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Study finds inadequate FDA oversight of prescribing of fentanyl products

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A study led by researchers at the Johns Hopkins Bloomberg School of Public Health suggests that the Food and Drug Administration (FDA) and manufacturers did not take action when evidence emerged that potentially lethal fentanyl products were being inappropriately prescribed to patients.

The study will be published February 19 in the *Journal of the American Medical Association*.

The study was based on a review of 4,877 pages of FDA reports and other documents obtained through the Freedom of Information Act (FOIA) from years 2012 to 2017; these materials, which were part of an FDA monitoring program, are not routinely made available to researchers or the general public. The study revealed that, even as evidence emerged that as many as half of patients taking highly dangerous medications, known as TIRFs, should never have been prescribed them, the FDA and fentanyl makers did not review prescribing records of even a single physician to consider disqualifying them from the program, which would have prevented them from prescribing the products.

"Both the FDA and the fentanyl makers failed to design and implement an effective monitoring program," says study senior author G. Caleb Alexander, MD, professor of epidemiology and medicine and co-director of the Center for Drug Safety and Effectiveness at the Bloomberg School.

The report comes as America's opioid epidemic continues to claim tens of thousands of lives annually, including nearly 50,000 overdose deaths in 2017, the latest year for which statistics are available. More than two million people living in the U.S. have an active opioid use disorder, and as many as two to three million additional individuals have a lifetime history of such a disorder. Millions more report non-medical use of opioids, yet may not fulfill formal diagnostic criteria of an opioid use disorder. There is widespread consensus that one major driver of the opioid epidemic has been the oversupply of prescription opioids.

The study focused on Transmucosal Immediate-Release Fentanyls, or TIRFs, which are more dangerous than most prescription opioids on the market due to their very high potency and rapid onset of action. TIRFs are designed to get into the bloodstream within seconds, and because of their risks, were approved by FDA only for adult cancer patients "who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain."

Lawyers from Yale Law School's Collaboration for Research Integrity and Transparency represented the researchers through the FOIA process and successfully negotiated release of the documents.

In late 2011, the FDA started a Risk Evaluation and Mitigation Strategy (REMS) program that required all doctors, pharmacists and patients to certify their understanding of the risks and proper use of these drugs in order to prescribe, dispense or take a TIRF product. The program consisted of a "closed distribution system," the most stringent type of REMS that the FDA uses. TIRF makers were also required to submit annual reports to the FDA demonstrating their compliance with the REMS requirements.

As part of its monitoring program, TIRF makers annually surveyed a sample of TIRF prescribers, pharmacists and patients to help determine

if they understood TIRF restrictions and if there was significant unsafe prescribing. The vast majority of survey respondents, who represented a small fraction of those enrolled in the REMS, reported that they did understand the key fact that TIRFs have an absolute contraindication—that is, are never to be used—in patients who are not already tolerant to opioids. This is because among individuals whose bodies are not already used to or "tolerant to" opioids the risks of potentially fatal respiratory depression and death are particularly high.

The surveys also uncovered some "red flags" suggesting significant potentially inappropriate prescribing. In the survey reported at the end of the program's second year (2013), for example, 39.4 percent of responding TIRF prescribers reported having prescribed TIRFs "off label" for patients with chronic, non-cancer pain—and similar proportions of prescribers responded this way in the third- and fourth-year surveys.

Following the third-year (2014) report from the TIRF makers, the FDA asked TIRF makers to analyze health insurance claims to provide a clearer picture of the level of inappropriate prescribing. These claims-based assessments, which were reported four years after the REMS program began, showed very high levels of inappropriate prescribing—more than half (51 percent) of patients receiving TIRFs were defined as lacking opioid tolerance. In a subsequent claims-based analysis submitted for their fifth-year report in 2016, the TIRF makers once again found that, depending on the specific TIRF drug, between 34.6 and 55.4 percent of TIRF patients lacked opioid tolerance.

"Despite the use of what should have been a very stringent monitoring program on the part of the FDA and TIRF makers, we found widespread TIRF use by patients for which the products had an absolute contraindication," Alexander says. "In other words, these patients should not have received TIRF drugs under these circumstances."

Although TIRF makers outlined a plan in which they would identify, investigate and even disenroll prescribers who inappropriately prescribed TIRFs to patients without opioid tolerance, the FDA noted in the two-year and each subsequent report that there were no instances in which such prescribers were identified, reported to the FDA or deactivated from the REMS program.

The FDA, in its own fifth-year evaluation of the TIRF REMS program, concluded that it "is not meeting its overall goal or most of the objectives," and requested that TIRF makers do further analyses of TIRF prescribing.

"The FDA and the TIRF manufacturers overly relied on surveys and failed to build a program from the ground up to prevent inappropriate TIRF use. They also missed important opportunities to make substantive revisions to the program even as alarm bells were sounding," Alexander says.

More information: Assessment of the U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy for Transmucosal Immediate Release Fentanyl Products, *Journal of the American Medical Association* (2019).

Provided by Johns Hopkins University Bloomberg School of Public Health