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Buprenorphine for the Neonatal Abstinence Syndrome

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The authors reply: Christiansen is correct that ethanol was used to stabilize the buprenorphine solution. Although a more rigorous placebo for buprenorphine also would have contained ethanol, we thought this option was not an acceptable ethical approach. Ethanol has hypnotic and sedative properties, but it does not have efficacy in treating symptoms of opioid withdrawal in adults. A blood level of 80 mg per deciliter (17.4 mmol per liter) is the legal standard for impaired driving, but a concentration for the onset of pharmacologic activity in neonates is not defined.

We have preliminary data on the blood concentration of ethanol in infants in our trial.[1] Ethanol was cleared rapidly between doses. No levels of ethanol were higher than 7 mg per deciliter (1.5 mmol per liter), which is less than the limit suggested by the American Academy of Pediatrics of less than 25 mg per deciliter (5.4 mmol per liter) after administration of a single dose.[2] Approximately one third of the infants had a concentration above the much lower limit of 1 mg per deciliter (0.2 mmol per liter) suggested in the 2014 guidance of the European Medicines Agency; this guidance is still in draft form.[3] Most of the infants with higher values were receiving concomitant phenobarbital, which also contains ethanol. Although ethanol is a common excipient in neonatal medications and neonates clear alcohol at a more rapid rate than adults, we agree that future attention should be directed at the development of an ethanol-free formulation.[4]

In reply to Whalen et al. and Grossman et al.: our trial focused on identifying the better opioid treatment and not on evaluation of nonpharmacologic therapies. Nonpharmacologic interventions are not universally defined, and they are not feasible in all practice settings. However, these approaches are safe, and we agree fully with their widespread application to reduce the severity of symptoms and ultimately the number of infants who require pharmacologic therapy.

All infants in the BBORN trial received the same nonpharmacologic intervention that included rooming in, promotion of breast-feeding, maternal engagement, and minimization of stimulation. Treatment was randomly assigned and administered in a blinded manner, so that the potential for inadvertent administration of differing levels of nonpharmacologic treatment was removed. We stratified randomization according to variables (the choice to breast-feed and maternal opioid use) that were out of our control. All other interventions

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were uniformly administered to all patients, eliminating the potential for uneven distribution that could attenuate or magnify the effect size of buprenorphine treatment.

Our dosing schedule was built on a model used for many years in clinical practice and that continues to be the standard approach in clinical practice. We welcome investigations into an on-demand approach to opioid treatment, which is not widely used and is an approach that was not tested in our trial design.

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