After decades of underrepresentation of females in preclinical and clinical research, there are substantial gaps in knowledge about opioid misuse in girls and women. As the difference in opioid misuse prevalence between men and women—characterized historically by a higher prevalence among men—narrows, the need to fill these knowledge gaps is becoming even more urgent.

The study by Bagley and colleagues provides important and timely information about trends in nonfatal opioid overdoses in adolescents and young adults, an age group with unique risk. The authors examined sex differences in opioid overdose in adolescents and young adults using insurance claims data and found sex differences in both the prevalence of overdose and the factors associated with overdose. There are three significant implications of this work for the study and treatment of opioid misuse: the importance of psychiatric comorbidity in opioid overdose, the overlap between suicide and opioid overdose, and the importance of considering sex differences in opioid research.

Bagley and colleagues found that among youths and young adults with history of nonfatal opioid overdose, psychiatric comorbidity was more common in girls and young women than their male peers. This is consistent with findings from McHugh et al that suggest that among adults with opioid use disorder, psychiatric comorbidity is more prominent in women than men. In the study by Bagley et al, two-thirds of girls and young women experienced depression or anxiety, and 16% experienced a traumatic stress related disorder. Furthermore, more than 60% experienced chronic pain, a rate higher than their male peers, which is also consistent with findings from the study of adults with opioid use disorder by McHugh et al. Bagley et al suggest that strategies targeting psychiatric factors may be indicated for the prevention of overdose, in addition to ongoing efforts to expand naloxone access. Although much of the attention on risk factors for opioid misuse and opioid overdose has focused on pain, psychiatric illness is also a significant risk factor. Indeed, negative affect and pain-related anxiety, more so than pain severity, is associated with increased risk for misusing opioids among people with pain. Although Bagley and colleagues found that psychiatric disorders were more common among girls and women, it is essential to consider that these are mean differences. Even though girls and women were more likely to be diagnosed with depression and anxiety, more than half of boys and men were also diagnosed with these illnesses, suggesting that attention to psychiatric disorders and symptoms may be an important prevention strategy in both sexes.

Consideration of psychiatric factors in this population should also include the potential contribution of suicidal motivation to opioid overdose. Suicidal ideation, attempt, and fatality are all highly prevalent among people with opioid use disorder. Although overdose and suicide are typically defined as discrete events based on the presumed intention of the behavior, suicidal motivation and intention occur along a spectrum of severity. Drug poisoning is a common method of attempted suicide, and opioids are the most commonly used drug in fatal suicidal drug poisonings. Furthermore, in survivors of opioid overdose, desire to die exists along a spectrum and often precedes an opioid overdose. The potential for misclassification of these events risks deploying inadequate prevention and treatment resources, particularly for targeting not only overdose rescue but also suicide prevention among people at risk for opioid overdose.

The results from Bagley and colleagues also underscore the importance of considering developmental differences by sex. They report that overdose was more prevalent in girls than boys in the younger cohorts (i.e., age 11-16 years); this shifts at age 17, after which more boys and men than
girls and women experienced a nonfatal overdose. These developmental shifts may reflect biological processes in development, sociocultural factors, or both. Indeed, evidence suggests that environmental and social context may contribute to observed sex differences in the prevalence of substance use disorders. Countries with more gender equity have a smaller gap between men and women in substance use disorders. When controlling for exposure or availability of a substance, sex differences in substance misuse decrease drastically, suggesting that differences may be attributable not only to biological risk factors. These findings highlight the importance of considering both sex (a biological category based on factors like chromosomes and hormones) and gender (the sociocultural construct associated with behavioral and role norms), as recommended by organizations such as the National Institutes of Health Office of Research on Women's Health.

As public health efforts to address the opioid epidemic, as well as other substance use crises, such as increases in stimulant-related overdoses and the death and disability associated with alcohol and tobacco use, continue to evolve, clinicians, researchers, and public health officials must consider how these epidemics affect groups and individuals differently. The study by Bagley and colleagues provides an important reminder that failure to consider factors, such as sex and age, in studies of opioid misuse may result in missing important differences with direct implications for prevention and treatment.