



## EDITORIALS

# Prescribing opioids and psychotropic drugs in pregnancy

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Increases in prescribing are a major concern

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Over the past two decades, increasing use of opioid pain relievers has led to myriad complications in communities throughout the US. In 2015, every 15 minutes one American died from an opioid related overdose—which is more frequent than deaths from vehicle crashes.<sup>1</sup> Given the rapid rise and scope of the US opioid epidemic, it should not be a surprise that nearly every segment of society has been affected, including pregnant women and their infants. Infants exposed to opioids are at risk of neonatal opioid withdrawal syndrome, also known as neonatal abstinence syndrome (NAS), which is commonly characterized by difficulty feeding, respiratory problems, irritability, hypertonia, insomnia, and seizures, leading to more complicated and costly admissions to hospital.<sup>2</sup> In the US, rates of neonatal abstinence syndrome grew fivefold over the past decade, reaching a rate of one affected infant born every 25 minutes.<sup>3</sup>

Importantly, not all infants exposed to opioids develop withdrawal, for reasons that remain unclear. In a linked paper, Huybrechts and colleagues (doi:10.1136/bmj.j3326) find a possible reason for differences in risk—concurrent prescription of psychotropic medications.<sup>4</sup> The authors used a US cohort of 200 000 pregnant women enrolled in the Medicaid program—a government sponsored program that pays for healthcare services—all of whom filled a prescription for an opioid. They examined whether the risk of neonatal abstinence syndrome was increased among infants whose mothers were co-prescribed a psychotropic medication. They found that use of antidepressants (relative risk 1.34, 95% confidence interval 1.22 to 1.47), benzodiazepines (1.49, 1.35 to 1.63), and gabapentin (1.61, 1.26 to 2.06) increased the risk. They also found that exposure to two or more of these medications more than doubled the odds (2.05, 1.77 to 2.37) compared with odds in pregnant women prescribed opioids alone.

These data were derived from hospital administrative records, which can be prone to misclassification bias and cannot account for illicit co-exposures (such as cocaine); nevertheless, the data are unique providing the power to detect rare outcomes, and these findings are important in targeting prevention efforts and potentially in tailoring treatment of opioid exposed infants.

Huybrechts and colleagues' study highlights how the opioid epidemic affects women and infants in the US, where rates of prescribing are nearly four times higher than in Europe.<sup>5</sup> While prescriptions for opioids have declined slightly in the US since 2012,<sup>5</sup> studies of the pregnant women enrolled in Medicaid found that, depending on the state, 9.5% to 41.6% were prescribed at least one opioid in pregnancy.<sup>6 7</sup> In addition, the growth of use of prescribed opioids has been temporally associated with an increase in opioid use disorder among pregnant women in the US,<sup>2</sup> particularly in rural areas.<sup>8</sup>

Policy approaches to the opioid epidemic must acknowledge that untreated opioid use disorder, anxiety, and depression are harmful for both mother and infant; put simply, healthier mothers have healthier babies. The large expansion of opioid prescribing and prescribing of psychotropic medications to pregnant women, however, raise major concerns. Most of all medications in use today lack enough information to determine their safety in pregnancy.<sup>9</sup> For instance, gabapentin is categorized as a pregnancy category C medication, with evidence of fetal harm in animal experiments but inadequate controlled studies in humans.<sup>10</sup>

## Treating for two

Use of medications in pregnancy must balance the health of the mother with the potential impact on developing fetus. These concerns led the US Centers for Disease Control and Prevention to launch an initiative called "Treating for Two," emphasizing

the value of better research and reliable guidance that will better inform women's and clinicians' decisions about medication use during pregnancy ([www.cdc.gov/pregnancy/meds/creatingfortwo/index.html](http://www.cdc.gov/pregnancy/meds/creatingfortwo/index.html)).

For clinicians who provide care for pregnant women and their children, these data have some additional important implications. Given clinical challenges in predicting risk of withdrawal among infants exposed to opioids, the American Academy of Pediatrics suggests that all such infants should be observed for four to seven days after birth to monitor for signs of withdrawal.<sup>11</sup> Huybrechts and colleagues found substantial differences in risk of withdrawal based on exposure to specific psychotropic agents, suggesting opportunities to tailor postnatal monitoring and treatment for the highest risk infants.<sup>4</sup>

Lastly, these findings suggest a clear need for a comprehensive, evidence informed strategy regarding opioid use in pregnancy. To be effective, the strategy would specify opportunities for intervention in clinical and public health settings in all time periods related to pre-pregnancy, antepartum/prenatal, peripartum/perinatal, and postpartum/infancy. There remains a paucity of clinical guidance for obstetricians and pediatricians caring for the mother-child unit; development of a strategy will help to prioritize the development of specific evidence.<sup>12</sup> As the US opioid epidemic accelerates in complexity, there is an urgent need to focus resources on this issue, including expansion of research funding for drug safety in pregnancy and improvement of outcomes for mothers and infants affected by opioid use disorder, more funding for the prevention of the disorder, and an expansion of treatment options for affected mothers and their infants.

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