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# Documented: Big Regulatory Barriers To Cancer Pain Relief Worldwide

BY HEATHER LINDSEY

More than half of the world's population lives in countries where regulations aiming to prevent opioid misuse leave cancer patients without access to pain medicines, according to new data from the Global Opioid Policy Initiative (GOPI) (***Ann Oncol; Dec 2013;24, suppl 11***).

Overall, the survey of 104 countries in Africa, Asia, the Middle East, Latin America and the Caribbean, and India "confirms what many of us thought when looking at opioid-consumption data," said James F. Cleary, MD, FAChPM, one of the authors and Associate Professor of Medicine and Director of the Pain and Policy Studies Group (PPSG) at the University of Wisconsin Carbone Cancer Center. "Few opioid medicines are consumed for medical and scientific purposes."

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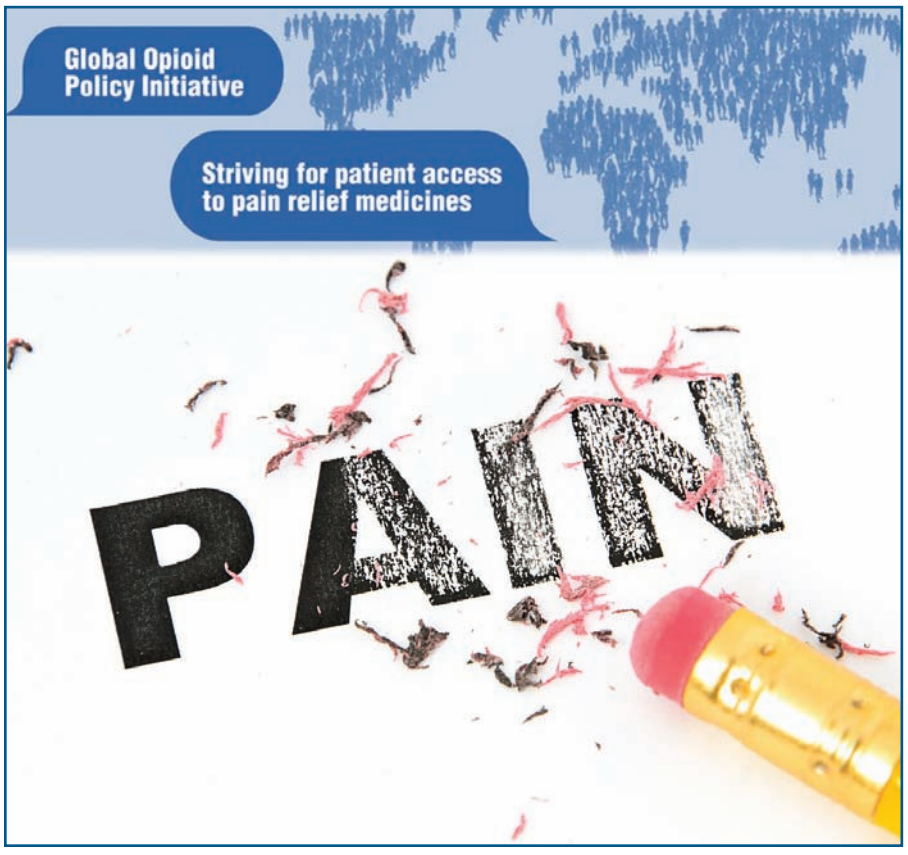


# ASCO Report on 2013 Advances: Progress, But Harm from Budget Cuts

BY PEGGY EASTMAN

The American Society of Clinical Oncology's year-end report on the major clinical cancer advances in 2013 documents much to celebrate, but sounds a strong note of alarm due to budget cuts for cancer research funding.

To keep cancer research strong and counter funding cutbacks, ASCO is seeking a fiscal year 2014 appropriation of $32 billion for the National Institutes of Health, including $5.2 billion for the National Cancer Institute.


While the recent Senate-House budget agreement is a step in the right direction of making up for what ASCO calls years of stagnant funding and cuts to NIH, the agreement falls short in protecting the nation's cancer care infrastructure, the

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## Sales and Marketing of Ponatinib Resume

The U.S. Food and Drug Administration has approved a revised U.S. Prescribing Information (USPI) and Risk Evaluation and Mitigation Strategy (REMS) for the leukemia drug Iclusig (ponatinib). In addition, the agency has asked Ariad Pharmaceuticals, the drug's manufacturer, to conduct post-market investigations to further characterize ponatinib's safety and dosing.

These required safety measures include:

- Label changes to narrow the indication;
- Providing additional warnings and precautions about the risk of blood clots and severe narrowing of blood vessels;
- Revising the recommendations about the dosage and administration; and
- Updating the patient Medication Guide.

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# REGULATORY BARRIERS TO CANCER PAIN RELIEF

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Complete data from 104 countries and states were available, representing 67% of those contacted, including about five billion people, or 87% of the target population.

Based on the data, "it's quite clear that there is inadequate access and education regarding prescribing of opioids," commented Jamie H. Von Roenn, MD, Senior Director of American Society of Clinical Oncology's Education, Science and Professional Development Department.

Overall, the survey provides a monumental series of data with in-depth analysis, said Daniel B. Carr, MD, MA, Professor of Public Health and Community Medicine and Program Director of the Pain, Research Education & Policy Program at Tufts University School of Medicine. "It's a fabulous blueprint or roadmap for clarifying the gaps in palliative care across different areas of the world."


JAMES F CLEARY MD, FACHPM, said that despite the problems, access to palliative care is already improving, with programs such as the UICC's Global Access to Pain Relief Initiative and other international organizations. "These groups are all working together, but we've got to make sure we're coordinated in the right way. Working with local advocates and champions is important, as well as with government authorities."

Many of the barriers documented in the study are well known, noted Eduardo L. Cazap, MD, PhD, FASCO, Founding President of the Latin-American & Caribbean Society of Medical Oncology (SLACOM), which was involved with the survey. "But when you're talking with regulators or with policymakers, it's necessary to have documentation to support your position."

## Study Details

The European Society for Medical Oncology (ESMO) and the European Association for Palliative Care conducted the survey, with the cooperation of the Union for International Cancer Control (UICC), the PPSG, the World Health Organization (WHO), and 17 international oncology and palliative care societies.

The researchers collected information about the availability of seven "essential" opioids for cancer pain relief: codeine, immediate-release (IR) and controlled-release (CR) oral morphine, injectable morphine, IR oral oxycodone, transdermal fentanyl, and IR oral methadone.

Additionally, investigators assessed the following factors:

- The presence of national palliative care organizations;
- Cultural and social barriers to opioid use;
- Changes in drug regulations during the past five years;
- Opioid availability to patients with prescriptions; and
- The accessibility of medication dispensers.

Complete data from 104 countries and states were available, representing 67 percent of those contacted. On a population basis, the dataset reflects 5.03 billion people, representing 87.3 percent of the target population. Overall, substantial formulary and regulatory barriers to opioid access were identified in the majority of countries surveyed.

The results showed that opioid availability in 25 African countries is "critically low," the study authors said. Codeine and morphine were the most common pain medications available, with no country having access to all seven essential opioids.

Most African countries used regulatory restrictions to limit opioid access. For example, 16 countries required special authorization for outpatients to receive an opioid prescription, while this was the case for inpatients in 15 countries.

Opioid availability was also found to be low in Asia, except for Japan and South Korea, with a total of 20 countries surveyed. Codeine and morphine were the most commonly available formulations, and only three countries had all seven essential formulations.

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# BRAIN METASTASES

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"Preserving neurological function and memory is key. Survival is dependent on getting the brain tumor and the body tumor under control."

11 months, including patients who had lung cancer, melanoma, renal cell carcinoma, and breast cancer, he said, noting that survival depends on many factors.

"What can we learn from patients who live much longer than anyone may have expected?" he asked. About one-third of these patients had only brain disease or the brain was the primary site of cancer. About another one-quarter had brain cancer plus nodes, and another 40 percent had brain cancer plus two or more organ sites.

In summary, Silverman said, "Preserving neurological function and memory is key. Survival is dependent on getting the brain tumor and the body tumor under control. Gamma knife radiosurgery can be used for any number of brain tumors. Close imaging follow-up is needed. WBRT may be used for specific patients. Long-term survivals are possible and will continue through innovation and research to improve outcomes."

In the future, researchers need to determine the optimal treatment for larger tumors following resection, and develop biologics and better radiotherapy for brain metastases. "We need to treat 'radio-resistant' histologies, such as those found among renal carcinoma and melanoma patients," he said. Areas still under question include decreasing toxicities and neuroprotection, novel imaging technologies, disruption of the blood brain barrier, and primary systemic treatment for brain metastases, as well as possible immunotherapies.

"We need to think more about neurosurgery to treat a larger burden of metastases. If we are able to do that, then we can reduce the neurocognitive complications that often accompany WBRT," Silverman said.

Trials are needed to compare WBRT with neurosurgery. He noted that some studies show that surgical resection plus WBRT does not necessarily improve survival. "At the moment, results for these two treatments—neurosurgery and WBRT—vary from center to center," he said, adding that in making a referral, clinicians need to look for a center that has experience in treating a large number of metastases.

Asked for her opinion, Katharine McNeill, MD, an instructor in the Departments of Medicine and Neurology at New York University Langone Medical Center, said, "It will be exciting to see more investigations into treating brain metastases in glioblastoma, which is a heterogeneous disease. Studies can identify genes from the patient that can be targeted for therapy. Then we can detail what genomic changes may be due to particular tumors, and target pathways in individual patients."

She predicted that this type of genomic therapy will be available for treating patients with brain metastases within the next five to 10 years.

## PAIN RELIEF

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Even in countries with very limited opioid formularies, transdermal fentanyl was available. The majority of countries reported at least four regulations impairing opioid access.

In the 16 Middle Eastern countries assessed, opioid availability was generally low. Several countries had severe formulary deficiencies, with opioids often being unavailable even when they were on formulary. Israel, Qatar, and Saudi Arabia had access to all seven essential opioids. While six countries didn't have immediate-release morphine and four had no sustained-release (SR) morphine, all but two reported having transdermal fentanyl available. All countries in the region, except Israel, experienced very high levels of restrictive regulations.

Data for 24 Latin American and Caribbean countries indicated low opioid availability throughout most of the region. However, formulary deficiencies did not appear to be a major barrier, with 15 of 24 countries surveyed having five or more essential opioids. Most countries in the region had four or more restrictive regulations.

Notably, three of six countries that did not have IR oral morphine did have transdermal fentanyl, which overall was available in 17 of 24 countries.

In India, opioid availability was low in the 24 states surveyed, with access generally limited to codeine and morphine. Opioids were often unavailable even when on formulary. Oxycodone, methadone, and fentanyl were accessible in a few states, and morphine consumption was quite low.

The investigators noted that after the 1985 Narcotic Drugs and Psychotropic Substances Act was enacted in India, the country experienced a significant reduction in opioid consumption.

### Formulary Barriers

Cleary said that although initially formulary issues don't seem as prohibitive as other barriers, even those medicines listed as "being available" are not always available, and that there are challenges to keeping a continuing supply of medicines once patients start taking them.

JAMIE VON ROENN, MD: "Based on the data, it's quite clear that there is inadequate access and education regarding prescribing of opioids."

As shown in the report, one of the main barriers to palliative care is not having morphine, noted Stephen R. Connor, PhD, Senior Fellow for the Worldwide Palliative Care Alliance (WPCA), which collaborated on the study. "Many countries don't have morphine at all or have only have the injectable form, making adequate pain relief almost impossible." And, even if countries have injectable morphine, they typically allow patients to have only a couple of doses a day, which is not enough to control cancer-related pain, he added.

Morphine is an incredibly cheap drug and is the gold standard for pain relief, said Von Roenn. Because IR and SR morphine are available in many different formulations, including oral, subcutaneous, injectable, or suppository, "you can give it in so many different ways depending on the health of the patient."

Although not a panacea, morphine is crucial to controlling cancer-related pain in the developing world, Carr said. Based on the survey, the administration of strong opioids, which is the final step of WHO's well-known three-step ladder for pain control (**who.int/cancer/palliative/painladder/en**), is not being followed—the literature indicates that 90 percent of cancer patients can have their pain controlled if their health care providers follow those three steps, he added.

### Regulatory Barriers

Regulatory issues are one of the greatest challenges oncologists and their patients have to contend with, Cleary

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## PAIN RELIEF

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said, noting, though, that unfortunately, governments don't realize that a dual system of control needs to exist in which they both ensure access to opioids for medical purposes and reduce harm and abuse.

To further complicate matters, many countries enforce dose limitations on opioids, audit the drugs, and have a commission that has to approve physician-written prescriptions, Connor said.

He called such regulations an example of the overreaction to 1961's Single Convention of Narcotic Drugs, which called for controlled substances to be used for medical and scientific reasons, while attempting to prevent their abuse—"Following the convention, governments got overly concerned about the potential for addiction and illicit use of drugs," he said.

Many regulations also reflect historical events, Cleary noted. For example, in India, control of opioids resides within the department of revenue because each state collected tax on opioids during the opium wars.

Codeine and morphine were the most common pain medications available, with no country having access to all seven essential opioids.

### Patient Barriers

Another challenge, Von Roenn said, is that patients may inaccurately think that the benefit from opioids can run out or that the side effects are so severe that palliation isn't worth it.

Patients in developing countries often expect less with pain management, said Meg O'Brien, PhD, Director of the American Cancer Society's international Treat the Pain Program. "It's much more commonplace for people to die there in excruciating pain."

Overall, the general population lacks opioid education and has been told for years that these drugs cause addiction, said O'Brien. Patients and their family members often don't understand that safe and effective drugs are available to address pain while simultaneously treating cancer.

Alonso Nichols/Tufts University

DANIEL B. CARR, MD, MA, said that based on the survey, the administration of strong opioids, which is the final step of WHO's well-known three-step ladder for pain control, is not being followed; the literature indicates that 90% of cancer patients can have their pain controlled if their health care providers follow those three steps.

EDUARDO L. CAZAP, MD, PHD, FASCO, said that overall he is optimistic about the changes under way in Latin America. "The region is experiencing a special momentum from a policy point of view on improving cancer care, pain management, and palliative care, and several countries in the region now have pain control and morphine access as a priority."

MEG O'BRIEN, PHD: "Patients in developing countries often expect less with pain management. Overall, the general population lacks opioid education and has been told for years that these drugs cause addiction. Patients and their family members often don't understand that safe and effective drugs are available to address pain while simultaneously treating cancer.

### Pharmaceutical Company Barriers

Because morphine is so affordable, the profit margin for pharmaceutical companies is minimal, Carr noted. Other formulations, such as a nasal spray or controlled release, may result in a higher profit margin. Typically, the rationale for a more costly, newer formulation is some benefit such as quicker onset or improved convenience.

Pharmaceutical companies are making sure more profitable fentanyl patches are available in low- and middle-income countries instead of morphine, Cleary said. "But the cost of fentanyl may be prohibitive in a low-income country."

Developing countries are a small market for pharmaceutical companies, O'Brien noted. "Having said that, I have never worked in a country where it wasn't possible to procure opioids. It may take more work to make those sales happen, but it is possible."

### Advocating and Educating

Cleary said that access to palliative care is already improving, with programs such as the UICC's Global Access to Pain Relief Initiative, which collaborates with Human Rights Watch, the International Association for Hospice and Palliative Care, WPCA, ASCO, and WHO, among others.

"These groups are all working together, but we've got to make sure we're coordinated in the right way. Working with local advocates and champions is important, as well as with government authorities."

Von Roenn acknowledged that the increasing number of international organizations addressing pain relief in cancer patients is encouraging. ASCO provides several international programs instructing health care providers about assessing pain and prescribing appropriate medication—"they go hand and hand," she said.

The ACS's Treat the Pain Program focuses on a step-by-step initiative to work directly with national governments to procure an in-country supply of opioids at low cost to patients, O'Brien said. "We also focus on distribution and training of health care workers training."

Developing relationships with drug companies willing to manufacture opioids and contend with regulatory requirements within various countries is also critical, said Connor.

Some individual governments are taking the initiative to establish such relationships, Cleary said. For example, the government of Nepal has overcome regulatory barriers and is working with pharmaceutical companies to provide both IR and SR morphine to patients.

Cazap said that overall he is optimistic about the changes under way in Latin America. The region is experiencing a "special momentum from a policy point of view on improving cancer care, pain management, and palliative care, and several countries in the region now have pain control and morphine access as a priority."

So far, very few reports of misuse or abuse or diversion of opioids have surfaced with palliative care initiatives, Cleary said. "These programs and regulations can be put into place quite safely."