

HØST 2016



**ANTIBIOTICS AS CONTROLLED MEDICINES
– AN ASSESSMENT**

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List of abbreviations

WHO – World Health Organization

INCB – International Narcotics Control Board

AMR – Antimicrobial resistance

Single convention – The Single convention on Narcotic Drugs 1961

UN – United Nations

TB – Tuberculosis

LMIC – Low and middle income countries

DDD – Defined Daily Dose

EU – European Union

ANVISA – The national health surveillance agency authorizes controlled medicines

QR – Quick Response

Art. – Article

SUMMARY

The global public health threat of antibiotic resistance has called for measures to ensure rational use of antibiotics. While new and critical antibiotics need to be conserved to prevent the development of antibiotic resistance, these medicines must also be accessible for those in need. It has been suggested that a binding international treaty similar to the Single Convention on Narcotic Drugs can be valuable for antibiotics.

The aim of the Single Convention on Narcotic Drugs is to achieve a balanced policy; prevent drug abuse and sustain availability for medical purposes. Every country reports to an international control board on their annual consumption data and estimates for the coming year. All imports and exports of opioids for medical use must follow a stringent set of licensing requirements. Moreover, governments around the world have implemented additional policies and laws to prevent misuse of opioids, resulting in extra control measures on top of those required under the treaty.

The aim of my thesis is to identify interventions that promote and barriers of a balanced policy for Opioids and discuss if these can be transferrable to regulation of antibiotics. This thesis used an explorative research design based on qualitative interviews and a literature review.

Based on my findings, I believe that an international convention similar to the Single Convention may be too stringent for antibiotics and exacerbate the already challenging access situation in many low and middle income countries. However, an agreement for selected “critical” antibiotics may be beneficial, adapting certain elements from the Single Convention, like a classification system, special prescription forms and monitoring systems. Also, many of the national measures implemented for opioids can be applicable for the regulation of antibiotic use. Especially education and training have been essential to achieve a balanced approach where rational use of controlled substances is achieved, which is also transferrable to antibiotics.

INTRODUCTION

Antibiotic resistance

Antibiotic resistance is a global public health concern. The existing antibiotics on the market are becoming less effective which threatens our ability to treat common infections. This results in a higher burden of diseases through prolonged illness, higher health care expenditure and greater mortality. Resistant strains occur as a result of defective replication or exchange of resistant traits between microorganisms, hastened by overconsumption and inappropriate use (1, 2). In addition to the increasing resistance lack of new antibiotics in the research and development pipeline poses a major threat. Governance is needed across states and societies, but policies and regulation must be able to address both excessive and inadequate access at the same time (3).

Antimicrobial drugs are medicines against infections caused by bacteria (antibiotics), viruses (antivirals), fungi (antifungals) and parasites (including antimalarials). When these microorganisms develop the ability to survive exposure to antimicrobial drugs, amr arises. WHO estimates that nearly 700,000 deaths are caused by antimicrobial resistance annually while about 5,7 million die due to lack of access to existing antibiotics (4). The number of deaths caused due to Antimicrobial resistance is predicted to increase 10 millions by year 2050 unless we take action now (5, 6). To combat the increasing morbidity and mortality responsible use must be ensured, where the dual aspects are addressed in policy making. Most literature on antibiotic stewardship is based on studies from high income countries where common examples of measures are prevention of infectious disease, efforts to improve disease control, education of both health personnel and the general population, promotion of behavioral change and incentivizing good prescription practices (7-9). While many of these efforts scientifically have improved rational use, these stewardship programmes can be more complex to implement in many low and middle income countries. Challenges vary depending on the health care system, over-counter sales, infrastructure, government commitment and the financial stability in a country. Interventions therefore must be adjusted accordingly (4, 10).

An example that illustrates the extent of antibiotic resistance is Colistin that belongs to the Polymyxin family and is a “last resort” antibiotic meaning it is the last line of defence against resistant bacterial infections. Colistin is an antibiotic primarily used for gram-negative bacterial infections, among them *Enterobacteriaceae*. Colistin resistance can be caused by mutations, but the resistance has been unstable and not capable of spreading to other bacteria. A major increase of colistin resistance was observed in animal foods, in a recent surveillance project on antibiotic resistance in China. They found that an *E Coli* strain that possessed colistin resistance could transfer this to another strain horizontally by plasmid mediation (i.e., spread from cell to cell). The plasmid carrying MCR1 gene has also maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. The MCR1 gene in *E Coli* was isolated from 21% of animals, 15% raw meat and 1% of patients with infection (11). This threat has become

global and findings in the study call for urgent action. Colistin is one of the most recent examples of the urgency of antibiotic resistance, and with few new antibiotics agents against gram-negative bacteria in the pipeline, stewardship is crucial.

With the complexity of antibiotic resistance many experts have suggested that antibiotics, especially the last resort and novel antibiotics, should be under international regulation like the model of controlled medicines(12, 13). Common for both antibiotics and controlled medicines is the need for duality, i.e., a balanced approach is needed to ensure both control to prevent abuse and access where medically appropriate. Opioids are the most commonly misused prescription drugs causing a growing concern in some countries (14). However, global and national efforts made to prevent opioid dependency have resulted in lack of access to analgesics for medical use(15). Restricted availability of analgesics has been a major challenge the last two decades. Today approximately 80% of the world's population lack or have no access to controlled medicines (16). Opioid unavailability leads to avoidable suffering and pain. Numbers from the Global Commission on Drug Policy state that more than 150 countries had little or no access as of 2014. Untreated chronic pain leads to reduced quality of life including conditions like sleeping disorders, depression, impaired activity, mood alterations, abnormal appetite, inability to focus, poor hygiene and decreased economic development (16).

Governance and policy for control of antibiotics are now being debated in national and international governing agencies. The lessons from the Opioid control policy might be valuable.

CONTROLLED SUBSTANCES

Impact and historical context of controlled substances

Opioids like morphine are regulated by both national provisions and laws as well as international treaties. As a response to the Chinese Opium endemic (17), the International Opium Commission was established in 1909 and held the first international conference on drug control to address the complex issue collectively. The outcome of the conference was the first international convention on controlled substances in 1912, The Hague International Opium Convention. The goal was to prevent abuse by controlling the drugs through regulations on production, use, trade, distribution, import and export of opium. In 1961 the Single Convention on Narcotic Drugs, hereafter referred to as the Single Convention, administered by The United Nations codified all existing international drug control treaties. The Single Convention had two main objectives: to limit abuse or misuse of controlled substances implementing provisions targeting every step in the chain from cultivation of the plants to trafficking of drugs and to ensure access for medical and scientific purposes. This milestone was followed by the establishment of the International Narcotics Control Board in

1968 (18, 19) .The Single Convention is vital in the history of drug control, the first to recognize the previously neglected issue of availability of opioids for medical and scientific purposes in addition to preventing harmful drug dependency. Ensuring access is an obligation for all states under the Single Convention . According to Article 9 “*states are responsible for ensuring availability for licit purposes, and gives the board mandate to monitor the availability*”(20).

The Single Convention was responsive to the growing misuse and dependency issue. Additionally, governments implemented stricter regulations than required under the international convention (21).

International regulation

Estimates of annual need, introduced by the 1931 convention are often mentioned as an essential part of the control system. Governments are obligated to submit annual estimates of their drug requirements and statistical returns on the production, manufacture, use, consumption, import, export, and stocks of drugs to the International Narcotics Control Board (INCB). INCB has fixed dates by when the estimate forms must be filled out by member states. The forms must include quantities of drugs estimated to be consumed for medical and scientific purposes the following year, utilized for the manufacture of other medicines, stocks of narcotic drugs at 31 December of each year, and location of land to be used for the cultivation of the opium poppy. The estimates also include the approximate quantity of opium to be produced, number of industrial establishments manufacturing controlled medicines and quantities of controlled medicines to be manufactured(22).

The import certification system created by the 1925 Geneva Convention required parties to license all manufacturers, traders and distributors. All transactions involving drugs have to be documented. All import and export of drugs except those carried out by a state enterprise have to be authorized. Every party permitting the import or export of drugs require a separate import or export authorization. Before issuing an export authorization parties shall require an import certificate, issued by competent authorities of the importing country or territory.

The production, trade and distribution of controlled medicines are licensed and supervised except where such trade or distribution is carried out by a state enterprise. The production of opium by any country or territory shall be organized and controlled in such manner that it ensures that the quantity produced in one year does not exceed the estimate of opium to be produced.

If the need exceeds the estimates the governments must submit adjusted annual estimates to INCB, until then they will not get authorization to import or to manufacture. Many countries have to adjust estimates during the year. If INCB by the end of the year finds that the

quantities of manufactured and imported narcotics exceeded the annual estimates, these shall be deducted from the quantity to be manufactured and imported from the total estimates the following year. The exporting countries shall not sell more than the annual national estimates allow (22).

ACCESS AND EQUITY

The treaty, together with the national measures implemented, has been significantly effective in preventing drug dependency through control measures on every level in the supply chain as well as strict penalties. Yet, it has also unintentionally hindered the other objective of the treaty (23). It estimated that 5,5 billion people have little or no availability to treatment of moderate to severe pain.(20) (24) The gap between medical need and access to controlled pain medication is biggest in low and middle-income countries. Since 1986 the consumption of morphine has increased significantly, but this rise is mainly seen in high income countries. It is estimated that 15% of the world's population are consuming 94% of the global morphine supply. The data illustrates a significant inequity in the access to morphine (25) (15).

However, a handful of wealthy countries are struggling with the opposite problem; opioid misuse and dependency. For example, in the United States opioid addiction is a growing epidemic with 18 893 deaths annually due to overdoses related to the prescription of pain relievers (26).

Analgesics for pain relief like morphine are controlled medicines on the WHO's Model list of essential medicines. In 2011 the WHO developed a set of guidelines for member states to be able to best promote access to controlled medicines through balanced policy (18).

Box 1 The principle of balance, from “WHO National guidelines on controlled medicines”

“The central principle of “balance” represents a dual obligation of governments to establish a system of control that ensures the adequate availability of controlled substances for medical and scientific purposes, while simultaneously preventing abuse, diversion and trafficking. Many controlled medicines are essential medicines and are absolutely necessary for the relief of pain, treatment of illness and the prevention of premature death. To ensure the rational use of these medicines, governments should both enable and empower healthcare professionals to prescribe, dispense and administer them according to the individual medical needs of patients, ensuring that a sufficient supply is available to meet those needs. While misuse of controlled substances poses a risk to society, the system of control is not intended to be a barrier to their availability for medical and scientific purposes, nor interfere in their legitimate medical use for patient care “(18).

Ketamine is an anesthetic drug used widely in low and middle income countries. The drug makes it possible to provide access to safe surgery in resource poor areas. China has pushed for international control of ketamine due to concerns of misuse. Major concern has been raised about a human rights and public health crisis in resource poor settings where ketamine is the only safe anesthetic. Experts have recommended against international control of ketamine with the argument that it would limit access to safe surgery (27).

OBJECTIVES

This thesis aims to identify balanced policies and best practices that promote access to controlled substances for medical use in different countries; and to identify patterns of access barriers, successful mechanisms, and interventions used to promote rational use of opioids transferrable to stewardship of antibiotics.

METHODS

The thesis used an explorative research approach, consisting of both a literature review and qualitative interviews.

Literature review

Search strategy and selection criteria

I searched for published articles in English using the keywords (“Controlled medicines” or Controlled substances or opioids”) and (“medical use” or “medical purpose”) and (“access” or “availability”) and (“regulation” or “policy” or “balanced policy” or “balanced regulation” or legislation) and (“consumption”) in multiple combinations on Pubmed. Medical Subject Heading (MeSH) terms were used for the keywords above. Studies were selected by reading the abstracts of the articles identified through the searches.

I included 33 scientific papers, in addition I also used reports. I have also used websites like WHO website, INCB website, and Pain Policy website.

Excluded studies: Opinion papers, and chronicles were excluded.

Morphine Equivalence minus methadone is the measurement I have used for consumption in the thesis. It is measured in milligrams and adjusted for population, the numbers represent consumption of Fentanyl, Hydromorphone, Morphine, Oxycodone, and Pethidine. By excluding Methadone we can eliminate Opioids used for medication-assisted treatment of opioid dependence and get a better illustration of the country’s consumption for pain management (28).

Interviews

A selection of countries to be interviewed was made on the criteria below.

Box 2: Selection criteria

1. Low, middle and high-income countries are represented
2. If possible the selection should be from different consumption groups (low, moderate and high)
3. The country should have comprehensive pain control and palliative care are embedded into health systems or (if LIC : developing national oral morphine-production programmes)
4. The person interviewed should be or have been involved in the regulation process of controlled medicines with experience or specialized knowledge in the field of controlled medicines

Of the 17 countries contacted I was able to schedule an interview with seven interviewees representing Brazil, Finland, India, Norway, Mexico, Singapore, and Uganda. Our interviewees were government officials, non-governmental organization representatives or private company representatives. In addition I interviewed one expert with an affiliation to an UN agency.

The interviews were semi-structured covering three main areas; the country's consumption, governance, and barriers and best practices or successful intervention to a balanced approach. The interview guide, which was adjusted according to the interviewee, can be found in annex 1.

Snowballing

Snowballing was used to identify literature as well as interviewees. References were backward chased from footnotes in reports and articles published by agencies including The International Narcotics Control Board (INCB), World Health Organization, ATOME and The Global Commission on Drugs.

RESULTS

The results in this thesis are structured by barriers to a balanced policy and interventions deemed successful by interviewees, strengthened by findings from the literature. Barriers to achieve a balanced policy identified through interviews, categorized into 5 types of barriers (Table 1, see below).

The interventions found were categorized into seven types (see Table 2). Within each type of intervention I have listed the specific interventions mentioned. Lastly I listed all the countries that mentioned this type as a successful intervention. The countries listed have not necessarily implemented all the specific interventions listed, but have implemented one or more of these.

For example, although all the countries mentioned prescription rights as a successful intervention, Uganda was the only one who mentioned implementing the specific intervention “extension of prescription rights to trained health workers”.

Barriers

Table 1: Barriers to balanced policies identified by interviewees

TYPE	BARRIERS	COUNTRIES
Accessibility	<ol style="list-style-type: none"> 1. Opioids accessed only in secondary and tertiary care 2. Opioids stocked/dispensed in some pharmacies and hospitals 3. Some specialist have prescription rights 4. Lack of trained health workers 5. Lack of hospitals/pharmacies in regions 	Brazil Mexico Singapore Uganda
Stigma	<ol style="list-style-type: none"> 1. Stigmatized to use opioids as medication 2. Fear of prescribing 3. Perceptions and attitudes 	India Norway Mexico Singapore Uganda
Lack of education and training	<ol style="list-style-type: none"> 1. Little or no training in pain management 2. Palliative care not apart of medical curriculum 3. Access is not recognized as a problem 	India Mexico Singapore Uganda
National legislation	<ol style="list-style-type: none"> 1. Strict legislation 2. Multiple licenses required to prescribe 3. Authorization from multiple agencies to dispense, import or export 4. Restricted rights to supply 	Brazil India Singapore Uganda
Regulatory barriers	<ol style="list-style-type: none"> 1. No standard way to measure access to opioids 2. Quanta /estimates 3. Supplier can only sell to selected doctors 4. Few licensed to manufacture nationally 5. Strict regulations on stocking and dispensing 6. Special prescription class 7. Special forms 8. Extra administrative measures 9. Border control 	Brazil Norway India Singapore

Accessibility

The lowest consumption per capita is in Afghanistan with 0.0048 mg/capita. Austria has the highest consumption with 485.83mg/capita(28). While a country's economic state might explain parts of the availability issue, countries like Kuwait, Qatar, Singapore, Finland, and Portugal are examples of wealthy nations with relatively low consumption (28). Other factors like poor training of clinicians, international drug control treaties, weak healthcare systems, cultural attitudes to pain and national restrictions are known barriers contributing to limited access to palliative care.

Accessibility was identified as a barrier mainly in low and middle income countries (see Table 1). In some countries opioids are only dispensed in specific pharmacies and/or prescribed only by some specialists. Also, long distances between pharmacies, stock-outs and lack of hospitals in rural areas are some of the obstacles to access opioids mentioned by our interviewees. Although opioids aren't expensive in most countries, the travel to the hospital and the pharmacy can be an expense for many patients. In some LMICs additional taxes are added to the price of morphine, for example in countries like Philippines the price of morphine can equal a month's salary for some (18).

Stigma

All the interviewees addressed stigma and fear in the society as an obstacle for opioid use (see Table 1). Also, fear among doctors to prescribe opioids was mentioned as a known barrier. The negative perceptions and attitudes towards the use of opioids for medical purposes were mentioned to be a result of the strict regulation of controlled medicines and the lack of awareness in the population. For many patients the stigma in the society or the fear of developing dependency becomes an obstacle to seeking healthcare. Yet the limited research that exists shows that only 0.43 % of the patients treated with morphine misused their medicines, and only 0,05 % developed dependence(18).

Some of the national control measures implemented to control the use of opioids have contributed to the stigma surrounding opioid use. For example, in Georgia the pharmacies dispensing opioids are based in police stations. This is socially stigmatizing and a barrier to accessing the required treatment (18).

Misperceptions and stigma among patients and societies were found to be a bigger barrier in some countries. For example, in Singapore stigma has been a major concern contributing to the low accessibility of opioids according to our interviewee, while in Norway it can only explain small geographical variations within the country without causing any actual obstacle for accessing opioids.

Lack of education and training

Lack of training and education is an acknowledged barrier for access to opioids. In India, where opioids have been over-regulated for a long time, most physicians have barely prescribed opioids after the act of 1985, and training in pain management has been limited. However, India has the last few years developed innovative education and training programs to improve access to opioids for medical use in the country, though it is too early to say anything about the actual impact (29).

A study looking at twelve eastern European countries found that nine of the twelve countries had inadequate training of physicians in pain management. Furthermore, doctors in five countries lacked recognition of pain management for chronic pain and other non-oncological pain. Also, lack of knowledge caused misperceptions and fear of consumption among patients, their family, and society this was found in seven of the twelve countries (23).

Our expert interviewee addressed weak medical curriculum on pain management as a challenge to secure availability. In our interview he mentioned lack of education in particular as a barrier to opioid access in East Europe, which is also strengthened by findings from the literature(30). An ATOME study found that in Eastern Europe medical students only have 3-5 hours of education and training in pain management whereas veterinarians receive 35 hours. (31)

National legislation

As shown in Table 1 licensing has been found to be a barrier in several countries. Licenses are required to supply, stock, manufacture, import and export controlled medicines under the Single Convention. Many countries have implemented additional requirements to those required by the Single Convention. In some countries such as Singapore licenses are limited to a few manufacturers so the government can maintain control. Furthermore, in Singapore opioids can't be sold to primary care facilities, only to special doctors and hospitals. In India there are strict restrictions related to the stocking and dispensing of opioids - requiring special licenses and governmental investigations. This led to fear among many pharmacies and hospitals with the consequence that many stopped stocking morphine (32). In Brazil «ANVISA» the national health surveillance agency authorizes controlled medicines generally, but for a list of twenty drugs an additional authorization is needed from the police, morphine is not one of these.

In India the 1985 Narcotic Drugs and Psychotropic Substances (NDPS) Act, caused a strict regulation on opioid consumption, with punitive legislations against misuse. The country's average opioid consumption per capita was 0,24 mg per 2013, lowest in the region, despite

that India exports 90 percent of the opium produced in the country (28). As a result of major international concern a new central government act passed in 2014 and is currently under implementation. The drug regulation has been shifted from state regulation to a national drug control. The model is inspired by the Kerala state-system, which has managed to secure access to palliative care through balanced policy for years (33).

Kerala, the southern state has been the host of 75% of the palliative care centers in India. The state is one of the few Indian states that are flexible in regulation of controlled medicines for the purpose of palliative and end-of-life care. The model used in Kerala has been a huge success. Knowledge and experience from Kerala have served as an example to improve palliative and end-of-life care across the country (32).

The 2014 national act made it possible to transport opioids from state to state, which was strictly forbidden under previous regulations.(33) Special licenses were required for a physician to prescribe opioids previously, in some states duplicate or triplicate prescriptions were required in addition to special forms that the physician had to buy. These prescriptions could often be valid for only a few days, and only selected pharmacies could dispense the opioids. The strict regulation led to stigma and fear of stocking and prescribing opioids, many pharmacies didn't have the drugs in stock. These are some examples of the regulations that can partly explain the low consumption rate in India for a long time (32). Although it was allowed to prescribe opioids for medical use most clinicians became hesitant to prescribe morphine.

Armenia with the strictest regulation regimes for opioids in Europe, had limited the access to patients only diagnosed with cancer, which must be confirmed by biopsy. Only injectable morphine was available and all prescriptions had to be issued with the agreement of a standing committee who had to see the patient in their own home. The prescription requires stamps from four different agencies and the patient would often be able to collect opioids for 24-48 hours. All the information of the patient had to be shared with the police (18).

The findings from the interviews and literature suggest that strict legislation has been a major barrier for access to opioids for medical use. Though it is widely agreed on that regulatory mechanisms are necessary to prevent abuse and misuse of opioids, strict legislation and regulation have caused stigma both in the population and among prescribing health workers. Many countries have criminalized the use and possession of illicit opioid, governments promoting the drugs as “dangerous” with restrictions on dispense and prescription creates fear among patient, clinicians and family. Complex national prescription rules leads to fear of prescribing among physicians.

Regulatory barriers

The consumption of opioids varies a lot from country to country. Government officials have in the interviews especially mentioned regulatory barriers as an important factor causing these differences; factors like strict licensing, restricted rights to prescribe and rights to dispense have limited consumption in certain countries. India, as mentioned above, is an example of a country where strict state regulation has caused a barrier to access. In other cases the differences between countries can be explained by poor monitoring systems. It can according to our interviewee also be a result of different reimbursement mechanisms.

Denmark and Finland are comparable countries with strong health care systems, well trained clinicians and stable economies. Despite the similarities the countries have varying consumption rates. According to 2013 data from INCB 131 mg/capita opioids were consumed in Finland and 455 mg/capita in Denmark being the highest consumption in Scandinavia (28). This difference might be explained by varying cultural understanding of pain, attitudes in the society or due to the incidence of cancer and other terminal diseases. For example Denmark has the highest incidence of cancer 338,1 per 100000 while in Finland the incidence is 256,8 per 100000 (34).

A standardized way of measuring access to opioids is missing (see Table 1). Even though INCB mentions that everything below 200 Defined Daily Dose (DDD) as inadequate in their report, the INCB does not establish a real level for adequacy. Our expert interviewee thinks it is inappropriate of an authoritative body like INCB to enforce such a level. He also emphasized that there is no justification for the 200 DDD figure.

Interventions

Table 2: Interventions deemed successful by interviewees to achieve balanced policies

TYPE	INTERVENTION	COUNTRIES
Training and education	<ol style="list-style-type: none"> 1. Training programs in pain management 2. Specialization of doctors 3. Certification courses in pain management 4. Pain management integrated in the Medical curriculum 	India Norway Mexico Uganda

Monitoring and surveillance	<ol style="list-style-type: none"> 1. Annual consumption report to INCB 2. National electronic systems with registers over consumption/Prescription 3. Registration of stock and dispense in pharmacies 4. Registration of amount of morphine laboratory imports 5. Validation of every prescription in pharmacies 6. Requirement to report stockouts in pharmacies 	Brazil India Norway Mexico Uganda
Prescribing and stocking rights	<ol style="list-style-type: none"> 1. Authorized doctors can prescribe 2. All Specialized doctors can prescribe 3. Only selected specialized doctors have prescription rights 4. Trained doctors, nurses and clinical officers have prescription rights 5. Training required to stock or dispense 	Brazil Finland India Norway Mexico Singapore Uganda
Prescription class system	<ol style="list-style-type: none"> 1. Special prescription forms are required 2. Prescription class with restrictions to validation/amount/rights to prescribe 	Brazil Finland Norway Mexico
National regulation	<ol style="list-style-type: none"> 1. Balanced national policies are implemented 2. Multisectorial approach to achieve balanced policies 3. Mandatory integration of palliative care in all levels in National health systems 4. National Drug Control system; platform for export and import 	Finland India Mexico
Financial Drug Coverage	<ol style="list-style-type: none"> 1. Drugs given free of charge 2. Drugs free of charge for chronic ill or terminally ill patients 3. State regulated coverage 4. Partly refunded /reduced price 	Brazil Finland India Norway Uganda
Other	<ol style="list-style-type: none"> 1. Collaboration with NGO to implement 2. Mandatory reserve supplies in pharmacies 3. Incentivize work in remote regions 4. Validation systems for targeted campaigns and surveillance 5. Awareness campaigns 	Brazil Finland India Mexico Uganda

Training and Education

Training and education were suggested as a successful type of intervention by all our interviewees (see Table 2). Our expert interviewee also recognized training and education as the single most important intervention to achieve a balanced policy. I found many different efforts from country to country. The most recognized by several of our interviewees, also mentioned in the literature (35), was training programs. Different examples of successful training programs were mentioned (found in Table 2: training and education), especially the success of Hospice Africa Uganda (36, 37). The hospice was established in 1993 and has worked to increase access to palliative care in Uganda through changing national government policies on importation, prescription rights and practices. The hospice has through close cooperation with the Ministry of Health worked on capacity building of health care workers by developing education and training programs. The programs include education of medical students, morphine prescription training, and volunteer workforce mobilization. Special prescription training programs for doctors, nurses and clinical officers have been implemented and are considered successful by ensuring that prescribers have the training and qualifications needed to provide good palliative care. Training programs can prevent overprescription as well as fear of prescribing amongst health workers (38).

Other specific interventions mentioned by interviews were certification courses in pain management and/or improvement of the pain management training integrated in medical curriculum. Medical certification courses are effective to update and train medical health professionals. Certification courses in pain management implemented in Norway are provided by the workplace depending on the patient group. For example, in geriatrics doctors are offered to join courses in palliative medicine, since end of life care often requires more pain management, this way doctors can update their knowledge in order to optimize the treatment given in the ward.

Lastly, specialization of health care workers in palliative care was mentioned by several of our interviewees. Some countries require specialization in palliative medicines or oncology to be able to prescribe opioids which can contribute to restricted access to opioids for medical purposes. Yet in Mexico an intervention is implemented where the aim is to invest in capacity building by educating more specialists within the field of palliative medicine and pain management, without any exclusive prescription privileges. This way they will strengthen their health system by increasing the expertise in the field of palliation. .

Monitoring and surveillance

All the countries studied in this thesis had monitoring systems in place (see Table 2: Monitoring and surveillance), and reported their annual estimates to INCB. However, countries collect data on national opioid consumption through different registration measures for the registration of imports, exports, stock levels, sales figures, prescription-based statistics in hospitals and community. For example some countries have electronic registration systems, like Brazil while others still use paper forms for registration.

The annual national reports with statistical data on opioids are mandatory and are sent in to the International Narcotics Control Board. These reports give an overview of consumption and makes surveillance easier. The consumption data is also the only way we can get an impression of the access to opioids in the countries, although it is argued by some of our interviewees that this data is not fully reliable. The reported data gives an approximate idea of the consumption in every country. Nationally the reported consumption data can be compared between regions within countries and the politicians can target campaigns to regions with alarming consumption or implement measures to increase availability in areas with low access.

In addition to the actual consumption data governments are also required to submit estimates or prognoses on the need for every controlled medicine for the coming year. Import and export licensing is thereby limited to the annual estimates, if the estimates are exceeded new estimates must be submitted before the country can import or export again. If the estimates are exceeded and not adjusted they will be deducted from the following year.

In addition to the estimates and reports required by the INCB, most governments had implemented additional registration and reporting systems. For example, a national electronic system with data on consumption and prescription of opioids has been implemented in Brazil. It has the ability to monitor outliers (i.e., those who rarely prescribe as well as those who prescribe frequently). However, outliers are rarely investigated unless there is a specific reason. In the Brazilian pharmacies every opioid prescription is validated electronically. The system receives information from the pharmacies regarding the dispensing of controlled medicines every seventh day. This also allows them to target their awareness campaigns, education and implementation of restrictions where needed. In Norway every prescription needs to be approved by a pharmacist. For controlled substances the paper prescriptions are kept in the pharmacy for at least five years. Every pharmacy is obligated to have a register and account of controlled substances, and this must also be kept for five years after dispense. Some pharmacies use a paper system for this purpose while others consider the transactions in the electronic system called “Farmapro” to be sufficient. The Norwegian Medicines Agency can demand to see the pharmacy registers for controlled substances as well as prescriptions and prescription information.

Prescribing rights

As shown in Table 2 I found huge variations in the prescribing rights for opioids between different countries. In some countries the prescribing rights are strictly regulated, for example only given to medical doctors specialized in palliative care. Other countries have extended the prescribing rights to include for example trained nurses and clinical officers in addition to general practitioners. This has led to increased accessibility of palliative care in the countries. In most countries all authorized doctors have the right to prescribe opioids, although often special forms are required for controlled substances. Some would argue that this is a liberal model for opioids, because it increases the risk of over prescribing and thereby dependency.

In Norway any doctor with an authorization within an institution in either a hospital or general practice has the right to prescribe opioids for medical use. The prescribing rights to all doctors ensure availability in every region, yet special prescription forms function as a control mechanism to hinder overconsumption and overprescribing. All prescriptions have a Quick Response (QR) code which is verified in the pharmacies. A QR code is a secure code containing the prescribers ID number and their rights to prescribe, this way falsifications can be prevented. These prescriptions are only valid for one single supply and the patient ID is required in order for the pharmacy to dispense the opioid(s).

Some countries require additional training or qualification to prescribe, stock or dispense opioids. In India three days of palliative care training has been required to stock or dispense morphine. Though control mechanisms are necessary, it should be ensured that these mechanisms are not limiting availability for medical purposes. In Singapore only a selected list of specialists have the right to prescribe. This has resulted in a lack of access to opioids, since patients might have to travel far to get the medical treatment they need. Also, the drugs are only accessible in secondary and tertiary care and affordability might be another barrier since Singapore has a private healthcare system.

As mentioned previously, adding trained nurses and clinical officers to the list of prescribers of opioids in Uganda exemplifies a successful intervention that has been able secure patient access to palliative care. All doctors, nurses and clinical officers are required to complete a mandatory nine-month training program in palliative care before they have the right to dispense or prescribe. Uganda being the pioneer in palliative care in Africa has been a model for neighboring countries, functioning as the center of expertise with the head office of African Palliative Care Association located in the capital.

Prescription class system

The prescription class system for controlled substances has been identified as successful intervention by several interviewees. Under the single convention controlled medicines are classified in schedules or groups (Schedule I-IV), according to potential of abuse and medical use. Depending of the schedule the controlled medicines are controlled in different levels, Schedule I being the group of controlled medicines with the high abuse potential and therefore under strictest control. It is implemented in both Norway and Brazil where the controlled medicines are classified depending on the potential of misuse or dependency and regulated accordingly. According to our interviewees from both countries, it has been beneficial to regulate opioids with higher potential of harm through limited dispensing rights, stricter registration, special forms and better monitoring. Through measures like limiting dispensing rights to certificated health workers, limiting validation of the prescription to one dispense only and electronic registration of every prescription. (20)

National regulation

National laws have been changed the last years in many of the countries studied in this thesis. India, Uganda, Mexico and Brazil have all loosened controls on opioids due to limited availability of pain management for those who need it(33). With these policies governments have committed to balance their approach and make sure patients who need it gets the medical treatment necessary.

For example Mexico passed a national agreement in 2014 with an obligation to integrate palliative care units in all levels of national health systems in both urban and rural areas, with a commitment to ensure enough resources to provide palliative assistance to those who need it. However, it is too early to say anything about the impact of these new laws, due to the recent implementation.

Financial coverage

Financial coverage measures are in place in several of the countries interviewed including Finland, Norway, Brazil and Uganda. In some countries only medication for chronic conditions are reimbursed, while in others like for example Finland all prescribed medication are covered by the government.

Price is often identified as an obstacle to access to medicines, but when it comes to opioids the price was not mentioned as a major barrier by any of the interviewees. Some of the differences in consumption may be partly explained by the different measures for financial drug coverage. For example, in Uganda and Kerala where the availability of opioids is considered to be reasonably good, morphine for medical use is free of charge. However,

Finland has a much lower consumption compared to Norway despite the fact that all prescription drugs are reimbursed whereas in Norway only medicines for terminal and chronic ill patients are reimbursed.

Other

Mandatory reserve supplies

In some countries they have a security mechanism to prevent stock-outs, a challenge that in many countries has led to decreased availability. In for example Finland they have implemented mandatory reserve supplies, which means that every pharmacy is obligated to have a minimum stock of morphine to avoid stock-out.

Collaboration

Collaboration to implement interventions has been a great success for morphine. In Uganda the NGO Palliative Care Association has assisted The Ministry of Health with implementing training programs for health workers and for medical students.

Ketamine

I have also studied the status of Ketamine since the anesthetic is classified as an essential medicine by WHO and is lifesaving in many countries. It is easy to use, and in many countries the only safe anesthetic, especially in under resourced health systems and emergency settings with little equipment available. Since it has been suggested to regulate the medicine under the Single Convention to prevent abuse many experts have expressed their concern and recommended against this with the argument that this can restrict access.

I asked each of the countries how Ketamine was regulated and what their expert opinion was regarding international control of the drug. It has been suggested that Ketamine should be controlled under the international drug convention. Based on the interviews I found that Ketamine is under national control in almost all the countries (see Table 3). Though the medication is under national control the interviewees did not recommend controlling it under the international convention for controlled substances. All our interviewees predicted limited access to safe surgery with serious consequences in resource poor areas if further control was implemented. India reported several cases of minor surgery that had been performed without anesthesia due to limited access after the implementation of national control on Ketamine.

Table 3: National control of Ketamine

Country	Control of Ketamine
Uganda	Controlled – For hospital use only
India	Controlled – special access needed
Singapore	Controlled
Finland	Not controlled
Norge	Controlled – Class A drug
Mexico	Controlled - Special license required
Brazil	Controlled – For hospital use only

DISCUSSION

Barriers

The issue of access to controlled substances for medical use was for a long time not recognized and the debate was imbalanced. Although antibiotic resistance rightfully has been a prioritized debate the last years, access to antibiotic is still a major challenge especially in many low and middle income countries (39). In these countries common conditions like pneumonia pose a bigger threat than resistant bacterias. There are many factors limiting the availability of antibiotics and are similar to the barriers to achieve balanced policies for opioids. Access is undermined by limitations like availability, infrastructure and human resources. On the other hand increased availability through internet sales, and over counter dispense of antibiotics is becoming a challenge that drives inappropriate use in many countries. (3)

While we must minimize excessive use of antibiotics, access must be increased in many parts of the world. Studies have estimated that if 101 countries improved access to antibiotics 75% of deaths caused by pneumonia among children under five years can be prevented (39). Even though newer antibiotics may be physical available in these countries, access is often limited due to price of the antibiotics, and remain out of reach for the most vulnerable in the societies (40).

Unlike for opioids, price is a known barrier to availability of antibiotics. It has been emphasized that universal access to antibiotics must be prioritized as a step in universal health coverage. The market failure for antibiotics requires initiatives like The Global Fund to fight AIDS, malaria and tuberculosis who provides financial assistance (39). Availability is also limited by weak health system and health services and strengthening of these on a national level should be a priority. In many LMICs international assistance is needed to ensure affordability to achieve this. Affordability and availability can be secured through initiatives like subsidized medicines, procurement models, and logistic where necessary (3).

Lack of education can become a serious barrier for a balanced approach, leading to overconsumption and overprescribing. Both the need for more education of general public and among health workers have been addressed globally for antibiotics. Although we have had initiatives like awareness campaigns for example in November 2015 the first world antibiotic awareness week was arranged where the theme was “Handle with care” promoting rational use, education among prescribers and health workers dispensing is also essential. Especially in LMIC with inadequate delivery systems where community pharmacists and drug shop owners are dispensing antibiotics capacity building through educational measures, and guidelines are crucial alongside community education and awareness (40).

While stigma for controlled medicines in many countries has been a barrier to access, the challenge is the opposite for antibiotics. Doctors are often pressured to prescribe antibiotics by patients or due to uncertain diagnosis. It is therefore important to make people aware of antibiotic use and update health professionals on guidelines and indication for antibiotic treatment. Awareness and education will prevent both over consumption of antibiotics and hinder misperceptions.

The missing standardized way to measure opioid requirements makes it difficult to monitor access. Measuring appropriate access for antibiotics might be easier since the clinical indications often are more objective, but good surveillance data is still lacking especially from low and middle income countries which leaves us with poor monitoring on access in these areas.

Differences in consumption of opioids between countries may partly can be explained by a missing international standard to quantify requirements of opioids. Other factors like varying threshold of pain between cultures, different burden of disease, attitudes in the society, and among health care workers, may also explain the differences.

Like Ketamine is essential for safe surgery in rural areas, antibiotics are life-saving medicines in the field of medicine. Our expert interviewee pointed out lack of access as a serious side effect to the current control system for Opioids and therefore did not recommend controlling antibiotics under a similar model. Yet a national control would not be enough due to the increasing resistance, we need common international guidelines, adjusted to each region based on the knowledge we have on resistance and rational use.

Interventions

Many of the specific interventions identified in this thesis as successful for the regulation of opioids can be transferable to antibiotics. For example, training and education are already broadly recognized interventions for antibiotics in order to ensure rational use and stewardship (41). The World Health Organization has also emphasized the importance of

both awareness among consumers and prescriber education coordinated by governments(42). Mexico's capacity building model can be applicable for antibiotics through investing in educating more infectious disease specialists with an expertise in antibiotics and resistance though this must be done in combination with other training and education measures that secures a general standard of competence among physicians overall.

Moreover, organized training programs for health workers implemented in cooperation with the government, like the training program developed in Uganda, can be beneficial for antibiotics. Training programs can update health workers on resistance patterns and prescription guidelines. This way physicians can avoid overprescribing and secure rational use. Also, optional certification courses for antibiotics, and especially for new antibiotics, can prove to be successful. Although it can be beneficial if these courses are made mandatory for prescribers of novel and critical antibiotics, some may suggest that such a requirement will limit access. However, conservation of these antibiotics is necessary, and mandatory certification courses can secure that only qualified health personnel can prescribe critical antibiotics.

Surveillance of antibiotic consumption documents trends of systematic use of antibacterials. The minimum WHO requirement for reporting on antibiotic consumption remains unmet by many countries (1). Good surveillance systems for antibiotics are cornerstone for targeted action, and could give useful information on how the consumption or prescription patterns change over time. It will enable us to identify areas with high consumption, compare consumption in a country from one year to another and consumption between different regions/countries. However, implementation of the INCB reporting model for antibiotics will be complex and resource consuming. Requiring both financing and international agencies that can govern this global reporting system. The main reason the system is functioning for opioids is that access is restricted if the given estimates are exceeded. Such a regulatory barrier can be catastrophic for antibiotics, as lifesaving drug across the medical field. Though existing systems for surveillance of antibiotics are not optimal, the strengthening of existing systems should be a priority rather than implementing new and complex measures. Also, this way duplication of efforts can be avoided. An example of an existing initiative is the European Surveillance of Antimicrobial Consumption programme (ESAC), a network of national surveillance systems. The network collects data on consumption from EU and EEA countries, from all primary, secondary and tertiary care units(43).

Surveillance of antibiotic resistance is considered crucial in order to assess global threats of antibiotic resistance and support public health interventions (12). For many years there have been global surveillance programmes monitoring resistance in specific bacterial pathogens as *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae*. While Surveillance programmes in selected geographical areas like Eastern European Surveillance of Antimicrobial Resistance (CAESAR), the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA) are in place

common standards of methods, data-sharing and coordination are lacking. Despite the existing programmes there are gaps in data on many bacterial pathogens causing common infections (1). The first global surveillance report on AMR published in 2014 found that only 22 countries were able to report on all the nine bacteria of public health concern (12). An example of promising efforts that aims to provide countries with a standardized approach to collect, analyse and share data on AMR globally is WHO's Global Antimicrobial Resistance Surveillance System (GLASS) (44).

Monitoring data can also indicate which antibiotics are at risk of developing resistance so preventive measures can be implemented. Also, through monitoring we can get an impression of the accessibility of different antibiotics. This can for example be done with a national registration system for prescriptions. Although several countries are talking about electronic prescription systems, we have to keep in mind that technology still is limited in resource poor settings meaning that registration must be done on paper forms. Financial assistance like The Fleming Fund, Wellcome trust and other initiatives supporting surveillance systems for AMR in LMIC are already in place(6).

Discussing prescribing rights and stewardship for antibiotics is a challenge since many countries do not have a functioning prescription system and over-the-counter sale is extensive. Authorization as a doctor should be aspired as a minimum criteria for prescribing antibiotics in all countries where feasible, for novel and critical antibiotics additional control mechanisms like special forms and electronic registration can be beneficial, such as in Brazil for Opioids. However this can cause limited access in low and middle income countries with few physicians in rural area, where antibiotics are usually accessed over-counter this. In these countries other control mechanisms should be considered for example training programmes as suggested in the next paragraph.

Even though the ideal dispense of antibiotics is requiring a prescription from a doctor, many countries do not have a functioning prescription system in place. In these countries health workers, pharmacists and drug shop owners are dispensing antibiotics. Quality assured training programs, can function as a control mechanism until a prescription system is implemented. In Uganda the nine month training program is mandatory for everyone who prescribe opioids. For antibiotics it should be discussed to make these programs mandatory for drug shop owners and pharmacists who have prescription or dispense rights (36, 38). Quality assured training of other health workers is an intervention that has been successful in many public health areas including palliative care and can prove itself valuable in countries with less infrastructure, weaker health systems and lack of doctors in rural areas, but this is only suggested as a temporary intervention until a prescription system is in place(45).

Antibiotics are used for a broad range of conditions and modern medicine is depended on the availability of the drugs. It is therefore not recommended to implement exclusive prescription

rights for Opioids like in Singapore where only selected specialists can prescribe, this might make antibiotics inaccessible.

A separate prescription class like for opioids can be an intervention advantageous to conserve and regulate critical antibiotics. Through such a classification interventions can be targeted towards critical antibiotics to achieve conservation. While controlled substances are classified according to risk of misuse, antibiotics should be classified according to risk of resistance for example stricter control of antibiotics targeting multi-drug-resistant bacteria. Also, last resort antibiotics like Colistin can be controlled as a separate class. This will function as a safeguarding mechanism and help us conserve these antibiotics through different interventions like limiting prescribing rights to only secondary and tertiary care, better surveillance and special training. Also, implementing measures such as limiting the duration of the prescription validity and the amount to be prescribed can be favorable, especially for new and critical antibiotics. Furthermore, implementing special prescription forms where every doctor gets a certain number of prescription forms which he or she has to order, in addition to an electronic prescription system, will make it possible to monitor the overprescribing or over consumption of antibiotics. The existing classification schemes for antibiotics are not based on resistance or degree of criticality but rather chemical structures. Although these are useful for general antibiotics a new classification can be profitable for regulation of last resort antibiotics. Such an intervention may promote rational use and secures that the drug is prescribed on the right grounds and indications. It would not be recommended to implement such a classification system for all antibiotics, since we can't differentiate based on resistance patterns, also this might further limit access to antibiotics in areas where availability already is restricted.

While good financial coverage measures were in place for Opioids antibiotics do not have the same financial coverage, Antibiotics unlike Morphine are expensive to develop and there has been much discussion around the price of new antibiotics. It is feared that new antibiotics will be so expensive that people who need them can't afford them. The IMI project Drive-AB is researching new research and development models like delinkage trying to ensure more affordable prices for new antibiotics. However, the condescending effect might reduce the prices of new antibiotics and make them available in markets where other alternatives of older antibiotics aren't accessible. How can we manage to conserve these newer antibiotics in these markets? There is therefore also a need for ensuring availability of and access to existing antibiotics in resource poor areas.

Collaboration efforts have been successful for opioids for example in Uganda where Ministry of health assisted Hospice Africa to implement training programs. Collaboration and a multi-sectoral approach will also be vital to secure responsible use of antibiotics since the challenge of resistance is a global, one health treat. In countries where prescriptions are not required and antibiotics are dispensed in pharmacies clear guidelines and reporting systems must be in

place to secure that antibiotics are only used when there is clinical indication, to prevent that financial interests cause misuse of the medication.

Table 4: The Table shows the current control regime of controlled substances and the level of control for the different regulations. Based on the findings I have also added recommendations for regulations that can be transferable to antibiotic control in the table.

Controlled substances regime	Control level	Recommendation for antibiotics	Recommended control level
Annual reports on consumption and estimates for the following year	Embedded in Single Convention (Art. 19-21)	A global comprehensive and standardized surveillance system for both consumption and resistance	International
License/Authorization to handle controlled substances import, export, manufacture, supply, stock or dispense	Embedded in Single Convention (Art 31)	Requiring licenses/authorization can be beneficial for conservation of the most critical group of antibiotics	National
Record keeping (for government authorities, manufacturers, traders, scientists, scientific institutions and hospitals); Extent of account depending on classification.	Embedded in Single Convention (Art 34)	The extent of record keeping (degree of information, double signatures, counting routines) for antibiotics should be depending on classification	National
Distribution to institutions restricted; depending on classification	Embedded in Single Convention (Art 30)	New and critical antibiotics can be considered to be distributed to secondary and tertiary care units only	National
Dispensing limits – depending on classification (Schedule 5 prescription drugs, While Schedule 2 drugs are often only dispensed through a medical institution.)	Embedded in Single Convention (Art 30) with additional national restrictions	New and critical antibiotics should be dispensed through a secondary or tertiary medical institution where feasible.	National
Manufacturing; requiring storage area or safe depending on schedule.	Embedded in Single Convention with additional national requirements	Special requirements for storage area and safe not necessary for antibiotics	None
Classification in schedule 1-5 depending on risk of abuse.	Embedded in Single Convention (Art. 2)	Classification of antibiotics depending on risk of resistance	National
Secure availability for medical and scientific purposes	Embedded in Single Convention (Art. 1, 2, 4, 9, 12, 19, and 49)	Access to antibiotics must be ensured for those who need it	International/ national

Prescription rights vary: only selected specialists/ task shifting/authorized doctors	Embedded in some national laws/policies	Authorization as a doctor should ideally be the minimum requirement to prescribe – in countries without a prescription system mandatory training of dispenser and a protocol should be in place.	National
Training and education of health personnel	Embedded in National/Local policy	Training and education programmes on antibiotics are recommended	National/local
Prescription registration system	National	Recommended for antibiotics where feasible	National

Strengths, limitations and weaknesses of the study

The results are mainly based on seven interviews, and supported by findings from the literature. The interviewees were a mix of experts, non-governmental representatives, private company employees and government officials in a national drug control agency. Even though the sample covers high, middle and low income countries, the sample of interviewees is limited and might not detect differences within continents. This should be kept in mind while reading the thesis. The interventions and barriers found are based on a set of questions adjusted according to interviewee. Therefore, depending on the country and the professional background of the interviewee the answers and thereby the findings vary. Different interventions and barriers were mentioned depending on which challenges the countries are experiencing and how balanced the implemented policy is. This means that a barrier to access in one country might also exist in the others without being recognized as an obstacle. The thesis has still managed to recognize interventions that have been successful and patterns of barriers in nations with different GDP, national regulation system and health system.

CONCLUSION

Through literature and interviews I found many interventions that can be transferable from opioid regulation to antibiotics. Especially the measures like education and training, prescription class systems, surveillance systems, public awareness and national policies securing access. These measures have mostly been implemented as a result of limited access to opioids and can be valuable to ensure access to and rational use of antibiotics.

Commitment is cornerstone when it comes to governance of antibiotics, yet over-regulation of antibiotics as a controlled medicine can result in disadvantageous side effects like restricted access. Based on the findings in the thesis an international convention like the single convention is not recommended for antibiotics. However, a global agreement for

antibiotics should be in place, in the form of guidelines and a classification system. These guidelines must be adjusted into country groups or by regions. Also, a binding international agreement can be beneficial for novel and critical antibiotics, to secure conservation and hinder resistance. Though the balanced approach is essential for antibiotics, the current regulatory mechanisms for Opioids can result in a serious public health risk. Antibiotics are life-saving drugs and restricted access can lead to fatal consequences.

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Annex

Annex 1: Interview guide

Consumption and governance

1. Do you consider the opioids for medical consumption in your country appropriate low/high?
2. Do you currently have a national controlled medicines policy? - Which agencies are involved in drug control? Does the consumption differ from neighboring countries?

Challenges

3. Does the policy apply and work successfully throughout the country (balanced)?
- Are there/or has there been any patterns of population groups that lack access?
4. Do you consider access to controlled medicines for medical purposes a challenge in your country?

Best practices and policies

5. Do you have examples of specific interventions implemented to secure that access to morphine/ controlled substances for medical purposes?
6. Which regulatory mechanisms do you have implemented to prevent drug dependency and misuse of opioids?
7. What do you consider essential best practices to achieve a balanced policy?
8. Is ketamine a controlled substance in your country? Is the drug's availability and accessibility ensured for medical purposes?