FDA documents analysis reveals inadequate monitoring of safe opioid use program

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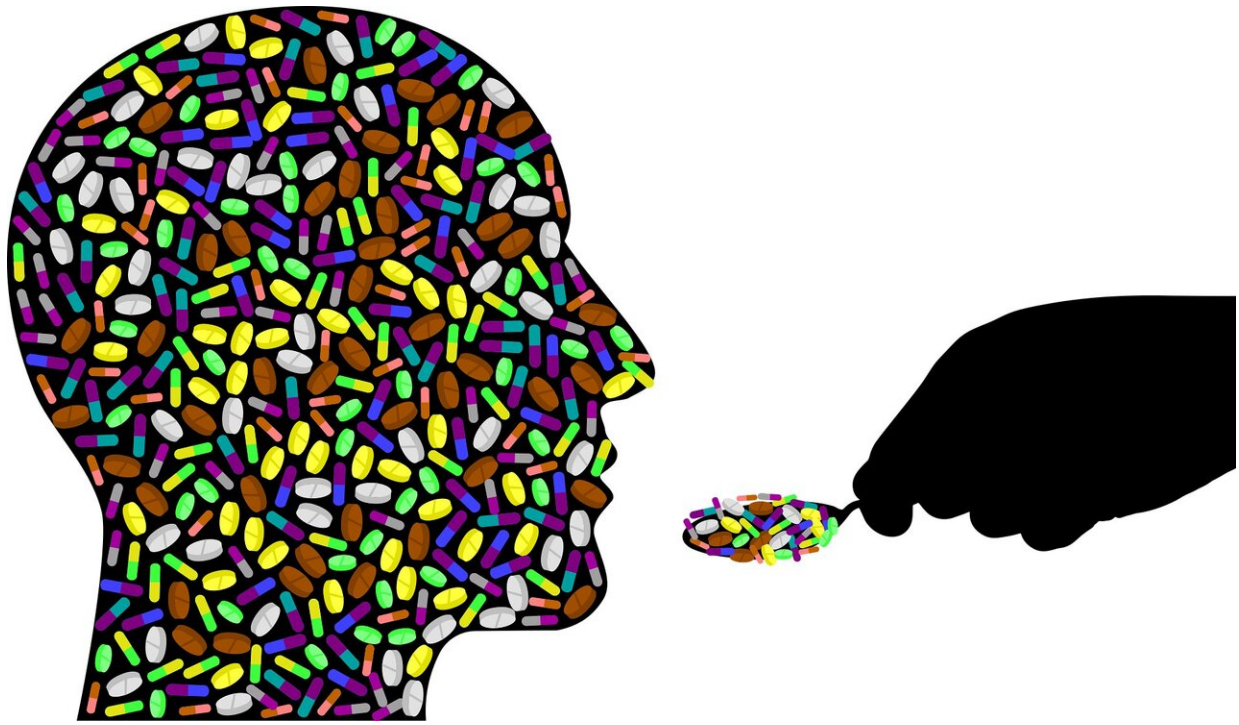

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A risk-management program set up in 2012 by the U.S. Food and Drug Administration to curb improper prescribing of extended-release and long-acting opioids may not have been effective because of shortcomings in the program's design and execution, according to a paper from researchers at the Johns Hopkins Bloomberg School of

Public Health. Extended-release and long-acting opioids, which include oxycontin, account for a significant proportion of the prescription opioid market and are among the most misused.

The paper was published online December 30, 2019 in *JAMA Internal Medicine*.

For their analysis, the researchers reviewed more than 9,000 pages of internal FDA documents, obtained through a Freedom of Information Act (FOIA) request, on the agency's Risk Evaluation and Mitigation Strategies program for extended-release and long-acting opioids. The authors concluded that the program never had proper evaluation procedures in place—essentially leaving the FDA without critical information about whether the program was working.

In their review, the authors found a number of critical design flaws in the evaluation program, including an over-reliance on surveys rather than other sources of health care information such as clinical records; use of non-representative and self-selected patient and prescriber populations; and a failure to directly link prescribing behaviors with program participation.

"The FDA's Risk Evaluation and Mitigation Strategies program is a primary way to promote the safe use of these medicines, but we found that the mechanisms for assessing the program's effectiveness were deficient from the start," says the paper's senior author Caleb Alexander, MD, professor in the Bloomberg School's Department of Epidemiology and former chair of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee.

The current opioid crisis in the U.S. originated largely from the wide availability and misuse risks of prescribed opioid painkillers. The crisis has now expanded to 50,000 opioid-related overdoses per year and

millions of cases of opioid-use disorder. Among the more dangerous prescription opioids are extended-release and long-acting versions of oxycodone, morphine, and other painkillers, designed to deliver opioids into the body over longer periods of time than immediate-release forms of these drugs. Studies suggest that compared to immediate-release forms, extended-release and long-acting opioids are more likely to be used non-medically, and more likely to lead to opioid use disorder as well as overdoses.

To reduce the risks of extended-release and long-acting opioids, the FDA set up a Risk Evaluation and Mitigation Strategies program for these drugs in 2012. It required extended-release and long-acting opioid manufacturers to provide FDA-approved educational materials to both prescribers and patients in order to instruct them on the safe and appropriate use of these products. During the program, extended-release and long-acting opioid manufacturers also were required to monitor and report annually on prescriber knowledge and behavior associated with these drugs, as well as on data related to patient access and safety.

For their study, Alexander and his colleagues obtained via a FOIA request access to over 9,700 pages of internal FDA documents, including annual Risk Evaluation and Mitigation Strategies assessments by manufacturers during 2012-2017 and the FDA reviews of those assessments. The team performed a narrative review, archiving and coding the documents and extracting both quantitative and qualitative information relevant to the design of the Risk Evaluation and Mitigation Strategies program.

The FDA documents suggested that Risk Evaluation and Mitigation Strategies' educational materials were consistent with FDA guidelines. However, the FDA documents also suggested that assessments of the impact of the program were for the most part inadequate. For example, to evaluate whether their prescriber education program was working,

FDA conducted cross-sectional surveys of some prescribers that provided snapshots of prescriber awareness of safe extended-release and long-acting practices. Yet, these surveys of select, non-representative groups of prescribers were snapshots and were not designed in a way that could have shown how prescriber awareness changed due to their participation in the Risk Evaluation and Mitigation Strategies educational programs.

Similarly, patient surveys were not representative of individuals using extended-release and long-acting products. Moreover, evaluations of extended-release and long-acting prescribing trends and adverse events associated with these drugs were not tied to Risk Evaluation and Mitigation Strategies program prescribers and patients in a way that could have enabled FDA to gauge the program's influence on these trends.

"Opioid manufacturers could have linked participation in the Risk Evaluation and Mitigation Strategies program with information on prescribing and health care utilization in order to understand precisely how the program was affecting prescriber behavior. It's unclear why they never did so," Alexander says. "Such information would have allowed the FDA to better understand how the program was performing and, if needed, make changes to strengthen it."

The FDA itself highlighted several of these problems in their own annual reviews, yet did little to fix them over five years of follow-up, the authors note. In some cases, the agency reacted by scaling back their Risk Evaluation and Mitigation Strategies assessment goals so that they no longer focused on determining the precise impact of the program on measures such as extended-release and long-acting prescribing or adverse events.

"In some cases the FDA identified deficiencies that should have been

apparent earlier," Alexander says. "We hope our analyses can serve as the basis for improving the design and conduct of these programs by opioid manufacturers and the FDA to yield accurate and insightful findings regarding both patient and prescriber behavior."

More information: James Heyward et al, Evaluation of the Extended-Release/Long-Acting Opioid Prescribing Risk Evaluation and Mitigation Strategy Program by the US Food and Drug Administration, *JAMA Internal Medicine* (2019). DOI: 10.1001/jamainternmed.2019.5459

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