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Article type : EBNEO Review

TITLE OF WRITE-UP

Morphine vs methadone in the treatment of neonatal abstinence syndrome.

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/APA.14846](https://doi.org/10.1111/APA.14846)

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MANUSCRIPT CITATION

Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, Marro P, Oliveira EL, Harvey-Wilkes K, Czynski A, Engelhardt B, D'Apolito K, Bogen D, Lester B. Comparison of Safety and Efficacy of Methadone vs Morphine for Treatment of Neonatal Abstinence Syndrome. *JAMA Pediatrics* 2018; 172(8):741-748. PMID: 29913015.

COMMENTARY, limited to 500 words

Misuse of opioids during pregnancy affects more than 5% of pregnancies in the United States (1). Infants exposed to alcohol or drugs in utero are at risk of developing neonatal abstinence syndrome (NAS). Several different approaches are used to treat NAS, and no universal standard exists. Morphine and methadone are commonly used pharmacological treatments (2).

This randomized, double-blind, intention-to-treat trial compared the short-term safety and efficacy of treatment with morphine versus methadone in infants with NAS.

Although 183 patients were consented, recruitment did not meet the sample size target as 66 infants did not require pharmacotherapy. Therefore, only 117 patients were randomized to treatment groups. Analysis was performed according to the intention-to-treat principle, projected to detect a difference in primary outcome of hospital length of stay (LOS) of 2.3 days. Secondary outcomes were considered exploratory given they were not accounted for in initial power calculations.

No significant difference was found in the primary outcome of hospital LOS with unadjusted analysis. Adjusted analysis showed a reduction in mean LOS of approximately 2.9 days with the use of methadone, compared with morphine. Recruitment did not meet the sample size target; therefore, power to detect the pre-specified difference in LOS was diminished.

However, when compared to the observational arm, the randomized group had shorter LOS, LOS due to NAS, and treatment length suggesting that protocolization of care practices itself may lead to improved outcomes.

The study was delayed initially given a lack of commercially available preservative free formulation of methadone suitable for infants. Recruitment was challenging with significant numbers of parents declining randomization citing reasons including fear of social or legal ramifications. Increasing focus on non-pharmacological management of NAS, such as the Eat, Sleep, Console assessment approach (3), was apparent over the course of the study with an overall decline in pharmacotherapy requirement. Recruitment ceased before the planned sample size was attained for reasons not explicitly stated.

Previous studies have similarly suggested shorter median treatment times using methadone for NAS, compared with morphine. A retrospective study by Patrick *et al.* involving 1424 infants from 14 centres showed methadone to be associated with reduced LOS, compared with morphine (4). Brown *et al.*, in a single-centre study of 31 infants demonstrated a shorter duration of pharmacotherapy with the use of methadone, compared with morphine (5). Contrary to these studies, a small retrospective study of 26 neonates by Young *et al.* found that methadone was associated with longer LOS, compared with morphine (6). A recent systemic review of 18 trials comparing a number of pharmacotherapies used in treatment of NAS suggested that buprenorphine is the optimal treatment with morphine the lowest ranked pharmacotherapy in terms of LOS and treatment time (7).

This study suggested treatment of NAS with methadone was somewhat better than morphine in terms of short-term outcomes and LOS. The long-term neurodevelopmental outcomes associated with methadone use are unclear and require further investigation.

Standardization of pharmacotherapy approaches to NAS would require further appropriately powered trials and evidence of long-term outcomes. Indeed, with increasing success with non-pharmacological management of NAS, the pharmacological options may become less relevant.

URL LINK

URL TO THE FULL REVIEW ON THE EBNEO WEBSITE

FUNDING

This study was supported by grant R01DA032889 from the National Institute on Drug Abuse (Drs Davis and Lester).

CONFLICTS OF INTEREST

None

REFERENCES, only for the Commentary section and limited to 9

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Title:

Morphine vs methadone in the treatment of neonatal abstinence syndrome

Date:

2019-09-01

Citation:

Cooney, H., Hodgson, K. & Davis, P. (2019). Morphine vs methadone in the treatment of neonatal abstinence syndrome. ACTA PAEDIATRICA, 108 (9), pp.1731-1731. <https://doi.org/10.1111/apa.14846>.

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