

berattacks potentially breaching confidential patient information, health care providers have not truly considered the physical harm that could befall our patients should an external party with malicious intent take over health service computers.⁴ This realization raises urgent questions about the necessity of equipping hospitals with fit-for-purpose IT. Digital security simply hadn't been an NHS priority until WannaCry's infection became the biggest cyberattack on critical infrastructure in U.K. history.

For NHS staff, the attack was stressful, grueling, and exhausting — not least for the legions of NHS IT workers who toiled all night to update and then patch thousands of health service systems. For doctors, it was a wake-up call. Underfunding ultimately left us horribly exposed to a pre-

dictable attack that threatened not just privacy but patient safety. If the WannaCry saga appears depressing, however — a realization of the perils of poorly funded health care — that was not the lesson we ultimately took from the experience. Facing adversity, with their backs against the wall, NHS staff quietly and resolutely got on with the job at hand.

But although — through our resilience — our most vulnerable patients were able to pull through the crisis this time, we cannot be complacent and wait for a next time. All health care workers now have a responsibility to educate ourselves about this emerging threat and demand that funds be made available to ensure that the software we use is as up to date as the medicines we prescribe. We wouldn't accept being told to use outdated equipment on our

patients, and our now-critical IT should be no different.

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Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern?

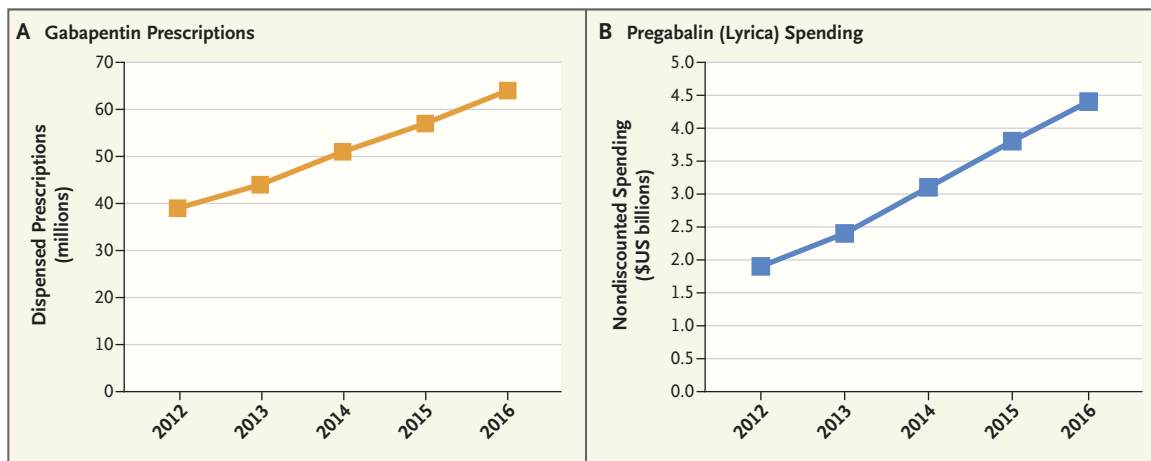
Christopher W. Goodman, M.D., and Allan S. Brett, M.D.

Treatment of chronic noncancer pain during the opioid epidemic has become challenging for clinicians. Patients want their pain to be adequately managed, and clinicians are searching for safe, effective alternatives to opioids. Recent guidelines from the Centers for Disease Control and Prevention (CDC) recommend that clinicians consider several other medication classes before turning to opioids for patients with chronic noncancer pain.¹ For example, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are mentioned as first-

line options for pain related to osteoarthritis and low back pain. However, acetaminophen is often ineffective, and NSAIDs are associated with adverse effects that limit their use, particularly in patients with complex conditions. The CDC guidelines also recommend gabapentinoids (gabapentin or pregabalin) as first-line agents for neuropathic pain. We believe, however, that gabapentinoids are being prescribed excessively — partly in response to the opioid epidemic.

The Food and Drug Administration (FDA) has approved gaba-

pentinoids for the treatment of postherpetic neuralgia (gabapentin and pregabalin), fibromyalgia (pregabalin), and neuropathic pain associated with diabetes or spinal cord injuries (pregabalin). However, while working in inpatient and outpatient settings, we have observed that clinicians in our practice community are increasingly prescribing gabapentin and pregabalin for almost any type of pain. Our experience is supported by national prescribing data.² In 2016, gabapentin was the 10th most commonly prescribed medication in the United States: 64



Dispensed Prescriptions for Gabapentin and Nondiscounted Spending for Pregabalin, 2012–2016.

Data are from IMS Health.

million gabapentin prescriptions were dispensed, up from 39 million in 2012. Brand-name pregabalin (Lyrica) ranked 8th in invoice drug spending (i.e., spending that excludes rebates and discounts) in 2016, with sales of \$4.4 billion — more than double the amount from 2012 (see graphs). Only three brand-name drugs typically prescribed by primary care physicians ranked higher in sales than Lyrica: Lantus insulin, Januvia (sitagliptin), and Advair (fluticasone-salmeterol). The remaining brand-name drugs that had higher sales are extremely expensive and usually prescribed by specialists for specific disorders (e.g., Humira [adalimumab] and Enbrel [etanercept] for autoimmune diseases and Harvoni [ledipasvir-sofosbuvir] for hepatitis C).

An increasing prevalence of diseases for which gabapentinoids are FDA-approved — or a growing tendency for clinicians to prescribe them for these conditions — probably can't explain the recent rise in gabapentinoid use. Rather, we suspect that clinicians who are desperate for alternatives to opioids have lowered their threshold for prescribing gaba-

pentinoids to patients with various types of acute, subacute, and chronic noncancer pain. For some of these patients, NSAIDs are contraindicated; for others, previous courses of acetaminophen and NSAIDs have proven inadequate or the patient or clinician may perceive them as “not strong enough.” Some patients, drawing on past experience, consider opioids to be their only source of adequate pain relief, and some specifically request opioid prescriptions. In such cases, clinicians may turn to gabapentinoids as one of the few nonopioid, non-acetaminophen, non-NSAID options.


Past marketing practices also help explain the growing use of gabapentinoids for various types of pain. Neurontin (the original branded gabapentin) was approved as an antiseizure drug in 1993. During the next several years, the manufacturer (Parke-Davis, a subsidiary of Warner-Lambert, which was later acquired by Pfizer) engaged in an extensive marketing campaign to increase off-label prescribing of Neurontin for pain.³ Research had suggested that the drug had analgesic properties, but

postherpetic neuralgia was the only pain-related indication for which there was sufficient evidence from clinical trials to justify FDA approval. Eventually, in 2004 (after Neurontin's patent had expired and gabapentin had become available as a generic), the manufacturer admitted to improper off-label marketing and paid a penalty.

Pregabalin, which is still available only as brand-name Lyrica, was approved for treating diabetic neuropathy and postherpetic neuralgia in 2004 and fibromyalgia in 2007. In 2012, the manufacturer paid a settlement for misleading promotion of the drug for off-label indications. In recent years, the company has used extensive direct-to-consumer advertising to promote Lyrica for painful diabetic neuropathy and fibromyalgia. Although Lyrica is approved for both these indications, the advertising probably promotes a perception that it has more general application as a pain medication. Some clinicians may implicitly use the fibromyalgia indication to justify off-label prescribing not only for ill-defined pain that appears similar

to fibromyalgia pain, but also for more defined conditions such as low back pain and pain from osteoarthritis. In addition, clinicians are probably influenced by guidelines and review articles that extrapolate from the literature on diabetic and postherpetic neuropathies and endorse gabapentinoids for any pain perceived as neuropathic.

But even if the increasing use of gabapentinoids reflects — at least in part — a desire among clinicians to prescribe possibly safer alternatives to opioids, we believe there are several reasons to be concerned about this trend. First, reasonably robust evidence supports the efficacy of some medications for off-label uses, but that isn't the case for gabapentinoids. We found that most recently published clinical studies of gabapentinoids for pain examined single-dose or short-course gabapentinoids for mitigating postoperative pain, an indication that isn't relevant to general outpatient practice. Relatively few clinical trials have assessed the use of gabapentinoids in the common pain syndromes for which they are prescribed off-label — and many of those trials were uncontrolled or inadequately controlled and of short duration. Among the few well-conducted, properly controlled, double-blind studies, results have been mixed

 **An audio interview with Dr. Goodman is available at NEJM.org**

at best. In a recent rigorously conducted placebo-controlled trial, pregabalin was ineffective for patients with pain-fibrosiatica.⁴

Second, gabapentinoids can have nontrivial side effects. Sedation and dizziness are relatively common, and some patients experience cognitive difficulties while taking these drugs. For example,

in the sciatica trial, 40% of patients taking pregabalin reported dizziness, as compared with 13% of those taking a placebo.⁴ Although these adverse effects aren't always severe and are reversible when the drugs are discontinued, gabapentinoids are often prescribed together with other drugs that have central nervous system side effects. Such polypharmacy might affect neurologic function in subtle but clinically important ways.

Third, evidence suggests that some patients misuse, abuse, or divert gabapentin and pregabalin.⁵ Some users describe euphoric effects, and patients can experience withdrawal when high doses are stopped abruptly. The likelihood of gabapentinoid abuse is reportedly heightened among current or past users of opioids and benzodiazepines. Whether misuse and abuse of gabapentinoids will become an important public health issue remains to be seen.

Finally, indiscriminate off-label use of gabapentinoids reinforces the tendency to view the treatment of pain through a pharmacologic lens. Clinicians assume (perhaps incorrectly, in some cases) that patients generally expect or demand to be given a drug prescription, and they feel pressure to satisfy these perceived patient expectations. Some clinicians express concern that resisting patients' demands for opioids might lead to lower scores on patient-satisfaction surveys, poor practice ratings, and even reduced income. However, appropriate management of both acute and chronic pain involves examining how the patient's pain is affecting activity and function and setting realistic goals that may include coping with or mitigating pain, not necessarily eliminating it. This ap-

proach requires time (which is often lacking in rushed outpatient practices), expertise in communicating about a difficult and often emotionally charged symptom, and patient access to timely follow-up and continuity of care. Writing a prescription and moving on is considerably easier and less stressful for clinicians. Although guidelines typically encourage nonpharmacologic approaches to chronic pain — such as cognitive behavioral therapy or referral to a multidisciplinary pain practice — such options may be unavailable or unaffordable for many patients.

Patients who are in pain deserve empathy, understanding, time, and attention. We believe some of them may benefit from a therapeutic trial of gabapentin or pregabalin for off-label indications, and we support robust efforts to limit opioid prescribing. Nevertheless, clinicians shouldn't assume that gabapentinoids are an effective approach for most pain syndromes or a routinely appropriate substitute for opioids. Although gabapentinoids offer an alternative that is potentially safer than opioids (and presumably more effective in selected patients), additional research is needed to more clearly define their role in pain management.

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Recognizing Sepsis as a Global Health Priority — A WHO Resolution

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“Some very important clinical issues, some of them affecting life and death, stay largely in a backwater which is inhabited by academics and professionals and enthusiasts, dealt with very well at the clinical and scientific level but not visible to the public, political leaders, leaders of health-care systems. . . . The public and political space is the space in which [sepsis] needs to be in order for things to change.”

So said Sir Liam Donaldson, the former chief medical officer for England and the current World Health Organization (WHO) envoy for patient safety, on May 24, 2017.¹ Two days later, the World Health Assembly (WHA), the WHO's decision-making body, adopted a resolution on improving the prevention, diagnosis, and management of sepsis.²

The term “sepsis” dates back to at least the time of Hippocrates, who considered it the process by which flesh rots and wounds fester. More recently, it has been defined as life-threatening organ dysfunction resulting from infection. Despite this long history, sepsis has existed in the backwater described by Donaldson, and as a result innumerable patients around

the world have died prematurely or faced long-term disability. This toll of unnecessary suffering drove Germany, with the unanimous support of the WHO executive board and at the urging of the Global Sepsis Alliance (GSA), to propose the resolution adopted by the WHA. The resolution urges member states and the WHO director general to take specific actions to reduce the burden of sepsis through improved prevention, diagnosis, and management (see table).

The true burden of disease arising from sepsis remains unknown. The current estimates of 30 million episodes and 6 million deaths per year come from a systematic review that extrapolated from published national or local population estimates to the global population.³ The likelihood that the result was a significant underestimate was recognized by the authors, who could find no data from the low- and middle-income countries (LMICs) where 87% of the world's population lives. Thus, their estimate is based on data on hospital-treated sepsis in high-income countries. This lack of data is compounded by the fact that sepsis is treated as a “garbage

code” in the Global Burden of Disease statistics, where most deaths due to sepsis are classified as being caused by the underlying infection. Improving the coding of sepsis and establishing a proper accounting in those statistics are essential steps envisaged by the WHA.

The resolution also calls for health care workers to increase awareness of sepsis by using the term “sepsis” in communication with patients, relatives, and other parties.⁴ National surveys consistently report low community awareness of sepsis, its signs and symptoms, its causes, and its toll of death and disability. In Australia, only 40% of surveyed people had heard of sepsis and only 14% could name one of its signs. In Brazil, the figures are even lower, with 7% of surveyed people aware in 2014 and 14% in 2017. In the United States, the United Kingdom, and Germany, high-profile campaigns have proven effective and increased awareness to 55%, 62%, and 69%, respectively.

Ensuring greater awareness on the part of both the public and health care workers is a crucial step in reducing the global burden of sepsis. Approximately