

Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative

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Background: Many patients in Europe do not receive adequate relief of pain because of excessive regulatory restrictions on the availability and accessibility of opioids. This is a major public health problem. The aim of the study is to evaluate and report on opioid availability and the legal and regulatory barriers to accessibility across the countries of Europe.

Methods: European Society for Medical Oncology and European Association for Palliative Care national representatives reported data regarding survey of opioid availability and accessibility. Formulary adequacy is evaluated relative to the World Health Organization (WHO) essential drugs list and the International Association for Hospice and Palliative Care list of essential medicines for palliative care. Overregulation is evaluated according to the guidelines for assessment of national opioid regulations of the WHO.

Results: Data were reported on the availability and accessibility of opioids for the management of cancer pain in 21 Eastern European countries and 20 Western European countries. Results are presented describing the availability and cost of opioids for cancer pain in each surveyed country and nine forms of regulatory restrictions.

Conclusions: Using standards derived from the WHO and International Narcotics Control Board, this survey has exposed formulary deficiencies and excessive regulatory barriers that interfere with appropriate patient care in many European countries. There is an ethical and public health imperative to address these issues.

Key words: cancer pain, Europe, laws and regulations, opioids

Introduction

For patients with cancer, and especially those with advanced and incurable cancer, adequate relief of pain is the central goal of care [1, 2]. Indeed, adequate relief of pain is now recognized as a patient right [3–5]. This right implies duties; the duties of clinicians to assess pain and to treat it in accordance with the best of contemporaneous practices (that prevailing resources will enable) and duties of governments and health care regulatory systems to ensure that patients can access the medications needed to relieve pain.

Opioid analgesics are critical to the effective relief of cancer pain. Effective treatment is predicated on sound assessments, individually tailored analgesic therapy and the availability and accessibility of the required medications. In some countries,

pain relief is hampered by lack of availability or barriers to accessibility of opioid analgesics. In many countries, excessively zealous or poorly considered laws and regulations to restrict the diversion of medicinal opioids into illicit markets profoundly interfere with the medical availability of opioids for the relief of pain. Often, the logistics of the treatment of pain with opioids is so burdensome or complex for physicians, nurses and pharmacists as to be a major disincentive to involvement.

These burdens are compounded for patients and their families who, in many situations, must cajole doctors, chase after permits, wait excessively in inconveniently located pharmacies and return for frequent refills of prescriptions or any correction on a prescription that may not have been written with adequate attention to required details. In some countries, the degree of legal intimidation is such that fear of criminal prosecution contributes to deliberate undertreatment by clinicians to avoid risk of persecution or prosecution.

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The consequences for health care professionals, patients and their families are manifold and profound. Excessive regulatory restrictions make it near impossible for many Europeans to achieve relief of cancer pain that undermines their quality of life. These issues are reflected in substantial differences in opioid consumption between European countries (Figure 1) and in profound differences in morphine consumption between Western and Eastern European countries (Figure 2). It is a public health travesty that many patients in Europe do not receive adequate relief of pain because of poorly considered regulations and deficiencies in public policy. These issues have been highlighted in a review of the barriers to the development of palliative care in Eastern Europe [6].

The problem of overregulation has been highlighted by the Open Society Institute International Palliative Care Initiative (www.soros.org/initiatives/health/focus/access/about), the International Observatory on End of Life Care (www.eolc-observatory.net), the International Narcotics Control Board (INCB) [7–10], the World Health Organization (WHO) [11, 12], the Council of Europe [13] and most recently by Human Right Watch [3].

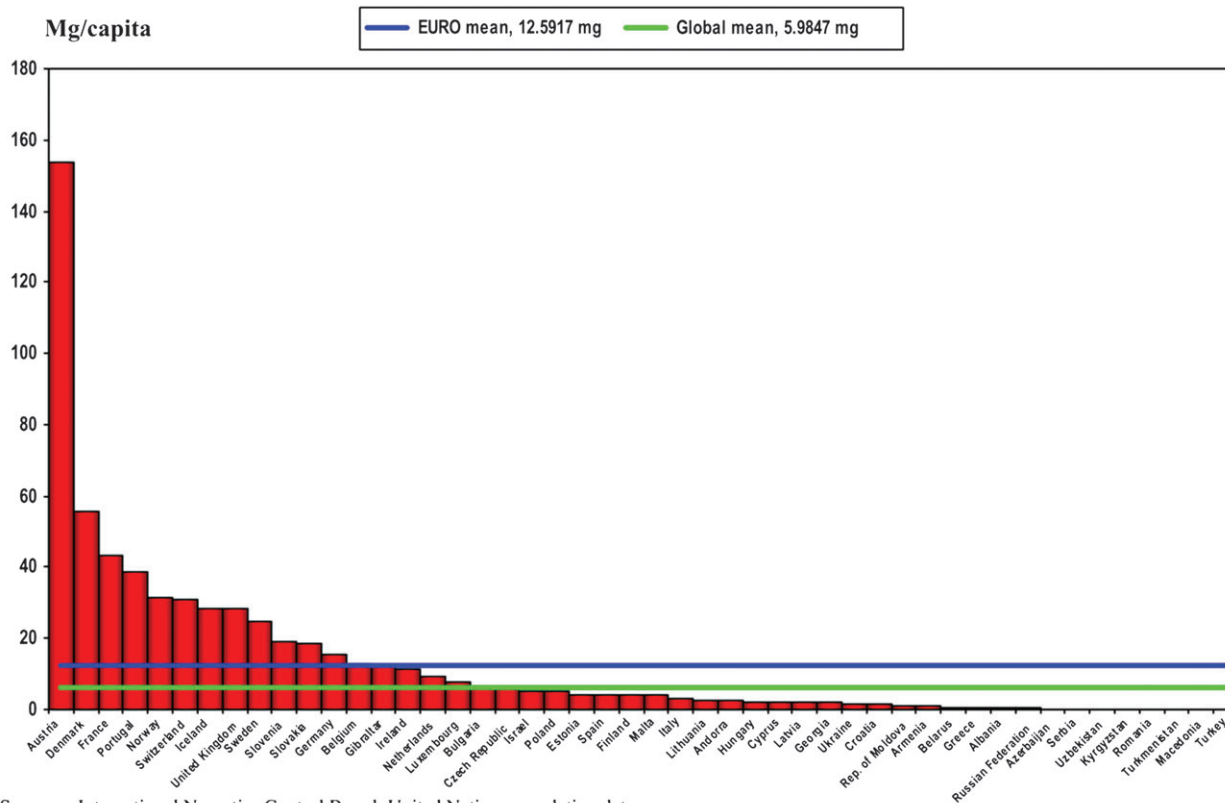
The largest bodies of cancer and palliative care clinicians in Europe, the European Society for Medical Oncology (ESMO) and the European Association for Palliative Care (EAPC), view this matter with utmost gravity [14]. To address this issue, they have developed a European Pain Policy

Initiative. The first aim of this initiative is to evaluate and report on opioid availability and the legal and regulatory barriers to accessibility across the countries of Europe. This paper reports the findings of the ESMO/EAPC survey of opioid availability and accessibility across Europe. The adequacy of formulary availability is evaluated relative to the WHO essential drugs list and the International Association for Hospice and Palliative Care (IAHPC) list of essential medicines for palliative care. Overregulation is evaluated according to the principles derived from the guidelines for assessment of national opioid regulations of the WHO [11, 12].

methods

On the basis of a review of the literature regarding opioid availability and accessibility, a questionnaire was developed to survey opioid formularies across the countries of Europe, the cost of the medications to patients and the regulatory barriers that adversely effect accessibility. The questionnaire included items relating to formulary; cost to patients; regulations relating to dose limits, prescribing, dispensing and emergency situations and the use of stigmatizing language in the opioid regulations (Table 1).

Both ESMO and EAPC distributed the questionnaires to national representatives in each of their European member countries in 2007 and 2008, respectively. These national representatives were all senior clinicians holding leadership positions in their respective countries in



Sources: International Narcotics Control Board; United Nations population data
By: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2008

Figure 1. European consumption of morphine, 2006.

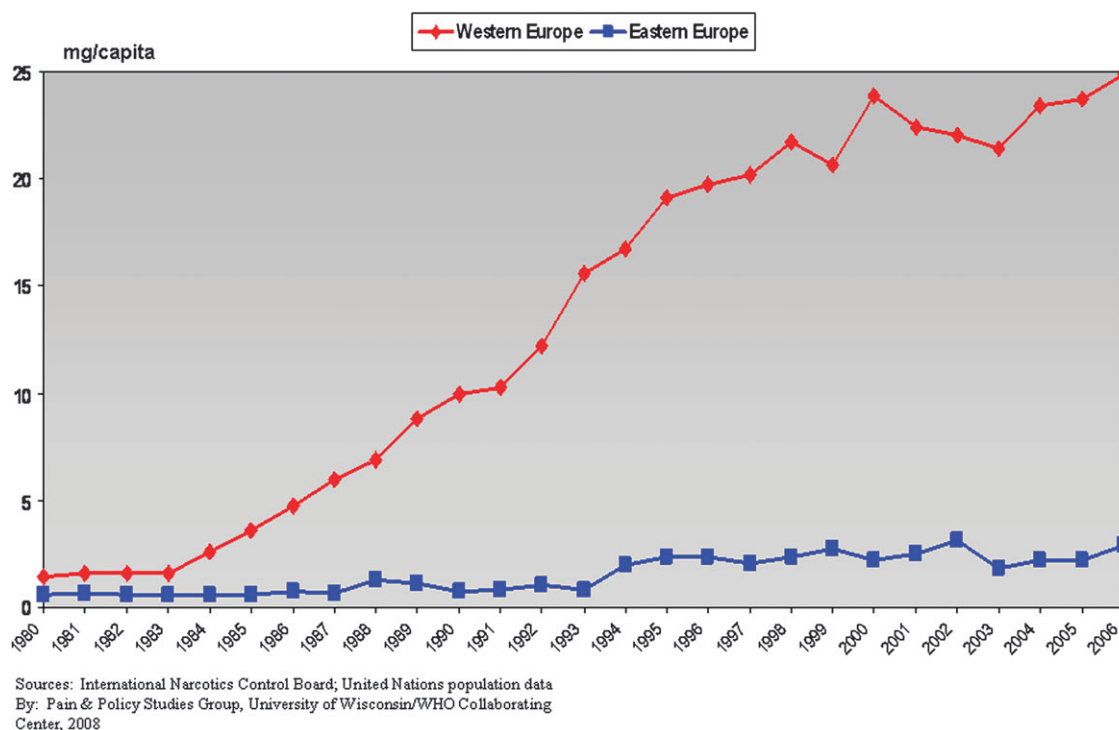


Figure 2. East versus West Europe: morphine consumption, average milligram per capita*, 1980–2006. *Average milligram per capita calculated by adding milligram per capita statistic for each country and dividing by the total number of countries.

Table 1. Opioid analgesics on essential drug lists

	WHO essential medicine 2007	IAHPC 2007
Codeine	X	X
Morphine, PO immediate release (tablet or liquid)	X	X
Morphine, PO controlled release	X	X
Injectable morphine	X	X
Oxycodone, PO immediate release		X
Fentanyl, TD		X
Methadone, PO immediate release		X

WHO, World Health Organization; IAHPC, International Association for Hospice and Palliative Care; PO, oral; TD, transdermal.

oncology or palliative care. The clinicians were requested to complete the questionnaire to the best of their knowledge and experience. In situations in which they lacked specific knowledge or information, they were instructed to seek advice from the local regulatory authorities in their country.

The questionnaires that were submitted by the national representatives were collated by NC, tabulated, graphically presented and redistributed for corroborating comments or feedback and validation. In January 2009, graphic presentations of the reports were recirculated to national representatives of the two organizations for updating and verification and to all the members of the EAPC for open peer review and verification. Amendments were collated, cross-checked and incorporated into the final report, which was completed in June 2009.

results

general

Data were reported on the availability and accessibility of opioids for the management of cancer pain in 41 countries in Europe: 21 East-European countries and 20 West-European countries (including Israel).

formulary availability and cost of opioids for cancer pain

The availability of opioids and their cost to consumer are summarized in Figures 3 and 4. Except for Greece and Turkey, the opioid formularies of most West-European countries avail a range of options with different opioids. In the majority of Western European countries, most opioids are available at no cost to patients with cancer pain. In Germany, Luxembourg, Spain, Switzerland, UK and Belgium, the opioid analgesics are subsidized >75% for cancer patients but are not free. In Iceland, opioid analgesics are not subsidized for any class of patients.

In general, the opioid formularies of many East-European countries are substantially more limited. Some countries such as the Czech Republic, Croatia, Latvia, Rumania, the Slovak Republic, Hungary, Estonia and Serbia avail both essential medicines and other options with most either free for the patient or at >75% subsidy. Not all countries avail codeine and oral morphine, which are on the essential medicines list of the WHO [15]. Severe formulary deficiencies, characterized by unavailability of essential medicines, are present in Lithuania, Tajikistan, Belarus, Albania, Georgia and Ukraine.

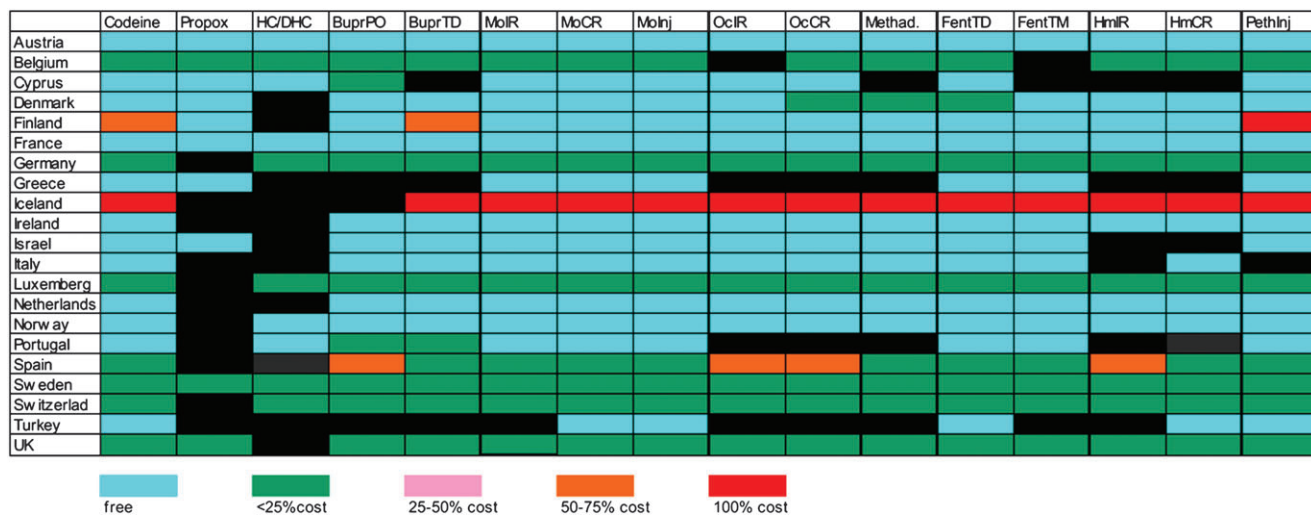


Figure 3. Opioid availability in Western European countries. Propox, propoxyphene; NC, hydrocodone; DHC, dihydrocodeine; Bupr, buprenorphine; Mo, morphine; Oc, oxycodone; Methad, methadone; Fent, fentanyl; Hm, hydromorphone; Peth, pethidine; PO, oral; Propox, propoxyphene; TD, transdermal; TM, transmucosal; Inj, injectable; IR, immediate release; CR, controlled release.

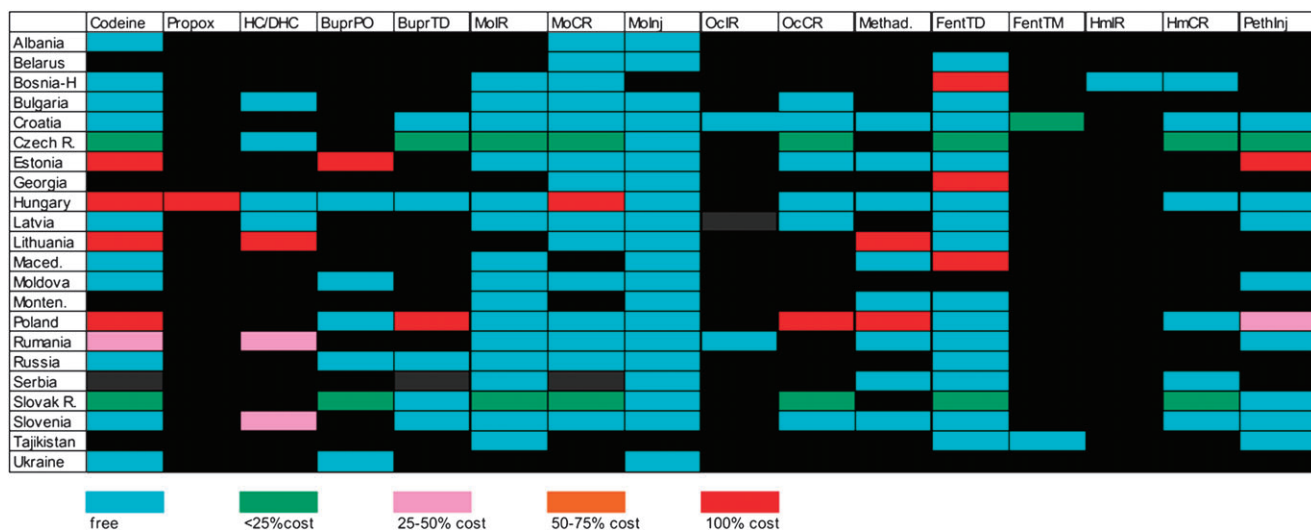


Figure 4. Opioid availability in Eastern European countries. Propox, propoxyphene; NC, hydrocodone; DHC, dihydrocodeine; Bupr, buprenorphine; Mo, morphine; Oc, oxycodone; Methad, methadone; Fent, fentanyl; Hm, hydromorphone; Peth, pethidine; PO, oral; TD, transdermal; TM, transmucosal; Inj, injectable; IR, immediate release; CR, controlled release.

regulatory restrictions to accessibility

Countries used a range of regulatory restrictions to limit accessibility of opioids. Overall, regulatory restrictions were much more common in East-European countries than in West-European countries.

requirement for permission/registration of patient to render them eligible to receive opioid prescription. Most of the East-European and a minority of the West-European countries require that patients, particularly outpatients, receive a permit or be

registered to be eligible to receive opioid prescriptions for the management of cancer pain (Figure 5). In some countries, this is also true for hospice patients.


requirement for physicians to receive a special authority/license to prescribe opioids. Some countries restrict the authority to prescribe opioids to physicians with special permits or to practitioners of certain subspecialties (Figure 5). Greece is the only West-European country with such restrictions; they are more prevalent in East-European countries. In Montenegro and Ukraine, the physicians

of some subspecialties do not have prescribing privileges and in Russian Federation, Montenegro, Bosnia–Herzegovina and Ukraine, privileges may be extended to some nononcologic subspecialties in emergency situations only.


requirement for duplicate prescriptions and special prescription form. All the East-European countries and most of the West-

European countries require that opioids be prescribed using duplicate or triplicate prescriptions (Figure 6). In most of these countries, special forms must be used. Difficulty in accessing the required prescription forms was reported in Bulgaria, Moldova, Russia, Montenegro, Macedonia, Albania, Lithuania, Tajikistan and Ukraine. In Latvia, Estonia, Albania and Denmark, physicians need to purchase the prescription forms.


	Regulations require patient permit/registration to receive opioid prescription			Physicians need a permit to prescribe opioids		
	out pts	in pts	Hospice pts	Oncologists	Family MD	Surgeon
Albania	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	No data
Belarus	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Bosnia Herzegovina	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Only permitted in emergencies
Bulgaria	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Croatia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Czech republic	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Estonia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Georgia	* Permit needed	Permit needed	Permit needed	* Permit needed	* Permit needed	* Permit needed
Hungary	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Latvia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Lithuania	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Macedonia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Moldova	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Montenegro	Permit needed	Permit needed	No Hospice	Permit needed	Only permitted in emergencies	Forbidden
Poland	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Rumania	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	No data
Russian Federation	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Only permitted in emergencies
Serbia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Slovak Republic	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Slovenia	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Tajikistan	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Ukraine	Permit needed	Permit needed	Permit needed	Permit needed	Forbidden	Only permitted in emergencies
Austria	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Belgium	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Cyprus	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Denmark	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Finland	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
France	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Germany	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Greece	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Iceland	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Ireland	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Israel	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Italy	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Luxemburg	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Netherlands	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Norway	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Portugal	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Spain	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Sweden	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Switzerland	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
Turkey	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed
United Kingdom	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed	Permit needed




No permit needed



Permit needed



Only permitted in emergencies



Forbidden

Figure 5. Requirement for authority to receive and prescribe opioids. *Only physicians who have applied for and received special prescription forms.

prescription limits. Among the West-European countries, only Turkey and Greece restrict prescriptions to <21 days' supply of medication (Figure 7). In contrast, many of the East-European countries restrict opioid prescriptions to <3 weeks' supply and eight countries (Moldova, Russia, Lithuania, Belarus, Albania, Georgia and Ukraine) restrict supply to a week or less. In Ukraine, prescriptions are limited to 1-day supply at a time.

dose limits. Several countries specify maximal daily doses for one or more of the opioids on formulary (other than over-the-counter codeine). Countries in which dose limits were reported include Germany (controlled release oxycodone), Turkey (controlled release and injectable morphine), Moldova (controlled release and injectable morphine), Rumania and Russia (morphine and immediate release oxycodone).

limitations on dispensing privileges. Representatives from Western European countries did not report restrictions of dispensing privileges (Figure 8). Restrictions were reported in most East-European countries. When restrictions exist, opioids were available from designated pharmacies, hospital pharmacies or regional pharmacies. In Georgia, dispensing privileges for outpatient opioids are restricted to special pharmacies in district police stations.

provision for opioid prescribing in emergency situations. An emergency situation is defined as the one when there is an immediate need to relieve strong cancer pain but the physician is not able to physically provide a prescription (Figure 9). Examples include a pain crisis at night, on a public holiday or in a remote region. Few countries allow physicians to prescribe by telephone or to fax a prescription to the pharmacist. In Lithuania and UK, both nurses and pharmacists may issue a limited emergency prescription.

pharmacist privilege to correct technical error on a prescription. In the situation of a patient presenting with a prescription that contains a technical error (no address, misspelling, missing value, etc.), few countries allow the pharmacist to correct the error even at the direction of the prescribing physician (Figure 9, last column).

use of stigmatizing term for opioid analgesics in regulations. Several countries in Europe continue to use pejorative or stigmatizing terms for opioid analgesics in the regulations controlling their prescription and dispensation (Figure 10). Ten countries referred to them as

	Duplicate or triplicate prescription	Special form	Accessibility of forms	Pay for presc. forms
Albania	Barrier	Barrier	Barrier	Barrier
Belarus	Barrier	Barrier	Barrier	Barrier
Bosnia Herzegovina	Barrier	No Barrier	Barrier	Barrier
Bulgaria	Barrier	Barrier	Barrier	Barrier
Croatia	Barrier	Barrier	Barrier	Barrier
Czech republic	Barrier	Barrier	Barrier	Barrier
Estonia	Barrier	Barrier	Barrier	Barrier
Georgia	Barrier	Barrier	Barrier	Barrier
Hungary	Barrier	Barrier	N/R	N/R
Latvia	Barrier	Barrier	Barrier	Barrier
Lithuania	Barrier	Barrier	Barrier	Barrier
Macedonia	Barrier	Barrier	Barrier	Barrier
Moldova	Barrier	Barrier	Barrier	Barrier
Montenegro	Barrier	Barrier	Barrier	Barrier
Poland	Barrier	Barrier	Barrier	Barrier
Rumania	Barrier	Barrier	Barrier	Barrier
Russian Federation	Barrier	Barrier	Barrier	Barrier
Serbia	Barrier	Barrier	N/R	N/R
Slovak Republic	Barrier	Barrier	Barrier	Barrier
Slovenia	Barrier	Barrier	Barrier	Barrier
Tajikistan	Barrier	Barrier	Barrier	Barrier
Ukraine	Barrier	Barrier	Barrier	Barrier
Austria	No Barrier	Barrier	Barrier	Barrier
Belgium	No Barrier	Barrier	N/R	N/R
Cyprus	No Barrier	Barrier	N/R	N/R
Denmark	No Barrier	Barrier	Barrier	Barrier
Finland	No Barrier	Barrier	Barrier	Barrier
France	No Barrier	Barrier	Barrier	Barrier
Germany	No Barrier	Barrier	Barrier	Barrier
Greece	No Barrier	Barrier	Barrier	Barrier
Iceland	No Barrier	Barrier	N/R	N/R
Ireland	No Barrier	Barrier	Barrier	Barrier
Israel	No Barrier	Barrier	N/R	N/R
Italy	No Barrier	Barrier	Barrier	Barrier
Luxemburg	No Barrier	Barrier	Barrier	Barrier
Netherlands	No Barrier	Barrier	N/R	N/R
Norway	No Barrier	Barrier	Barrier	Minor
Portugal	No Barrier	Barrier	Barrier	Barrier
Spain	No Barrier	Barrier	Barrier	Barrier
Sweden	No Barrier	Barrier	Barrier	Barrier
Switzerland	No Barrier	Barrier	Barrier	Barrier
Turkey	No Barrier	Barrier	Barrier	Barrier
United Kingdom	No Barrier	N/R	N/R	N/R

Barrier (Red)
No Barrier (Blue)

Figure 6. Requirement that opioids be prescribed in multiple copies or on special prescription. N/R, not relevant.

Maximum number of days supplied on one prescription		Maximum number of days supplied on one prescription	
Austria	90	Albania	7
Belgium	open	Belarus	3
Cyprus	30	Bosnia Herzegovina	no data
Denmark	open	Bulgaria	30
Finland	90	Croatia	max total dose
France	30	Czech republic	90
Germany	30	Estonia	max total dose
Greece	5	Georgia	7
Iceland	30	Hungary	30
Ireland	open	Latvia	15
Israel	30	Lithuania	5
Italy	30	Macedonia	7
Luxemburg	21	Moldova	7
Netherlands	90	Montenegro	15
Norway	open	Poland	open
Portugal	60	Rumania	30
Spain	30	Russian Federation	5
Sweden	90	Serbia	14
Switzerland	open	Slovak Republic	30
Turkey	10	Slovenia	30
United Kingdom	28	Tajikistan	no data
		Ukraine	1



Figure 7. Prescription limits (days).

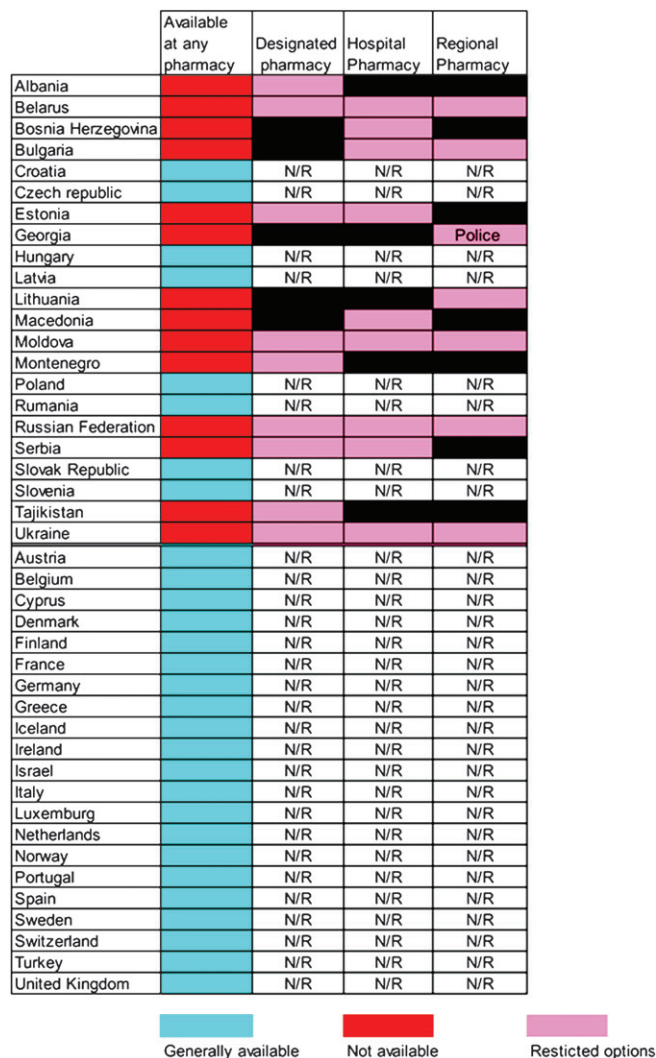


Figure 8. Limitations on dispensing privileges. N/R, not relevant.

drugs of addiction, four as dangerous drugs and two as poisons.

cross-correlation of availability and accessibility

The countries with the most limited opioid formularies tended also to have the greatest number of regulatory barriers to accessibility. Among the Western European countries, Turkey and Greece had more limited formularies and more accessibility barriers compared with the other countries.

Among the East-European countries, there was much greater heterogeneity. Some countries like the Czech Republic, Croatia and Hungary had formulary availability and accessibility that was as good as most of the Western European countries. In contrast, several countries including Russia, Montenegro, Macedonia, Bosnia–Herzegovina, Lithuania, Belarus, Albania, Georgia and Ukraine had very restricted formularies and multiple barriers to accessibility.

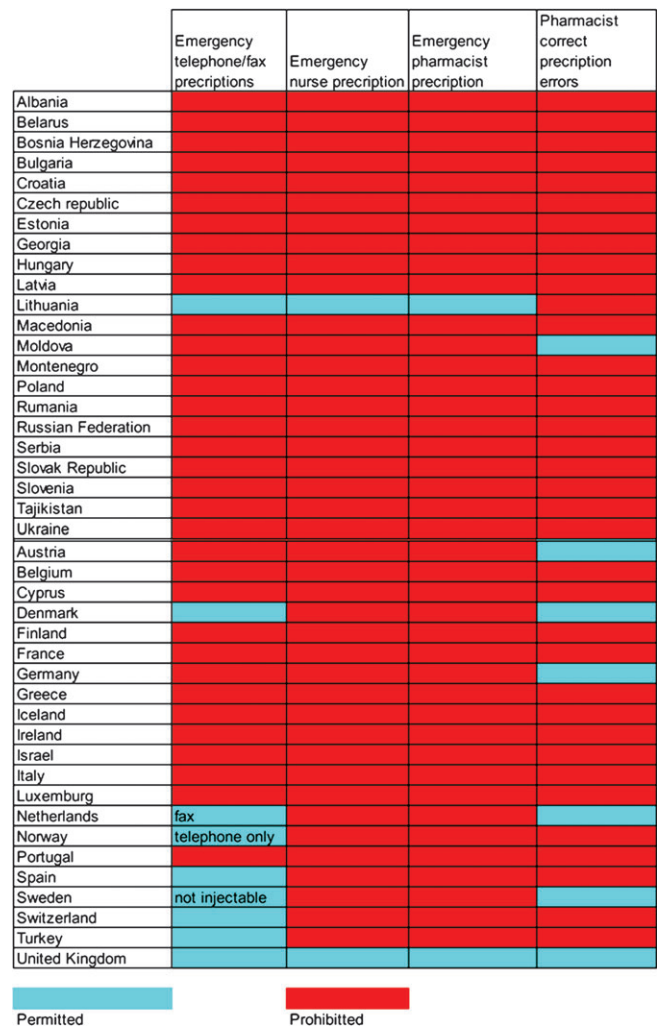


Figure 9. Emergency provisions.

discussion

There is a fundamental need to ensure that opioid analgesics are available to the patients who need them and to prevent these drugs from becoming a source of harm or abuse. Drug abuse is a significant global problem. Although most of the opioids abused on a worldwide scale are derived from illicit channels [16], a proportion are prescription medications which have been diverted through fraud, theft, forged prescriptions, illegal pharmacies [16, 17] and *via* unscrupulous health professionals or poor clinical practice. These considerations demand that the parties involved in the legal manufacture, distribution, prescription and dispensing of opioid medications for medical purposes be mindful of their substantial abuse potential.

Ideally, international and local regulations of opioid manufacture, distribution, storage, prescription and dispensing should aim to maintain a balance between good patient care and diversion prevention. Preventing drug abuse is important, but it should not hinder patients' ability to

	Language used in opioid regulations	Stigmatizing terminology used		
		Drugs of addiction	Dangerous drugs	Poisons
Albania		N/R	N/R	N/R
Belarus	No data	No data	No data	No data
Bosnia Herzegovina		N/R	N/R	N/R
Bulgaria		N/R	N/R	N/R
Croatia	No data	No data	No data	No data
Czech republic				
Estonia	No data	No data	No data	No data
Georgia				
Hungary		N/R	N/R	N/R
Latvia				
Lithuania		N/R	N/R	N/R
Macedonia				
Moldova				
Montenegro		N/R	N/R	N/R
Poland		N/R	N/R	N/R
Rumania		N/R	N/R	N/R
Russian Federation		N/R	N/R	N/R
Serbia				
Slovak Republic		N/R	N/R	N/R
Slovenia		N/R	N/R	N/R
Tajikistan		N/R	N/R	N/R
Ukraine		N/R	N/R	N/R
Austria				
Belgium		N/R	N/R	N/R
Cyprus		N/R	N/R	N/R
Denmark		N/R	N/R	N/R
Finland				
France				
Germany		N/R	N/R	N/R
Greece		N/R	N/R	N/R
Iceland		N/R	N/R	N/R
Ireland		Misuse		
Israel				
Italy		N/R	N/R	N/R
Luxemburg		N/R	N/R	N/R
Netherlands		N/R	N/R	N/R
Norway		N/R	N/R	N/R
Portugal		N/R	N/R	N/R
Spain		N/R	N/R	N/R
Sweden	narcotic	N/R	N/R	N/R
Switzerland		N/R	N/R	N/R
Turkey				
United Kingdom		N/R	N/R	N/R

Neutral language Negative language

Figure 10. Stigmatizing language in regulations. N/R, not relevant.

receive the care they need and deserve. This is the approach of the WHO and the INCB [8, 9, 12, 16, 18]. Both recommend that opioids should be available for cancer patients at hospital and community levels and that physicians should be able to prescribe opioids according to the individual needs of each patient.

While most governments allow physicians to prescribe opioids for patients, regulations vary among nations and in many countries, regulations to reduce substance abuse and to restrict the diversion of medicinal opioids into illicit markets unduly interfere with medical availability for the relief of pain. This is the basis for the internationally recognized public health problem of overregulation.

Bases on the findings of our survey we will address three issues:

- 1 Are opioid formularies in European countries consistent with the essential medicines list of the WHO and the IAHPC?
- 2 How compliant are European countries with the guidelines of the WHO and the INCB regarding opioid regulations for cancer pain?
- 3 Do regulations make allowances for efficient emergency prescribing and dispensing of opioids for patients with strong pain in out-of-hours situations?

are opioid formularies in European countries consistent with the essential medicines list of the WHO and the IAHPC?

The WHO essential medicines list [15] presents a minimal formulary for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. In addition to listing codeine and morphine (immediate release, controlled release and injectable) for pain in the most recent version, the WHO Expert Committee indicates that it has invited submission for specific medicines for palliative care to be considered for inclusion in the next version. Indeed, the WHO requested that the IAHPC develop an expert-generated essential medicines list for palliative care on the basis of criteria of efficacy and safety. This list of recommendations, published in 2007 [19–22], is endorsed by the WHO Cancer Control Program [2]. The IAHPC lists all the formulations on the WHO essential pain medications along with three others: transdermal fentanyl, oral methadone and oral immediate release oxycodone (Table 1).

Most West-European countries in Europe provided broad opioid formularies with a range of drugs appropriate for different routes of delivery. Most are fully compliant with the formulary recommendations of the IAHPC and the WHO. Exceptions included the exclusion of oral immediate release morphine in Turkey; exclusion of immediate release oxycodone in Portugal, Greece, Belgium and Turkey and exclusion of oral methadone in Portugal, Cyprus, Greece and Turkey.

The situation is substantially different in the East-European countries where, in general, formularies are more restrictive. Of the 21 East-European countries surveyed, only Croatia and Rumania carried all the IAHPC-recommended opioid formulations. Eleven countries (Czech Republic, Latvia, Slovak Republic, Hungary, Estonia, Serbia, Bulgaria, Poland and Russia) provided at least five of the seven IAHPC-recommended opioid formulations. The formularies of seven countries (Bosnia–Herzegovina, Tajikistan, Lithuania, Belarus, Albania, Georgia and Ukraine) were particularly deficient, excluding four or more of the seven IAHPC essential opioid analgesics.

how compliant are European countries with the guidelines of the WHO and the INCB regarding opioid regulations for cancer pain?

In 2000, the WHO [11] in cooperation with the INCB published a guideline ‘Achieving balance in national opioids

control policy: guidelines for assessment' to assist policy makers to assess the balance of laws and regulations. This document emphasizes the concept of balance that regulations should be sufficient to prevent diversion and trafficking but that they should not compromise access for genuine medical need. The document outlines criteria for fair and valid regulations that are consistent with the aims of the INCB (Table 2). Important safeguards to prevent abuse, misuse and diversion include health care provider and pharmacist education, safe storage, documentation of medication dispensed, return of unused medications and sound clinical practice consistent with standards of care.

Many of the regulations regarding opioid prescribing and dispensing identified in this survey are inconsistent with the WHO and INCB recommendations insofar as they seek to:

- 1 limit entitlement to receive opioid analgesics to relieve severe pain only to patients with special authorizations (requirements for patient permits),
- 2 limit the empowerment of some physicians to prescribe to patients with medical need (restrictions on prescriber privileges),
- 3 interfere with clinical decision making regarding drug dosing (dose limits),
- 4 preclude provision of an adequate supply of medication to meet individual clinical needs (limits on duration of prescription, i.e. 7 days' supply only),
- 5 reduce accessibility to patients (restriction on opioid dispensing),
- 6 increase bureaucratic burden (complex prescription form requirements, poorly accessible prescription forms, complex reporting requirements) and
- 7 intimidate health care providers and pharmacists (intimidatory legal sanctions).

Table 2. Criteria for fair and valid regulations that are consistent with the aims of the International Narcotics Control Board

1. Recognize the medical imperative to treat pain (Guideline 2)
2. Empower medical professionals to provide opioids to patients with medical need (Guideline 10)
3. Allow professionals to prescribe, dispense and administer 'according to medical needs' (Guidelines 15 and 16)
4. Do not interfere with legitimate medical use and reasonable patient care either through excessive bureaucratic burden or fear of prosecution
5. Ensure that an adequate supply is available to meet legitimate demands (Guidelines 3–8 and 11).
6. Ensure accessible dispensing arrangements to optimize access for patients with medical need (Guideline 12)
7. Regulations should be developed and evaluated in collaboration with responsible health care providers (Guideline 9)
8. Promote effective responsible practice through education (Guidelines 12 and 14)

As problematic as each of these violations are alone, when they are sequential in the process of prescribing and dispensing, their affects are multiplied, and the impact on patient care is profound. This appears to be the situation in many East-European countries, particularly in Russia, Montenegro, Macedonia, Bosnia–Herzegovina, Lithuania, Belarus, Albania, Georgia and Ukraine.

do regulations make allowances for efficient emergency prescribing and dispensing of opioids for patients with strong pain in out-of-hours situations?

Problems of severe cancer pain do not respect physicians' working hours. Indeed, situations arise when patients have urgent need for the relief of severe pain when a physician may not be able to attend to them. In such circumstances, potential options for opioid prescription include (i) presenting to an emergency room, (ii) contacting the physician by phone or faxing an emergency prescription to a pharmacist, (iii) having the attending nurse generate an emergency prescription or (iv) having the pharmacist generate an emergency prescription. Very few countries in Europe make regulatory provision for these circumstances.

disclaimers and limitations

The information presented in this survey was derived from practicing clinicians and not from state authorities or statutory bodies and this may have allowed for the introduction of some inaccuracies in the data. Several steps were undertaken to minimize the risk of inaccuracy. In circumstances in which the reporting physicians were unsure of a regulation or formulary issue, they were requested to consult with regulatory authorities. Veracity of the information was strengthened by opening the data to peer review by members of the EAPC, the Open Society Institute, the International Observatory for Palliative Care and the WHO Collaborating Center/Pain & Policy Studies Group.

The reported opioid availability refers only to formulary availability. In situations in which national authorities have not submitted requests for adequate supply of the formulary medication from the INCB, actual availability may be restricted. There is strong evidence that requested quantities of opioids are far below levels of actual need in many countries, particularly among the East-European countries.

The degree to which any one regulatory restriction on opioid accessibility actually reduces patient access is variable and is influenced by specific procedural requirements and logistic arrangements.

Other factors besides the regulatory issues highlighted in this report may contribute to the undertreatment of cancer pain. These include the attitudes of patients and their families toward opioid medications and the knowledge and attitudes of the prescribing physicians regarding the use of opioids; the management of strong pain and the availability and accessibility of other modalities of treatment of cancer pain

(such as radiotherapy) may also effect the management of cancer pain.

facilitating regulatory review and reform

The Opioid Policy Group of the ESMO and the EAPC is committed to encouraging and catalyzing the regulatory reforms necessary to ensure that all cancer patients in Europe will have ready access to opioid medications needed to provide adequate relief of their pain. Our approach is supported by international human rights law which requires that governments must provide and ensure accessibility of essential medicines including opioid analgesics—as part of their minimum core obligations under the right to health [23].

In many countries reported in this survey, the dominant paradigm of opioid regulations is most consistent with a ‘criminalization model’ to mitigate crime and addiction rather than a ‘public health model’ to facilitate care and reduce harms. Using standards derived from the WHO and the INCB, this survey has exposed formulary deficiencies and excessive regulatory barriers that interfere with appropriate patient care in many European countries. There is an ethical and public health imperative to address these issues vigorously and urgently.

The experience of the University of Wisconsin Pain & Policy Studies Group, a WHO Collaborating Center, has demonstrated that policy evaluation and collaboration between interested parties and regulators can facilitate constructive formulary and regulatory reforms. This process has been successfully initiated in Germany, Romania [24, 25], Italy [26, 27], India, including the state of Kerala [26], Colombia [28] and Uganda. Other countries have undertaken reforms without this assistance: in the UK, the Shipman tragedy precipitated a review of regulations [29] and in Poland [30] and Israel, reforms were initiated in response to intense lobbying by the pain and palliative care clinicians and patient advocacy groups.

The ESMO and the EAPC encourage an approach in which regulatory reform is combined with education initiatives to ensure clinically appropriate and responsible prescribing and dispensing. We emphasize the importance of maintaining the recommended safeguards of including health care provider and pharmacist education, safe storage, documentation of medication dispensed, return of unused medications and sound clinical practice consistent with standards of care.

major recommendations

1 Formulary restrictions: We endorse the standards of the WHO essential medicines list as a minimal standard for opioid formulary. This minimal formulary should include oral codeine, immediate release morphine, controlled release morphine tablets and injectable morphine. We concur with the more expansive formulary described by the IAHPIC as a preferred minimal standard but we view this as aspirational at this time. Furthermore, we endorse the policy of the IAHPIC that governments should not approve controlled

release morphine, fentanyl or oxycodone without first guaranteeing widely available immediate release oral morphine.

- 2** Regulatory restrictions: The ESMO and the EAPC echo the WHO and the INCB in calling for government examination of drug control policies and repeal of over vigilant or excessive restrictions that impede good clinical care of cancer pain. Examples of such restrictions include requirement for patients to have a special permit or restrictions on care settings where opioids can be prescribed, restrictions on prescribing privileges to limited physician specialties, arbitrary dose limits, excessive restrictions on the number of day’s supply that can be prescribed at one time and severe restrictions on the sites of opioid dispensing.
- 3** Emergency prescribing: Regulatory provision should be made for emergency prescriptions of opioids for patients in severe pain who cannot obtain a physical prescription. The ESMO and the EAPC support the approach of the Drug Enforcement Administration of the United States which permits emergency prescription by telephone or facsimile to the pharmacist. The pharmacist must ensure the veracity and validity of the prescription before dispensing the controlled substance and the prescriptions must be transcribed to hard copy by the pharmacist and retained (Title 21, Code of Federal Regulations section 1306.21).
- 4** Special prescription forms: The requirement for special prescription forms is not considered an excessive burden *per se*. It is essential, however, that forms be readily available to prescribers and that the process of procuring them not be excessively burdensome so as to provide a disincentive to do so.
- 5** Dispensing: Pharmacists must have the authority to correct technical errors in consultation with the prescribing physician.

nonphysician prescribing

Nonphysician prescribing by specially trained nurses and pharmacists is advocated by some as a means of providing a backup system of prescribing in situations when there is no physician availability. Among European countries, regulations and procedures for nonphysician prescribing are best developed in the UK. The regulations, legislated in 2001 and initiated in 2003, distinguish between ‘independent nonmedical prescribers’ who have prescribing privileges within their area of professional competence and ‘supplementary prescribers’ who are not authorized to initiate courses of treatment but may extend or modify courses of treatment after initial diagnosis by a doctor or other independent prescribers [31]. The nurse and pharmacist prescribers program extends prescribing privileges to specially certified nurse prescribers with access to a defined formulary of prescription medicines including some opioid analgesics. Supplementary prescribing enables qualified nurses and pharmacists to prescribe any medicine (including controlled drugs), within the framework of a patient-specific clinical management plan, agreed with a doctor. Nurse prescribing has also been described in

resource-poor settings to facilitate opioid accessibility in rural Africa [32].

Nonphysician prescribing remains contentious and is opposed by many medical authorities. The Opioid Policy Group of the ESMO and the EAPC consider that this may be a beneficial approach, especially in emergency situations. Further study of this experience is warranted.

conclusions

There is evidence that in many European countries, particularly among the East-European countries, patient access to the medication needed to relieve cancer pain is profoundly restricted by inadequate formulary availability and overregulation. The undertreatment of pain and the suffering that ensues is a public health catastrophe. Advocacy initiatives by stakeholder and international organizations partnering with authorities and regulators have demonstrated that regulatory reform is possible. Urgent and intensive efforts are needed to expand this process, particularly in the countries with the most severe restrictions of availability and accessibility. The ESMO and the EAPC have undertaken a joint program to lead these initiatives.

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appendix 1

Table A1. National representatives from ESMO and EAPC who contributed data

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George Marcoullis, Barbara Pitsillides	Cyprus
Lubos Petruzelka, Ondrej Slama	Czech Republic
Gedske Daugaard, Bodil Abild Jespersen	Denmark
Simon Van Belle, Dirk Schriver, Trudie van Iersel	Belgium
Eva Saliminen, Tarja Korhonen, Tarja Heiskanen, Tiina Saarto	Finland
Jean-Yves Blay, Marilène Filbet	France
Nino Sharikadze	Georgia
Joachim Schmoll Hans, Christof Müller-Busch, Marianne Kloke	Germany
Dimitrios Bafaloukos, Kyriaki Mystakidou, Ioanna Sifaka, Vadalouca Athina	Greece
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Oscar S. Breathnach, Regina McQuillan	Ireland

Table A1. (Continued)

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Dmitry Nosov, Anonymous	Russian Federation
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Johann De Bono, Nigel Sykes	UK