Barriers to access to opioid medicines: a review of national legislation and regulations of 11 central and eastern European countries

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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.

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Introduction

Opioid analgesics are essential for the treatment of moderate to severe cancer pain.[1] 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.

See Online for appendix

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 legislation[28] 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), and 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.

	Potential barrier	Related WHO policy guideline	Examples identified in legislation
Authorisation to prescribe is restricted	A potential barrier if the competence (ie, after being trained) to prescribe controlled medicines is restricted to a limited number of medical specialists (eg, oncologists only) and other appropriately trained and qualified physicians are not authorised to prescribe controlled medicines	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	A potential barrier if only designated institutions are allowed to prescribe controlled medicines or if a special permit or license is needed for prescribing controlled medicines, in particular if the application procedure is complex and if high fees apply to applicants	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	A potential barrier if special forms or multiple copies are needed, particularly, if these special prescription forms are not readily available or are not free of charge or entail many administrative requirements for health-care professionals, or all of the above, particularly if unintended violation of these administrative requirements results in severe sanctions	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 127×158 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	A potential barrier if patients in need of controlled medicines, especially patients with chronic disorders, have to visit the physician and pharmacy frequently, particularly if additional rules aggravating the effect apply, such as rules that limit the total amount of controlled medicine to be prescribed	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	A potential barrier if patients who need medical treatment with controlled medicines for a longer period have to visit the physician and pharmacy frequently, particularly if, in addition to this potential barrier, the validity of a medical prescription for controlled medicines is restricted	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]
Daily dosage is limited	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	Guideline 11	"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]
No clear distinction between medical use and illicit use or misuse	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	Guideline 10	"Preventive measures (…) in order to reduce the supply of narcotic and psychotropic substances (…)"[39] "(…) when the use of narcotic and psychotropic substances was the main reason causing death"[40]
Incorrect definitions of all terms are used	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	Guideline 10	"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]
Unclear language is used	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	Guideline 10	"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]
Controlled medicines are referred to as dangerous, toxic, or addictive drugs	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	Guideline 10	"For medical products, containing intoxicating substances, the packing must be marked diagonally by two red strips (…)"[43]

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

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 (κ=0·87).

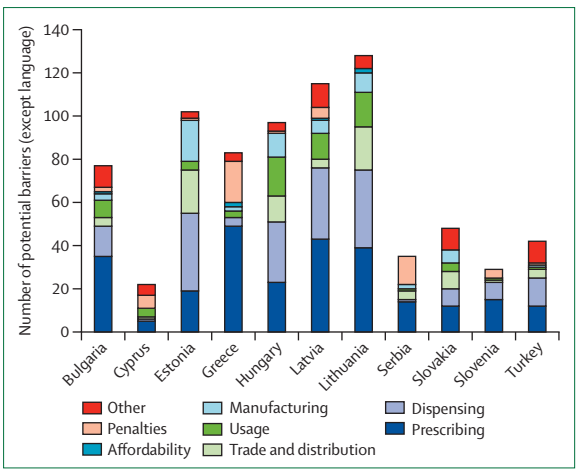

Figure 1: **Number of potential barriers quantitatively identified according to category (except language) per country**

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.

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

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,

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**

*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 health-care 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.


Item
Bulgaria
Cyprus
Estonia
Greece
Hungary
Latvia
Lithuania
Serbia
Slovakia
Slovenia
Turkey
Affordability
Prescribing
Authorisation to prescribe is restricted
Permit/licence required for prescribing
Special prescription forms required
Multiple copies required
Limited prescription validity
Amount of controlled medicine to be prescribed is limited
Daily dosage is limited
Prescribing of (designated) controlled medicines is limited
Administrative requirements for prescribing*
Amount of controlled medicine to be prescribed is limited to complete package units
Patient supervision requirements for prescriber
Dispensing
Limitations on dispensing privileges: special licence needed
Limitations on dispensing privileges: special licence pharmacy/designated pharmacies
Limitations on the dispensing of (designated) controlled medicines
Administrative requirements for dispensing
Requirements for storage (dispensing)
Delivery restrictions of controlled medicines
Limited prescriptions validity (dispensing)
Amount of controlled medicine to be dispensed is limited
Dispensing in emergency situations/correction of small errors restricted
Usage
Possession of controlled medicines by patients restricted
Geographical restrictions
Continuation of treatment restricted
Access to pain treatment for HIV patients or patients with (a history of) dependence
Strict requirements for accessing dependence treatment
Administrative requirements for receiving controlled medicines
Limitations for specific patient groups
Possession of utensils
Trade and distribution
Requirements for storage (trade and distribution)†
Administrative requirements for trade and distribution‡
Requirements for transportation§
Trade and distribution limited to designated parties
Manufacturing
Requirements for storage (manufacturing)¶
Administrative requirements for manufacturing||
Costs of controlled medicines**
Penalties
Punitive sanctions for health-care professionals
Punitive sanctions (other)
Punitive sanctions for patients
Punitive sanctions for people involved in manufacturing/trade and distribution
Other
Medical activities restricted††
Violation of privacy
Requirements for the destruction of controlled medicines‡‡
Storage requirements (other)§§
Administrative requirements (other)
Limited access to education
No potential barriers identified
1–5 potential barriers identified
6–10 potential barriers identified
11–15 potential barriers identified
16–20 potential barriers identified
≥21 potential barriers identified

	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, methylphenidate, 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
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

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

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

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).

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.

Discussion

The reviewed national legislation and regulations contain many potential barriers to access to opioid medicines that are indispensable for the management of cancer

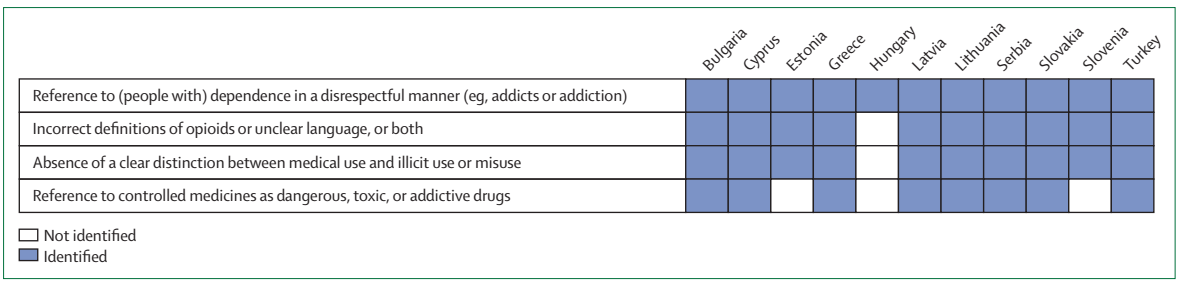

Figure 3: **Potential barriers in the legislation and regulations of controlled medicines per country (language category only)**

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 colleagues[29] 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 colleagues[29] 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

Search strategy and selection criteria

We searched PubMed and Google Scholar for relevant articles published in English. We used the following keywords in titles or abstracts: "barriers" OR "impediment(s)" combined with the search terms "legislation", OR "legal", OR "regulation(s)" AND "opioids", OR "opioid medicines", OR "opioid analgesic(s)", OR "narcotic drug(s)". The search was not limited to year of publication. The relevance of the publications was established by a preliminary review of the abstracts. The reference list of relevant documents were also searched to identify additional applicable publications.

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 health-care 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.

Contributors

WS conceived the idea for the study and WS, LR, SJ, and SP developed the concept. MJMV, M-HDBS, and AKM-T designed the study. MJMV obtained the data. MJMV, M-HDBS, and JAL analysed the data. AKM-T, MJMV, M-HDBS, and JAL interpreted the data. WS, LR, SJ, AKM-T, M-HDBS, JAL, and MJMV contributed to the data validation. MJMV, AKM-T, and M-HDBS drafted and finalised the report. All authors critically reviewed the manuscript, and provided final approval for submission.

Declaration of interests

We declare no competing interests.

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