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# Methadone dose and neonatal abstinence syndrome: systematic review and meta-analysis

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Review published: 2010.

## CRD summary

This review did not find a consistent statistically significant difference in the incidence of neonatal abstinence syndrome in infants of opioid-dependent pregnant women maintained on differing doses of methadone. This was a well-conducted systematic review and the authors' conclusions are likely to be reliable.

## Authors' objectives

To assess the relationship between maternal methadone dose in pregnancy and incidence of neonatal abstinence syndrome (NAS).

## Searching

MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched to 2009; search terms were reported. The reference lists of relevant studies and review articles were also checked for additional studies. No language restrictions were applied.

## Study selection

Randomised controlled trials (RCTs) and cohort studies of methadone use in opioid-dependent pregnant women that reported outcomes related to NAS were eligible for inclusion. Studies had to report the dose of methadone during pregnancy and the incidence of NAS.

The included studies were conducted in the UK, Europe, USA, New Zealand and Australia. Methadone doses varied considerably with the following commonly reported dosages used in the analyses: 20mg, 30mg, 40mg, 50mg, 80mg and 110mg. Most studies reported the incidence of NAS as the proportion of exposed neonates who were treated medically for NAS. The measurement and reporting of NAS was inconsistent across studies and diagnostic criteria were often not clearly defined, where they were defined they included the Green Neonatal Narcotic Withdrawal Index, the Finnegan Neonatal Abstinence Score, the Lipsitz Score, the Rivers Score and other scoring systems. Of the studies that used an objective scoring system, the incidence of medically treated NAS varied between studies from approximately 45 to 97%.

Two reviewers independently assessed studies for inclusion; disagreements were resolved by discussion.

## Assessment of study quality

One reviewer assessed the quality of the included studies using a modified version of the US Agency for Healthcare Research and Quality's Systems to Rate the Strength of Scientific Evidence. This checklist included questions to assess whether there was a clearly focused research question, if confounding was assessed, if outcomes were measured appropriately and if the study's conclusions were supported by the results. Only studies in English were assessed.

## Data extraction

Two reviewers independently extracted data on the dose of methadone used and the incidence, severity and duration of NAS. The authors of the included studies were contacted for additional information, where required.

## Methods of synthesis

Studies that reported the number of cases of NAS for different maternal methadone dosage bands were pooled using a random effects meta-analysis and results were presented as relative risks with 95% confidence intervals. The cut-off dosages used were 20mg, 30mg, 40mg, 50mg, 80mg and 110mg. Heterogeneity was quantified using $I^2$. Pre-planned sensitivity analyses were undertaken by including only prospective studies and only studies that used an objective scoring system for the diagnosis of NAS. Funnel plots were used to

assess publication bias. Meta-regression was used to examine the relationship between mean study methadone dose and incidence of NAS.

## Results of the review

Sixty-seven studies, including 5,139 neonates (range six to 444), were included in the review: two RCTs, 37 prospective cohort studies and 28 retrospective cohort studies. Most studies reported a clearly focused objective and described the study population and exposure to methadone and other substances adequately. Few studies assessed the effect of potentially confounding factors on NAS, such as concomitant illicit drug use, smoking, use of prescribed medication or gestation at delivery. Only three studies reported blinded assessment of NAS.

Nineteen studies found a relationship between methadone dose and the incidence, severity or duration of NAS, 18 did not find such a relationship and 30 studies did not report on the relationship between methadone dose and NAS.

Twenty-nine studies reported adequate information to be included in the meta-analysis. Using a range of cut-off points, there was no statistically significant difference in the incidence of NAS between lower and higher methadone dosage groups for most cut-off values, with the exception of the cut-off values of 20mg (RR 0.52, 95% CI 0.33 to 0.81; 10 studies; $I^2$=67%) and 40mg (RR 0.69, 95% CI 0.51 to 0.94; nine studies; $I^2$=65%); corresponding to a 48% reduction in the risk of NAS for pregnant women taking methadone at a dose of 20mg or less and a 31% reduction in the risk of NAS for pregnant women taking methadone at a dose of 40mg or less. There was substantial statistical heterogeneity for most of the comparisons. In sensitivity analyses that included only studies that used an objective scoring system and prospective studies only, the results were no longer statistically significant for the cut-off values of 20mg and 40mg.

Results of the meta-regression analyses were reported in an appendix. The authors reported that there was no significant evidence of publication bias.

## Authors' conclusions

The review did not find a consistent statistically significant difference in the incidence of NAS in infants of opioid-dependent pregnant women maintained on differing doses of methadone.

## CRD commentary

The review question and inclusion criteria were clear. An adequate search of relevant sources was undertaken, with no language restrictions. Publication bias was assessed and no significant evidence for its presence was found. Study selection and data extraction were undertaken in duplicate, which reduced potential for reviewer bias and error. The quality of the included studies was assessed using appropriate criteria and full results of the quality assessment were presented. Appropriate methods were used to pool the included studies and assess statistical heterogeneity; sensitivity analyses were also performed.

The authors acknowledged that the lack of blinded assessment of NAS meant that the diagnosis of NAS was potentially biased by knowledge of the maternal methadone dose in the majority of studies. In addition, most studies did not assess the effect of potentially confounding factors on the incidence of NAS. Many of the included studies were small, with around half of the studies including less than 50 neonates. These quality concerns reduce the reliability of the results of the included studies, although they were mitigated by the use of sensitivity analyses restricted to the better quality studies in the review.

This was a well-conducted systematic review and the authors' conclusions are likely to be reliable. However, it should be noted that no evidence of a statistically significant difference does not necessarily mean that there is no difference.

## Implications of the review for practice and research

Practice: The authors stated that NAS was only one of many factors that patients and their physicians needed to consider when deciding upon appropriate methadone doses during pregnancy; control of maternal withdrawal symptoms and maintenance of stability should take precedence.

Research: The authors stated that further adequately designed studies were required to investigate all potential determinants of NAS. They acknowledged that a randomised trial, randomising women to low- or high-dose methadone would have ethical and practical difficulties, and suggest a large prospective cohort study with careful, objective measurement of all potential confounders and blinded assessment of outcomes related to NAS, to determine if methadone dose was an independent predictor of the occurrence of NAS.

## Funding

The lead author was funded by the charity Friends of the Coombe and the School of Pharmacy, Royal College of Surgeons in Ireland.

## Bibliographic details

Cleary BJ, Donnelly J, Strawbridge J, Gallagher PJ, Fahey T, Clarke M, Murphy DJ. Methadone dose and neonatal abstinence syndrome: systematic review and meta-analysis. Addiction 2010; 105(12): 2071-2084. [PubMed: 20840198]

## Indexing Status

Subject indexing assigned by NLM

## MeSH

Cohort Studies; Databases, Bibliographic; Dose-Response Relationship, Drug; Female; Humans; Infant, Newborn; Methadone /administration & dosage /adverse effects; Narcotics /administration & dosage /adverse effects; Neonatal Abstinence Syndrome /epidemiology /etiology; Opioid-Related Disorders /drug therapy; Pregnancy; Pregnancy Complications /drug therapy; Prenatal Exposure Delayed Effects; Randomized Controlled Trials as Topic; Severity of Illness Index

## AccessionNumber

12011000370

## Database entry date

16/08/2013

## Record Status

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CRD has determined that this article meets the DARE scientific quality criteria for a systematic review.



PMID: 20840198