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Comment on 'The Complex Factors Determining Neonatal Abstinence Syndrome and Its Management'

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We are pleased to respond to the comment written by Professor Robert Newman and Susan Gevertz on our publication entitled 'Influence of Site Differences between Urban and Rural American and Central European Opioid-Dependent Pregnant Women and Neonatal Outcome Characteristics' [1].

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study was the first prospective, randomized, double-blind, double-dummy multi-site trial comparing safety and efficacy of methadone and buprenorphine in pregnant opioid-dependent women with a special focus on neonatal outcome [2, 3]. This clinical trial is unique in its design and could serve as a role model for evidence-based research studies on other chronic medical conditions, requiring special treatment in pregnancy.

To explain the heterogeneity of results and structure, despite having the same protocol, we have to focus on different requirements in Europe compared to the USA. In Europe, to meet good clinical practice requirements and to guarantee insurance coverage, a stringent adherence to protocol is mandatory. The principal investigator in clinical pharmaceutical trials must be a physician. In contrast to this, in the USA, protocol implementation is in the principle investigator's responsibility. Therefore, at the European site, neonates had a minimum hospitalization length of 9 days, independent of developing neonatal abstinence symptoms (NAS), as initially submitted to IRB and based on the insurance policy. For the first time ever the rating of NAS was done under strictly blinded conditions, meaning that the neonatal research staff was blinded to intrauterine medication exposure and to urine toxicology results. At the European site, all neonates remained hospitalized over the time frame of NAS ratings (with and without NAS morphine treatment, but based on standardized NAS rating on a rooming-in basis with their mothers). At US sites different conditions were given because neonates were frequently discharged from hospital somewhat earlier. The minimum hospitalization periods of neonates in urban and rural US sites were only 2 and 4 days, respectively, with considerable variation between the sites. This could explain some of the differences in neonatal outcome.

At the Viennese site a comparable mean duration of neonatal treatment with no significant differences between the two opioid medications was noted. No significant differences pertaining to the amount of mean total morphine medication administered to neonates were found. However, at the European site, a significantly lower mean total morphine dose for NAS treatment compared to urban US sites became evident. In particular, the mean total morphine dose for methadone-exposed children was considerably higher including a high standard deviation, suggesting a heterogeneous newborn sample with regard to NAS.

Non-pharmacological aspects which should be considered in multi-site research planning, study implementation and interpretation of results like screening procedures as well as sociodemographic, therapeutic and clinical variables may have also played a substantial role in site differences [4, 5]. However, these aspects were not investigated on a standardized basis.

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