In the US, there is currently a major push to expand access to medications for opioid use disorder (OUD) treatment such as buprenorphine in response to the overdose epidemic. Efforts to improve health outcomes by increasing access to OUD treatment are being challenged by the recent rise in co-use of stimulants, driven primarily by methamphetamine use. The emergence of this "twin epidemic" has major implications for OUD treatment: concurrent methamphetamine use has been shown to be associated with persistent opioid use and nonretention. There are currently no US Food and Drug Administration–approved medications to treat stimulant use disorders. However, a systematic review and meta-analysis found low-quality evidence that stimulant medication for treatment of attention-deficit hyperactivity disorder (ADHD) may be of some benefit for methamphetamine and amphetamine use disorders. Furthermore, the literature shows ADHD to be more prevalent among persons with substance use disorders compared with the general population; thus, a substantial proportion (as much as one-quarter) of individuals with OUD may have an underlying diagnostic indication for these medications. Buprenorphine prescribers are not uncommonly faced with requests to prescribe stimulant medications for their patients, and to date there has been a lack of evidence on risks and benefits to guide clinical decision-making. A recent study in JAMA Network Open by Mintz et al addresses this important gap in the literature.

In their study, Mintz et al performed secondary analyses of administrative claims data from commercial and Medicaid databases from January 1, 2006, to December 31, 2016, evaluating whether stimulant medications for ADHD were associated with drug-related poisonings (ie, overdose) and examining treatment retention among individuals aged 12 to 64 years prescribed buprenorphine who had already experienced at least 1 drug-related poisoning. The prerequisite of a prior drug-poisoning event was necessitated by the within-person repeated-event case-crossover cohort study design that required the sample to experience the outcome of interest. The analyses included 13,778,567 person-days of observation time among 22,946 individuals who experienced a drug-related poisoning, of whom nearly half (49.7%) were women and the mean (SD) age was 32.8 (11.8) years. The mere size of this sample and the relatively young age bear witness to the magnitude of the overdose crisis. Stimulant medications were prescribed for 10.8% of the sample; per diagnosis code data, 5.0% were diagnosed with ADHD and 11.1% with stimulant use disorder. The main findings of the study were nuanced: stimulant treatment days were associated with modestly increased odds of drug-related poisoning (odds ratio [OR], 1.19 [95% CI, 1.06-1.34]) compared with nontreatment days, yet they were also associated with decreased odds of attrition from buprenorphine treatment (OR, 0.64 [95% CI, 0.59-0.70]), which itself was strongly protective against drug poisoning (OR, 0.62 [95% CI, 0.59-0.65]). Taken together, these results suggest that among persons with OUD, prescription stimulants are associated with a modest increase in the risk for overdose and drug-poisoning, but this risk is offset by improved retention in buprenorphine treatment, which affords protection.

Such a message may sound familiar to clinicians who practice addiction medicine, because there are parallels with prior research on the risks and benefits of prescribing benzodiazepines among persons with OUD receiving opioid agonist therapy. A prior observational study of Massachusetts residents who were treated with buprenorphine from 2012 to 2013 found that benzodiazepine...
prescriptions were associated with an increased risk for drug poisoning, yet they were also associated with decreased risk for buprenorphine treatment discontinuation. Lest parallels with benzodiazepine prescribing be overconflated, it is worth pointing out that the increased odds for drug poisoning associated with stimulant prescriptions was modest when contrasted with the odds associated with benzodiazepine use (OR, 1.19 vs 1.93 [95% CI, 1.84-2.03]). Nonetheless, therein lies the paradox with which clinicians must grapple: prescribing stimulant medications may lead to better engagement and retention in buprenorphine treatment, which is associated with a host of health benefits, and yet this may come at a cost of a modest increase in drug poisoning risk. An awareness of such trade-offs is important for both patients and clinicians, because it can inform shared decision-making discussions about the risks and benefits of treatment.

For clinicians who prescribe stimulant medications to patients who are stably retained in buprenorphine treatment, the results reported by Mintz et al should provide some reassurance of the net benefits to continued prescribing. For those who prescribe buprenorphine in settings where there is a high prevalence of co-use of methamphetamine, such results might also serve as an opportunity to question existing treatment paradigms, particularly considering the increasing harms due to fentanyl contamination and methamphetamine-related drug poisonings. There are important limitations to the study by Mintz et al that can and should be addressed in future research. By design, it focused on persons who had a documented episode of drug poisoning and thus may not generalize to lower-risk populations. Also, there was no information to shed light on whether drug-poisoning risk or retention might differ by the specific indication for the prescribed stimulant (ie, ADHD or off-label use for a stimulant use disorder), although it is perhaps notable that more patients in the sample had a recent diagnosis code of a stimulant use disorder than ADHD.

The current “fourth wave” of the opioid epidemic as characterized by combined stimulant and opioid use threatens to undermine progress gained by expanding treatment with medications to prevent overdose such as buprenorphine. Patients who use methamphetamine and opioids desire and deserve a full range of treatment options, including medications that may benefit their health and long-term engagement in addiction treatment services. The study by Mintz et al represents an important step toward understanding the trade-offs of prescribed stimulant medication for patients with OUD receiving buprenorphine, which should stimulate conversations among clinicians, patients, researchers, and policy makers alike.

ARTICLE INFORMATION
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