FDA mandate to limit acetaminophen in acetaminophen-opioid medications associated with reduced serious liver injury

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Jayme Locke, M.D. Credit: UAB

A United States Food and Drug Administration mandate to limit the dosage of acetaminophen in pills that combine acetaminophen and

opioid medications is significantly associated with subsequent reductions in serious liver injury, researchers report in the medical journal *JAMA*. The federal mandate was announced in 2011 and implemented in 2014.

"The FDA mandate that limits acetaminophen dosage to 325 milligrams per tablet in combination acetaminophen-opioid medications was associated with a significant and persistent decline in the yearly rate of hospitalizations and proportion per year of acute liver failure cases involving acetaminophen and opioid toxicity," said study leader and University of Alabama at Birmingham surgeon-scientist Jayme Locke, M.D. At UAB, Locke directs the Comprehensive Transplant Institute in the Marnix E. Heersink School of Medicine.

Patient safety—while still providing pain relief—is the reason to combine different analgesic classes in a medication. Together, the multiple drugs should provide additive synergistic analgesia while minimizing toxicity by using lower doses of each component.

The challenge was that too-high doses of acetaminophen, also known as paracetamol, are toxic to the liver. By 2005, one study found that 43% of acetaminophen-induced acute liver failure cases involved combination acetaminophen-opioid medications taken as therapy. So, an FDA advisory panel in 2009 recommended prohibiting sale of the combo acetaminophen-opioid medications, though the FDA instead acted to limit the dose of acetaminophen in those combination acetaminophen-opioid medications to 325 milligrams. Before the FDA mandate, such medications contained 325 to 750 milligrams of acetaminophen.

To examine the effect of this change, researchers in the *JAMA* study looked at yearly rates of hospitalization and acute liver failure cases in two independent, contemporaneous data sources, the National Inpatient Sample, or NIS, and the Acute Liver Failure Study Group, or ALFSG. The NIS is a very large U.S. hospitalization database with more than 473

million hospitalizations from 2007 to 2019. The ALFSG is a prospective, 32 U.S. medical-center cohort of adult patients with acute liver failure from 1998 to 2019.

In each data source, Locke and colleagues found similar declines in the yearly rates of hospitalization and acute liver failure cases associated with acetaminophen-opioid medications after the mandate. They also compared toxicity seen from acetaminophen-opioid medications versus toxicity from acetaminophen alone. In contrast to the declines from acetaminophen-opioid medications after the mandate, rates of hospitalization and acute liver failure cases associated with acetaminophen alone—where the dosage is not constrained by the FDA—continued to rise after the combination drug mandate.

The detailed results looked at four groups: NIS acetaminophen-opioid toxicity, NIS acetaminophen-alone toxicity, ALFSG acetaminophen-opioid toxicity and ALFSG acetaminophen-alone toxicity. Three different time frame analyses were done for each group: 1) before and after the FDA announcement date in 2011, 2) before and after the FDA implementation date in 2014, and 3) a washout comparison of cases before the 2011 announcement date and after the 2013 implementation date.

As an example of detailed findings, in the NIS group, the predicted incidence of hospitalizations associated with acetaminophen-opioid toxicity one day prior to the FDA announcement was 12.2 cases per 100,000 hospitalizations. By Q4 2019, it was 4.4 cases per 100,000 hospitalizations. The odds of a hospitalization involving acetaminophen-opioid toxicity increased 11 percent per year before the announcement and decreased 11 percent per year after the announcement.

In the ALFSG group, the predicted percentage of acute liver failure cases from acetaminophen-opioid toxicity one day prior to the FDA

announcement was 27.4%. By Q3 2019, it was 5.3%. The percentage of acute liver failure cases involving acetaminophen-opioid toxicity increased 7% per year before the announcement and decreased 16% a year after the announcement.

The NIS database included 39,606 cases of hospitalizations involving acetaminophen-opioid toxicity, and the ALFSG database had 2,631 patients hospitalized with acute liver failure, including 465 with acetaminophen-opioid toxicity.

The authors caution that the study shows association, not causality. The changes in hospitalizations could also have come from increased public awareness and stiffer label warnings required by the FDA as part of the mandate, or changes in clinician prescribing patterns. However, in Canada, changes in labeling without an accompanying limit in the acetaminophen dosage was not associated with a decline in hospitalizations.

More information: Association of FDA Mandate Limiting Acetaminophen (Paracetamol) in Prescription Combination Opioid Products and Subsequent Hospitalizations and Acute Liver Failure, *JAMA* (2023). DOI: 10.1001/jama.2023.1080

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