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Opioid Shortages Force Improvisation—and Cancellations

The proliferation of opioid abuse and its alarming death toll have become major issues in both medical care and politics, but while many have spent the last several months decrying opioids, alarm has been slowly building over shortages of these same drugs.

Shortages of many injectable forms of opioids have reminded patients, federal agencies and clinicians alike of the vital role they play in a variety of health care settings, and left institutions nationwide scrambling to find alternative medications and analgesic routes. Although these efforts may ultimately somewhat slake our thirst for opioids and promote multimodal analgesia, the immediate fallout of the shortage has left patients in pain, caused the cancellation of elective procedures, and raised the specter of serious medication errors.

"When you're in my position, it's like trying to run uphill all day long," said David Craig, PharmD, the pharmacist lead of supportive care medicine at Moffitt Cancer Center, in Tampa, Fla.

Craig is certainly not alone in his frustrations. Every day, clinicians of all stripes begin their workdays by trying to juggle an ever-changing supply of injectable opioids. "It consumes me on a daily basis," said Anthony Laurent, RPh, MBA , the director of pharmacy at the University Medical Center New Orleans, in Baton Rouge. "Every day, I have to ration our limited supplies to the areas that are most in need. What's worse is that by the time we get notified of a medication shortage, it's already affected our resources."

A Nationwide Phenomenon

The shortage—which is primarily affecting injectable formulations of morphine, hydromorphone and fentanyl, including prefilled syringes, small ampules and vials for IV delivery—started last summer but has intensified in recent weeks. It is a nationwide

phenomenon affecting academic institutions, community hospitals and surgical centers alike; regional variations seem to be the product of storage and inventory differences, not differential distribution patterns.

Manufacturing problems at Pfizer, which controls at least 60% of the market for injectable opioids, are primarily to blame. The company reported a production cutback in June 2017 while upgrading its plant in McPherson, Kan.

That came on the heels of a February 2017 FDA report that found significant violations at the McPherson plant. In that report, the federal agency cited "visible particulates" floating in the liquid medications and a "significant loss of control in [Pfizer's] manufacturing process [that] represents a severe risk of harm to patients."

Other manufacturers, such as West-Ward Pharmaceuticals and Fresenius Kabi, have tried to mitigate the market shortfall but lack the capacity to make up the difference. "With most injectable drugs, there are only two or three suppliers of those products, and usually one company has the majority of the market share," said Erin R. Fox, PharmD, the director of drug information at University of Utah Health, in Salt Lake City, who has been tracking national drug shortages since 2001. "And that's exactly what we have with opioids."

Fox said it's unrealistic to expect other companies to ramp up production on short notice, especially given the way the Drug Enforcement Administration (DEA) metes out raw materials: Companies are given specific allocations each year based on perceived need and production history. Compounding the problem, these allocations have come under increasing scrutiny in the past few years because of the abuse of prescription opioids currently plaguing the country.

Indeed, a bipartisan group of senators introduced a bill in March that would strengthen the DEA's ability to lower manufacturers' quotas on controlled substances such as opioids, based on, among other things, national overdose statistics. The DEA doesn't seem to need the added power: It cut opioid production by 25% in 2017, and has proposed another 20% reduction for this year. Importing opioids isn't an option in such a heavily regulated arena, either.

For its part, Pfizer has communicated regularly with its clients, although its news has not been particularly encouraging. In its July 2017 letter to customers, the company anticipated "recovery of prioritized products" by the end of 2018's first quarter. By Nov. 27—when the company issued its second update on the shortage—it had pushed back the complete recovery date for prioritized prefilled syringes to the first quarter of 2019.

Then, on Jan. 31, 2018, the company issued another letter stating it was temporarily halting delivery of all Carpuject and iSecure prefilled syringes, “due to an issue with a third-party incoming component.” A Pfizer product availability report from early April indicated that virtually every formulation and dosage of morphine, hydromorphone and fentanyl was out of stock.

Cascading Shortages

In the meantime, the shortage of the three primary opioids has created a run on other drugs, subsequently causing them to fall into shortage as well, placing further strains on already stretched institutions. For example, anesthesiologists have turned to regional anesthesia as an alternative analgesic, only to find that local anesthetics, such as bupivacaine, lidocaine and ropivacaine, also are in short supply.

“It’s typical with all these shortages that people switch to other drugs, and then *they* go in short supply,” said Beverly K. Philip, MD, a professor of anesthesia at Harvard Medical School, in Boston, and the vice president for scientific affairs at the American Society of Anesthesiologists (ASA). Fox concurred, noting that less commonly used opioids, such as sufentanil and remifentanil, also are falling into shortage as hospitals rely on them more.

In light of the bad news, relevant medical associations have not been content to stand by and watch their members—and the patients they serve—suffer. In late February 2017, the American Hospital Association, ASA, American Society of Health-System Pharmacists (ASHP) and American Society of Clinical Oncology all cosigned a letter to Robert W. Patterson, the acting administrator of the DEA. In that letter, the organizations urged the agency to use its discretionary authority to adjust aggregate production quotas for injectable opioids "in order to mitigate ongoing drug shortages" by allowing other manufacturers to supply product until the shortages resolve.

The signatories also stressed that injectable opioid shortages may threaten patient care. "Rather than selecting a product that might be most clinically efficacious for patients, during shortages prescribers are forced to order whichever IV opioid is available," they wrote. "Furthermore, dosing equivalency between the IV opioids differs significantly, which can lead to dosing errors."

And yet, little relief seems to be on the way, which has left institutions and clinicians frustrated and scratching their heads for alternatives. The ASA has reported that some elective surgeries, including cholecystectomies and herniorrhaphies, have been postponed. Flexibility is the new name of the surgical game, with physicians seeking out different drugs and routes of administration to provide pain relief for their patients.

Amidst the Chaos, Opportunity?

"In the last five years, we've seen a major uptick in drug shortages, specifically with anesthesia drugs," said Alan D. Kaye, MD, PhD, a professor and the chairman of anesthesiology at Louisiana State University, in Baton Rouge. "It requires us to be creative and to strategize, because we still have to do surgery."

Among the many strategies being employed in U.S. institutions are:

- supplementing oral opioids for injectables where appropriate;
- using alternative injectable products, such as morphine or fentanyl, when hydromorphone is unavailable;
- revising high-volume order sets that incorporate routine orders for hydromorphone to include alternative agents;
- stressing nursing education regarding use of oral opioids, where appropriate;
- employing multimodal analgesia with agents such as nonsteroidal anti-inflammatory drugs, acetaminophen and GABAnergic agents to reduce the need for opioids; and
- using local anesthetics and regional anesthesia where appropriate.

“Utilizing multimodal techniques is almost considered best practice, anyway,” said Dr. Kaye, who is a member of the editorial advisory board of *Anesthesiology News*. “So now would be a good time to get on board, especially for those places that haven’t gotten around to it and are still practicing the way we did a decade ago.”

“If you’re optimistic, you can look at this situation and say it’s offering us an opportunity to use non-narcotics for pain control,” said Allen J. Vaida, PharmD, the executive vice president of the Institute for Safe Medication Practices (ISMP). “And to tell the truth, I think a lot of people are taking advantage of that. But from the OR [operating room] and anesthesia standpoint, you still need your morphine, hydromorphone or fentanyl.”

However, all is not rosy when it comes to alternative analgesic strategies. Almost every clinician and organization recognizes that these shortages—and the mitigation strategies they promote—have the potential to increase the possibility of medication errors and adverse events.

For one thing, clinicians now find themselves turning to second-line drugs that they turned away from years ago, mostly due to their side effect profiles.

“For example,” said Dr. Philip, “we commonly use hydromorphone for surgical analgesia due to its fast onset time and outstanding side effect profile. Now we have to switch to morphine, which causes a host of known side effects. Yes, these side effects are manageable and safe, but the drug just isn’t as good.

“And of course now morphine is going into shortage, too, so we’re going into even older drugs like meperidine, which have an even less favorable side effect profile,” Dr. Philip said.

The other problem with using these less common drugs is that they have different potencies than their more common brethren, and require different formulas and dosages. “For example,” Dr. Kaye said, “sufentanil is 1,000 times more potent than morphine, and can potentially be overdosed quite easily if you’re not familiar with it or you miscalculate on the infusion rate.” Although no deaths have been attributed to the shortage (two patients died from overdoses during the last major opioid shortage in 2010), the ISMP has reported several incidents where patients received potentially harmful doses of alternative agents.

“As we know, the doses of these medications are vastly different,” Vaida said. “So if you get one drug on Monday and a different drug on Tuesday, it could lead to serious implications.”

“Health systems all over are trying to access whatever product they can and physicians are having to switch between products, and it’s not always a clean conversion,” Fox added. “Not only that, but clinicians are being forced to use much larger vial sizes, and in some cases, waste the rest.”

At the same time, some patients are not getting the drugs—or pain relief—they need. Although multimodal analgesia may be the wave of the future, not all clinicians are literate in its use. Less potent medications like acetaminophen clearly do not provide as much analgesia as opioids. And as Moffitt’s Craig knows all too well, cancer patients have been caught in the crossfire between the opioid crisis and opioid shortage. Just a few minutes before he was contacted for an interview, Craig fielded a call from a pharmacist at his institution about a cancer patient needing to be admitted for uncontrolled pain. “They wrote him a prescription for IV opioid PCA [patient-controlled analgesia], but we didn’t have any drug to fill the order,” he said.

Cancer patients also have found it challenging to fill opioid prescriptions at community pharmacies—a direct result of the government’s efforts to curb oral opioid misuse. “Many pharmacies are not stocking supplies like they used to, for multiple reasons,” Craig explained. “They either don’t want to serve those kinds of patients, or they’re fearful of litigation by dispensing too much.

“I don’t think anybody really wants to see cancer patients go without,” he added, “but I can tell you that every new law and every new proposal affects our patients here. It’s not supposed to affect cancer patients, but it actually does.”

Medical Associations Propose Action

The good news is that national associations are not taking the situation lightly, and are urging legislators to take steps to ensure such shortages do not recur. More recently, the five signatory agencies of the July 2017 letter to the DEA—plus an additional two: the American Society for Parenteral and Enteral Nutrition and the Children’s Hospital

Association—followed up with a series of recommendations to Congress on what should be done to minimize patient effects from drug shortages in the future. These strategies include:

- requiring manufacturers to provide the FDA with more information on the causes of the shortages and their expected duration;
- requiring manufacturers to establish contingency plans and/or redundancies;
- requiring more transparency from manufacturers;
- examining drug shortages as a national security initiative; and
- asking the Federal Trade Commission to include in its review of drug company merger proposals the potential risk for drug shortages.

Clearly, these agencies are concerned with the effect of market consolidation on manufacturers' abilities to consistently meet demand. "We've seen that over the last decade," Vaida said. "Where there were once four or five manufacturers of a drug, now it's down to two. So if your plant in North Carolina produces 80% of the country's supply of a certain product and something happens to that plant, nobody is going to be able to pick up the slack. That's something that we saw with the saline shortage: All of a sudden, a major hurricane hit Puerto Rico, and nobody had taken the time to realize that Baxter produces 80% of the country's saline and it all comes from Puerto Rico. Even with nuclear power plants, there are two or three reactors, not one."

"Looking at some of the older data, some 56% of drugs in shortage have two or fewer companies that can manufacture them," Dr. Philip added.

The way Dr. Philip sees it, one way to alleviate these issues in the future is to give the FDA more teeth when it comes to certain drugs. "We need to support the FDA to get more authority to address some of the root causes of these drug shortages," she commented. "There have been some astute regulatory increases that allow FDA to take firmer action, but it's not able to do enough yet.

"The FDA should also consider creating some kind of critical medications list," Dr. Philip continued. "Of course you can't force companies to produce these drugs, but you can have a contingency plan in case of interruption or shutdown. Is there any way we can incentivize manufacturers to address these more critical drugs?"

The University of Utah's Fox has a similar take on it. "Unfortunately, the FDA has no authority to compel a company to produce anything, no matter how lifesaving or critical it is. And that's one of the reasons why I'm so passionate about this and like to generate awareness about it. I mean, really, should this be going on in the United States in 2018?"

Fox has her own ideas about creating a long-term solution to the drug shortage issue. “For drugs that are considered vital, should the government consider them to be part of the critical infrastructure?” she asked. “Of course they can’t require anything, but they can strongly recommend that manufacturers have a backup plan for resiliency and business continuity. Or when the FDA approves a new drug, they should ensure that the manufacturer actually has the manufacturing capacity to supply the market.”

“There’s a public need that doesn’t apply to regular manufactured goods,” said Jillanne Schulte-Wall, JD, the director of regulatory affairs for ASHP. “This is something that people need to survive.”

Along with the other signatories of the letter to Congress, Schulte-Wall is optimistic that changes can be made to prevent such shortages in the future. “There was legislation a few years ago that helped a little, but we’re still running into the same problems that we had in previous years. So essentially we’re giving the Hill some options as they look at putting together legislation to address these issues.

“This is something that should be a bipartisan issue—everyone takes medication and everyone has family members who do,” she added. “So it’s something that touches everyone’s lives.”

Dr. Philip is equally optimistic that congressional action will ultimately make drug shortages a thing of the past. “The long-term answer is going to be through congressional action to give the FDA stronger requirements for manufacturers,” she said. “I’m not criticizing pharmaceutical companies, because it’s a business, and in a business model if something doesn’t make any money there’s no obligation to produce it. But the government can do things like list critical medications, create contingency plans for these drugs, and prevent mergers that create single-source products that are produced in only one plant.”

The last thing the ISMP’s Vaida wants to see is the issue resolve itself with no long-term solution in place. “We know that with medication errors, everyone is upset about it for a while, and then six months later everyone forgets about it. That’s exactly what we don’t want to have happen here.”

In the meantime, physicians across the country continue to improvise, all the while knowing they are likely not serving their patients as best they otherwise could. “One of the scariest things is knowing that you have a patient that needs something and not being able to give them what they need,” Schulte-Wall said. “And it’s through no fault of your own. You’re doing everything you can to ensure you have a steady supply of drugs, but all these factors that are beyond your control make it impossible to get what you need to treat your patient.”

Neither the FDA nor DEA replied to requests for interviews. ASHP (courtesy of data from Erin Fox and the University of Utah) publishes a list of drugs currently in shortage at www.ashp.org/?Drug-Shortages/?Current-Shortages/?Drug-Shortages-List?page=CurrentShortages.

—Michael Vlessides

The interviewees reported no relevant financial disclosures.