoe opioïde geneesmiddelen op een verantwoorde manier voor patiënten toegankelijk kunnen zijn, zonder stigmatisering van legitiem medisch opioïdengebruik. We stellen een aanpak voor waarbij overduidelijke belemmeringen voor een adequate toegang in wet- en regelgeving worden verwijderd indien zij geen bijdrage leveren aan de preventie van niet-medisch gebruik en de illegale handel. Daarnaast stellen we voor dat behandelrichtlijnen en beleid worden opgesteld die het verantwoorde en adequate voorschrijven van opioïden bevorderen op basis van solide wetenschappelijke gegevens, die de risicofactoren weerspiegelen die samenhangen met de ontwikkeling van opioïdenafhankelijkheid. Dit zou vergezeld moeten gaan met het opleiden van zorgverleners, patiënten en beleidsmakers om het verantwoorde en rationele gebruik te stimuleren en de stigmatisering van legitiem opioïdengebruik te voorkomen. Ten slotte is het belangrijk dat een evenwichtiger beeld wordt gepresenteerd in de media en in de wetenschappelijke literatuur. Met dit proefschrift wilden we bijdragen aan een beter begrip van de verschillende soorten belemmeringen vanuit een juridisch en beleidsoogpunt, om de adequate toegang tot opioïde geneesmiddelen te verbeteren voor patiënten die deze middelen nodig hebben.



CHAPTER 7

ADDENDUM





CHAPTER 7.1

DANKWOORD



DANKWOORD

Met veel plezier heb ik de afgelopen jaren aan dit proefschrift gewerkt. Tijdens deze periode heb ik me niet alleen mogen verdiepen in een onderwerp dat me na aan het hart ligt, maar ook mogen samenwerken met geweldige collega-onderzoekers. Graag dank ik iedereen die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Een aantal personen wil ik in het bijzonder bedanken.

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CHAPTER 7.2

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CHAPTER 7.3

LIST OF PUBLICATIONS



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CHAPTER 7.4

ABOUT THE AUTHOR



ABOUT THE AUTHOR

Marjolein Josephine Margarethe Vranken was born on December 18th, 1979 in Brunssum. She studied pharmacy (MSc, PharmD 2008) and law (LLB 2007, LLM in Private Law 2012) at Utrecht University, the Netherlands. As part of her master pharmacy study, she completed a research internship on access to expensive medicines in the Netherlands at the Association Innovative Medicines (Vereniging Innovatieve Geneesmiddelen). Her master thesis in private law discussed access to opioid medicines in the Netherlands.

After graduating as a pharmacist, Marjolein worked in two community pharmacies in 2008 (Wilhelmina Apotheek and Apotheek van Keule, Utrecht) and in a hospital pharmacy from 2009-2012 (Diakonessenhuis, Utrecht).

From 2011 to 2014 she worked as a junior researcher on the European Union Seventh Framework Programme funded project “Access To Opioid Medication in Europe (ATOME)” at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Science of Utrecht University. The work conducted as a part of the ATOME project provided the basis for the studies presented in this thesis and has been supervised by prof. dr. A.K. Mantel-Teeuwisse, prof. dr. H.G.M. Leufkens and mr. dr. M.D.B. Schutjens.

Since June 2013 she has been working at Novartis Pharma in Arnhem.

