In most surgery patients, length of opioid prescription, number of refills spell highest risk for misuse

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The possible link between physicians' opioid prescription patterns and subsequent abuse has occupied the attention of a nation in the throes of

an opioid crisis looking for ways to stem what experts have dubbed an epidemic. Most clinical efforts have focused on minimizing risk through dosage management, but a new study led by investigators at Harvard Medical School suggests that the dose may not always make the poison.

The findings, to be published Jan. 20 in *BMJ*, show that among surgery patients with no history of recent or chronic opioid use how long a person takes the drugs for is a more potent predictor of abuse and overdose than how much medication a patient takes. Dosage, however, emerged as a powerful risk indicator among those who took the medications for extended periods, the research found.

The study—based on analysis of more than a half million records of privately insured patients who received opioids after surgery between 2008 and 2016—represents the largest effort to date to quantify opioid misuse following surgery.

The findings provide much-needed insight and nuance into the complex dynamic that may fuel opioid misuse, the researchers said. The results, they added, could help inform field-specific guidelines for a medical specialty that, more than any other, relies on opioid pain management. Indeed, research shows that surgery patients are four times more likely than other patients to receive opioids.

"We are in the midst of an epidemic, and physician prescription practices play no small part in it," said study senior investigator Nathan Palmer, a biomedical informatics researcher at Harvard Medical School. "Understanding differences in risk for opioid misuse across various patient populations and clinical contexts is critical in informing the creation of narrowly tailored guidelines, clinical decision making and the national conversation on this topic."

The findings highlight the need to pay particular attention to the duration

of treatment and the number of refills, the team said, and also suggest that surgeons should be swift to refer patients to chronic pain specialists for symptom management if their discomfort persists.

"As surgeons, we often struggle to balance the risk of abuse with our duty to manage pain, but our findings underscore how potent a single stroke of the pen can be in fueling this risk," said study co-first author Gabriel Brat, instructor in surgery and in biomedical informatics at Harvard Medical School and a trauma surgeon at Beth Israel Deaconess Medical Center.

"Our results indicate that each additional week of medication use, every refill is an important maker of risk for abuse or dependence"," said co-first author Denis Agniel, a statistician at the RAND Corporation and a part-time lecturer in the Department of Biomedical Informatics at Harvard Medical School.

Over the past 15 years, the rates of opioid overdose in the United States have tripled. Opioid overdoses now rank as a leading cause of nonintentional death, and most of these deaths can be traced back to an initial prescription opioid. Previous research suggests that between 3 percent and 10 percent of patients who receive opioids for the first time go on to become chronic users.

In the new study, none of the 560,000 patients had a record of chronic or extended opioid use leading up to surgery. For the purposes of the research, patients were deemed non- opioid users if they had not taken opioids in the two months prior to their surgery, or if they had used opioids for fewer than seven days prior to their procedure.

Of the more than half million patients, 0.6 percent, or 5,906, developed dependence, symptoms of abuse or experienced a nonfatal overdose—collectively defined as opioid misuse. A third of the misuse

diagnoses occurred within a year of the surgery. Each additional week of opioid use increased the risk for dependence, abuse or overdose by 20 percent. Each additional refill boosted the risk by 44 percent, the analysis showed, with the first refill more than doubling the risk. To calculate the risk, researchers measured the number of abuse, overdose and dependence cases against the total number of combined years patients were followed, a common statistical method for gauging risk. Among those who had a single prescription with no refills, misuse occurred at a rate of 145 cases per 100,000 patient years, compared with 293 per 100,000 among those who had a single refill following the original prescription.

By contrast, dosage—the amount of medication a patient takes over 24 hours—played a far smaller role, the analysis showed. In fact, the researchers noted, among people taking opioids for short periods—two weeks or less—the risk for misuse was no greater even among patients on dosages that were twice as high. However, higher dosage did propel risk significantly among those taking opioids for nine weeks or longer, a finding that suggests a potent confluence of duration and dosage among long-term users, the team said.

Current guidelines on opioid pain management are generic and do not address specific patient populations. The new findings, however, suggest that clinical context matters, and that opioid decision making should vary with the context.

"As physicians, we face a dilemma with each opioid prescription, so we need a more nuanced understanding of how to weigh the risks and benefits of opioid pain management immediately after surgery, including factors that influence misuse," said Isaac Kohane, co-senior author on the study and head of the Department of Biomedical Informatics at Harvard Medical School. "These results provide much-needed clarity."

More information: Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study, *BMJ* (2018). www.bmj.com/content/360/bmj.j5790