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THE COMPARATIVE SAFETY OF BUPRENORPHINE VERSUS METHADONE IN PREGNANCY—WHAT ABOUT CONFOUNDING?

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Abstract

Preferential treatment of high-risk opioid-dependent pregnant women with methadone limits evidence of the comparative safety of buprenorphine versus methadone on infant outcomes. Adjustment for maternal characteristics that affect both treatment choices and birth outcomes is necessary to provide valid estimates of the effect of prenatal opioid agonist therapy exposure.

Keywords

Birth outcomes; buprenorphine; infants; methadone; neonatal abstinence syndrome; pregnancy

The study by Zedler *et al.* aimed to assess systematically evidence of the safety of prenatal buprenorphine versus methadone and to provide a quantitative treatment effect [1]. Some published studies have shown less severe neonatal abstinence syndrome (NAS) [2–5] and greater gestational age at birth [4], birth weight [4,6] and head circumference [6,7] after prenatal buprenorphine exposure compared to prenatal methadone. What has been difficult to disentangle, however, is whether these improved birth outcomes are due to the protective effect of buprenorphine compared to methadone or to confounding from maternal treatment choices [8].

Buprenorphine treatment often involves out-patient prescriptions, while methadone is given through observed daily dosing at a methadone clinic. Maternal characteristics have been shown to influence clinical prescribing, with methadone being used typically in less stable opioid-dependent pregnant women [4,9–12]. Women with poorer clinical profiles, such as those taking concomitant psychotrophic medications [2], are more likely to have neonates

Declaration of interests

None.

with worse birth outcomes than women with better clinical profiles [13]. When a regression model of prenatal buprenorphine compared to methadone is unadjusted for confounding—such as differences in maternal clinical profiles by treatment choice—the estimated measure of effect (i.e. risk ratio) is a mix of both the effects of prenatal treatment and the confounder on the infant.

While we commend Zedler *et al.* for their efforts, their publication does not clarify the available evidence. The confidence interval for their overall summary estimate would be narrower than those from the individual studies due to the reduction in random error achieved by the larger pooled sample size. This pooling of data, however, does nothing to adjust for systematic error (i.e. confounding bias, information bias, selection bias). Pooling studies that are confounded produces an overall summary estimate that also is confounded. Zedler *et al.* would have provided a more valid effect estimate had they attempted to remove some of the uncontrolled confounding from their pooled estimate, perhaps by bias analysis simulation [14], as was performed in our meta-analysis published in 2014 [15]. We showed that confounding in published cohort studies and confounding and/or selection bias in randomized controlled trials from study dropout could contribute to the observed protective effect of buprenorphine versus methadone on the neonate.

Increasing rates of opioid dependence in pregnant women and of NAS in their neonates are major health issues in the United States. NAS has implications for the long-term health of the infant and is associated with soaring hospital costs and decreasing neonatal intensive care unit resources [16]. Efforts are needed urgently to reduce NAS and other adverse birth outcomes in these infants.

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