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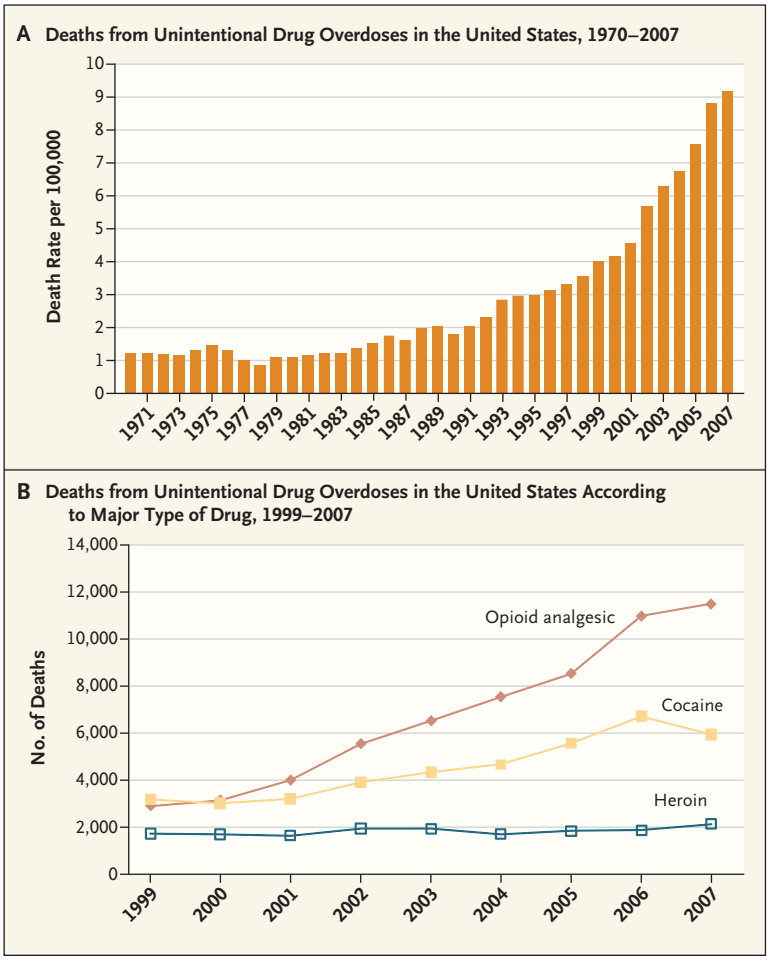
A Flood of Opioids, a Rising Tide of Deaths

Susan Okie, M.D.

Faced with an epidemic of drug abuse and overdose deaths involving prescription opioid pain relievers, the Food and Drug Administration (FDA) plans to require opioid makers to provide training for physicians and patient-education materials on the appropriate prescribing and use of extended-release and long-acting versions of these drugs. But since July, FDA officials have been scrambling to revise their proposed Risk Evaluation and Mitigation Strategy (REMS), after an advisory panel (the agency's Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee) voted 25 to 10 against the FDA's plan, saying it didn't go far enough. Advisors urged that training in appropriate use of opioids be made mandatory for all physicians who prescribe them.

In the eyes of many patients, these opioids "are essentially legal heroin," advisory committee member Lewis Nelson of New York University School of Medicine commented during the panel's discussion. "We need to think about how we would construct a REMS if we were going to be marketing heroin." With more than a million prescribers of controlled substances registered with the Drug Enforcement Administration (DEA) and about 4 million U.S. patients receiving long-acting or extended-release opioids each year, the FDA's opioid REMS will affect far more people than any existing REMS for high-risk medications. Any discussion of restricting the use of pain medicines provokes emotional debate, with some advocates warning that people in chronic pain may be undertreated or stigmatized and others arguing that access to powerful painkillers leads to thousands of deaths each year.

There is ample evidence that action is needed. According to the Centers for Disease Control and Prevention (CDC), deaths from unintentional drug overdoses in the United States have been rising steeply since the early 1990s (see bar graph) and are the second-leading cause of accidental death, with 27,658 such deaths recorded in 2007. That increase has been propelled by a rising number of overdoses of opioids (synthetic versions of opium), which caused 11,499 of the deaths in 2007 — more than heroin and cocaine combined (see line graph). Visits to emergency departments for opioid abuse more than doubled between 2004 and 2008,[1] and admissions to substance-abuse treatment programs increased by 400% between 1998 and 2008, with prescription painkillers being the second most prevalent



U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.

Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.

type of abused drug after marijuana.[2]

These escalations parallel an increase by a factor of 10 in the medical use of opioids since 1990, spurred in part by aggressive marketing of OxyContin, an extended-release form of oxycodone approved in 1995, and by efforts to encourage clinicians to become more proactive in identifying and treating chronic pain. Between 1997 and 2002, sales of oxycodone and methadone nearly quadrupled. Although both per capita opioid sales and death rates from the drugs vary widely among the 50 states, studies have found a strong correlation between states with the highest drug-poisoning mortality and those with the highest opioid consumption; per capita sales are most strongly linked with methadone- and oxycodone-related mortality.[3] "In some ways, this is an unintended consequence of an intent to treat pain better," said Robert Rolfs, Utah's state epidemiologist.

The increase in opioid deaths has been accompanied by a striking shift in the prevalence of fatal drug overdoses from urban to rural counties. The highest rates now occur in predominantly rural states, including West Virginia, New Mexico, Utah, Louisiana, Oklahoma, Nevada, Kentucky, and Tennessee — although some other rural states have low rates. Leonard Paulozzi, a medical epidemiologist with the CDC's Division of Unintentional Injury Prevention, said that the increases in opioid prescribing and sales during the 1990s brought "abusable" drugs into rural areas where no distribution network had existed for illicit drugs, such as heroin or cocaine. "Everybody's within a few miles of a pharmacy," he said, though he admits that increased availability is not the only relevant factor.

States' systems for investigating deaths vary in comprehensiveness, and Paulozzi said the CDC's figures underestimate the total number of overdose deaths. Nevertheless, certain patterns seem clear. For example, although rates of suicide caused by drug overdoses have also increased somewhat, most opioid-overdose deaths are accidental. More often than not, laboratory tests reveal the presence of one or more substances in addition to the opioid, suggesting that the depressant effects of alcohol or other drugs on the central nervous system were additive with those of the pain reliever in causing death.

In almost every age group, men have higher death rates from drug overdoses than women. The highest mortality for both sexes occurs among people 45 to 54 years of age, although young adults abuse opioids and other drugs more frequently and are more likely to be seen with drug-related symptoms

in emergency rooms. Whites and Native Americans have higher death rates from drug overdoses than blacks. National prescription-tracking data show that more than 40% of opioid prescriptions are written by general or family practitioners, osteopaths, or internists, most commonly for diseases of the musculoskeletal system and connective tissue. More than 3% of U.S. adults currently receive long-term opioid therapy for chronic noncancer pain, and patients taking high daily doses appear to be at increased risk for overdose.[4]

Reducing deaths from opioid overdoses is challenging because such deaths stem from multiple factors, including providers' inappropriate prescribing or inadequate counseling and monitoring, patients' misuse or abuse of drugs, sharing of pain pills with relatives or friends, "doctor shopping" to obtain multiple prescriptions, and diversion of opioids leading to illicit sales and abuse. A study of unintentional-overdose deaths during 2006 in West Virginia (the state with the highest rate of death from such overdoses) showed that almost everyone who died had one or more indicators of drug or substance abuse; additional risk factors included having a low level of education and living in one of the state's poorest counties.[5] About half of those who died had a medical history of pain treatment. Opioids were involved in 93% of deaths, with methadone implicated far more often than any other drug. Methadone sales for chronic pain have increased partly in response to pressure from insurers and Medicaid programs, because the medication has been viewed as a cheaper and potentially less abusable alternative to other long-acting pain relievers. However, its very long half-life makes it tricky to manage and especially dangerous when combined with other drugs.

Experts said that tracing the sources of drugs that are implicated in individual overdose deaths is difficult. "It's really impossible to say with any certainty, 'This death obviously was a therapeutic error,' or 'This death was misuse of the drug,' or 'This death was obviously abuse,'" said Edward Boyer, chief of the division of medical toxicology at the University of Massachusetts and an advisory committee member.

"Clearly, getting [prescription pain relievers] from doctors" is common in such cases, added Utah's Rolfs. "Many of these people have chronic pain, and you might want to consider prescribing an opioid for them, but they also tend to be people, at least in retrospect, who have a lot of risk factors" for abuse.

John Jenkins, director of the Office of New Drugs at the FDA's Center for Drug Evaluation and Research, said the opioid REMS will use training programs and educational materials to try to ensure that physicians prescribe the drugs only for appropriate patients and indications, prescribe them properly, and counsel patients on their safe use and disposal. He said the agency proposed limiting the REMS to long-acting and extended-release opioids because the "unique pharmacology and delivery system" of these formulations make them riskier than immediate-release opioids. For patients with no previous exposure to such drugs, 80 mg of OxyContin "might be a fatal dose, even if you take it correctly," Jenkins said. In addition, fewer health care providers prescribe long-acting opioids than immediate-release ones, so limiting the REMS to the longer-acting drugs would reduce the burden on the health care system. However, many advisory committee members argued that the REMS should cover all opioids, and some suggested that methadone deserved special attention.

Under the proposed REMS, companies marketing opioids would develop training content (subject to FDA approval), recruit doctors, and assess their programs' effectiveness, but training would be voluntary. The FDA could require such training, but officials said doing so would be costly and would duplicate the DEA's registration system for prescribers of controlled substances. To make pain-management training mandatory for obtaining a DEA number, a change supported by the advisory committee, Congress would have to pass legislation. Alternatively, state medical licensing boards could require such training (California, Rhode Island, and West Virginia already do to some extent), but each state sets its own licensing requirements.

In its proposed REMS, the FDA also opted not to require registration of persons receiving long-acting opioids or signed patient–provider agreements regarding proper use. Though such measures might strengthen the program, critics predicted they would create barriers to treatment and stigmatize people with chronic pain. Once the agency notifies manufacturers of its REMS requirements, they'll have up to 120 days to submit a program for approval, so details of the final plan will probably not become public until early next year.

Regulating Opioid Use in Washington State

Once a new law goes into effect in mid-2011, opioid prescribers in Washington State will have to enter their patients' clinical responses to treatment in a statewide database and consult a pain specialist if a patient's daily dose goes above a specified threshold.

Deaths by poisoning (90% of them caused by drug overdoses) surpassed motor vehicle crashes several years ago as the commonest cause of accidental death in the state. The law that was passed earlier this year, which also mandates uniform pain-management guidelines and the use of a prescription-monitoring program, is the first state-government effort to require assessment of doctors' outcomes in managing chronic pain. The new rules will not apply to cancer pain, pain treated as part of palliative or end-of-life care, or acute pain after an injury or surgery.

Dr. Alex Cahana, chief of the Division of Pain Management at the University of Washington and an architect of the measure, said physicians have not substantially changed their practices in response to treatment guidelines and voluntary educational programs. However, they will do so "if they know their success in treating patients is being measured," he predicted. At the time that patients initially present with pain, they will be asked to complete a confidential computerized questionnaire assessing factors such as daily pain level, mood, quality of life, and history of mental illness or substance abuse. At each subsequent visit, they will complete a brief follow-up questionnaire. Health care providers can review each patient's longitudinal record in making treatment decisions, and studies of de-identified patient data can be used to measure population-wide outcomes and set policy. Cahana hopes that clinical feedback will help shift practitioners away from an "overreliance on pills, devices, and surgical procedures" and toward the use of nondrug treatments, such as graded exercise or behavior-modification programs.

A working group drawn from Washington's boards of health care professionals is drafting rules to implement the law. Critics predict that there will be too few pain specialists to meet the consultation demands and that some providers may opt out of prescribing opioids altogether. The new requirements "may lead practitioners to be far more hesitant to treat," said Dr. Perry Fine, a professor of anesthesiology at the University of Utah School of Medicine and president-elect of the American Academy of Pain Medicine.

Still, Fine added, Washington's new law may provide "the opportunity for measurable, monitorable" results of policies aimed at "getting the outcomes we all want."

Meanwhile, other federal agencies, state and local governments, and private entities are striving to reduce opioid abuse and overdose deaths. The DEA prosecutes doctors accused of illegally prescribing opioids at bogus pain clinics and recently tightened its regulation of online pharmacies. In September, it oversaw the first 1-day prescription-drug take-back program, encouraging consumers to turn in unused pain medications. Florida, Texas, and Louisiana recently passed laws to crack down on "pill mills," imposing state registration and other restrictions on pain clinics. Forty-one states have established programs allowing physicians and other authorized users to check a patient's history of receiving controlled-substance prescriptions, but some of these programs are unfunded or nonoperational, and few prescribers have signed up to use them. Next June, the country's most sweeping law aimed at regulating opioid use and improving pain-management practices will become effective in Washington State (see side bar), and health officials nationwide will be watching closely.

Ultimately, "we probably need a complicated, multifaceted solution" to the problem of opioid abuse and overdose, said Utah's Rolfs. "I don't think we have the answer."

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

Dr. Okie is a medical journalist and a clinical assistant professor of family medicine at Georgetown University School of Medicine, Washington, DC.

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Geographic Variation in the Quality of Prescribing

Yuting Zhang, Ph.D., Katherine Baicker, Ph.D., and Joseph P. Newhouse, Ph.D.

Medicare spending on pharmaceuticals varies substantially among U.S. localities and hospital-referral regions, even after adjustment for variation in demographic characteristics, individual health status, and insurance coverage.[1] If the drugs that are prescribed in high-spending regions are necessary and appropriate, the high spending may be justified by the health improvement they generate. But if such prescribing is not appropriate, the higher use could have serious adverse consequences. The elderly are twice as likely as people under 65 years of age to have adverse events associated with drugs and almost seven times as likely to be hospitalized as a result.[2] Although we have established that regions with higher drug spending do not seem to have offsetting reductions in medical spending (after adjustment for variation in medical risk),[1] little is known about how, if at all, the quality of prescribing varies among regions and whether any of the variation in quality, rather than quantity, is associated with variation in medical spending.

To assess geographic variation in the management of medication in the elderly, we used two quality measures from the Healthcare Effectiveness Data and Information Set (HEDIS): the use of medications that are considered to be high-risk for the elderly and potentially harmful drug–disease interactions (see maps).[3] The former measure assesses whether a Medicare beneficiary received at least one drug that should be avoided in the elderly; these drugs include some antihistamines, long-acting benzodiazepines, thioridazine, and some skeletal muscle relaxants, among others (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The latter measure assesses whether Medicare beneficiaries with evidence of one of three underlying diseases — dementia, a history of hip or pelvic fracture, or chronic renal failure — are given a prescription in an ambulatory care setting that is contraindicated for that condition.

We used pharmacy and medical claims data from a random sample of 5% of Medicare beneficiaries who were enrolled in stand-alone Medicare Part D plans in 2007.[1] We restricted our sample to beneficiaries who were between 65 and 99 years of age in 2007, were alive on December 31, 2007, and were enrolled for the full year in Medicare Parts A and B and a stand-alone Part D plan. We assigned each person in the resulting sample of 533,170 beneficiaries to one of the 306 Dartmouth hospital-referral regions on the basis of the ZIP Code of residence.

To determine the amount of variation in the use of high-risk medications, we calculated the proportion of beneficiaries in each hospital-referral region who had received at least one high-risk drug in 2007. We assessed the potentially harmful drug–disease interactions for each of the three conditions separately and used a combination measure indicating the proportion of patients with at least one of the three conditions who were taking any potentially harmful drug. For instance, we first identified the earliest indication of dementia during 2007 and determined whether beneficiaries with such an indication had received any drug classified as potentially harmful for persons with dementia in 2007, at the time of or after the first indication. We then calculated the proportion of beneficiaries with dementia in each hospital-referral region who had received a potentially harmful drug in 2007. In our sample, 16% of beneficiaries had received a diagnosis of dementia, 5% had a history of hip or pelvic fracture, and 16% had chronic renal failure; 29% had one or more of these conditions.