

# Growth and Neurodevelopment Outcomes of Caffeine Therapy in Neonates

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## Abstract

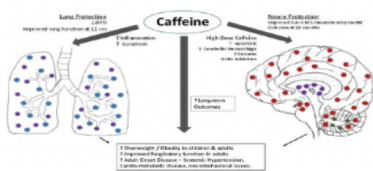
Caffeine therapy is one of most administered drugs in neonatal medicine for the management of apnea of prematurity (AOP). Regardless of this, the long-term effects of its use are not well researched for other organs systems, therefore its safety and efficacy are unknown. The objective of this literature review is to evaluate the role of early caffeine therapy has on neurodevelopment and growth of newborns. A systemic investigation of the current literature was completed with access to research pertaining to the varying outcomes of caffeine therapy in the neonatal population. Multiple studies show the use of early caffeine therapy in neonates led to a decrease in neurologic injuries/impairment. Injuries such as cerebral palsy and language/visual impairment, were assessed based on the Bayley's Scale III. A score of <70 is known to be severe impairment, however, after the caffeine therapy the score was improved to a score of <85 (mild impairment). Studies also found a significant reduction in the incidence of developmental coordination disorder.

Rank	Medication	Exposure <sup>a</sup>
1	Ampicillin	681
2	Gentamicin	676
3	Caffeine citrate	156
4	Vancomycin	91
5	Beractant	82

Table 1. Showcasing the most commonly used medications in NICU

## Background

Caffeine, a class of Methylxanthines, is among the most preferred medications in preterm infants for more than 40 years. It is clear that this drug has many positive pharmacological effects including stimulation of the respiratory center, increased sensitivity to CO<sub>2</sub>, increased diaphragmatic contraction, increased minute ventilation and more. Although this drug has many benefits for neonatal outcomes including reduced bronchopulmonary dysplasia (BPD), decreased mortality rates, and a reduced risk of other common morbidities, it is still unknown as to how much of an adverse effect it can have on neurodevelopment and growth of the child. Assessing the effects of this therapy assures health care workers that the treatments they apply are providing more benefits than adverse effects when treating respiratory disorders such as apnea of prematurity, hypoxemia, extubation failure in neonates.



## Objective

The objective of this literature review is to evaluate the role of early caffeine therapy on neurodevelopment and growth of newborns. Studies in the effectiveness of caffeine therapy over other commonly used medications can provide patients with better outcomes and make us aware of all the unrecognized consequences associated with them. As further research into this therapy is developed, caffeine can become the standardized treatment for preterm infants with significant benefits. This work expands our knowledge of the negative and more often, positive neural effect's that caffeine therapy has on its patients, reiterating how effective of a drug it is in this given population.

## Method

A systemic investigation of the current literature was completed with access to research pertaining to the varying outcomes of caffeine therapy in the neonatal population. In one study, a retrospective observational cohort was used. Preterm infants <29 weeks gestation were eligible for the study at participating ICU's, so long as they did not present with severe congenital abnormalities, die before day 3 or born moribund. Two groups were then analysed, the first were those who were exposed to caffeine therapy within two days and the second was those who were exposed after. Both groups were given a 10mg/kg loading dose and 2.5-5mg/kg maintenance dose after 24 hours. Participants were then assessed for their neurodevelopment outcome 18-24 months later using the Bayley III scale.

## Results

Multiple studies show the use of early methylxanthine therapy -a natural occurring substance found in caffeine- in neonates led to a decrease in neurologic impairment. Caffeine therapy enhances the Adenosine A1 receptors which leads to greater neuroplasticity of receptors as well as larger sizes of the dendrites. This resulted in improved cognitive function, cerebral cortical activity, as well as improvements in auditory processing. In a study conducted by Abdel-Hady, a higher survival rate was observed for neonates without neurodevelopmental disability with the caffeine treatment when compared to the placebo group (59.8% vs 53.8%). The Bayley's scale was also used to depict the results. Injuries such as cerebral palsy and language/visual impairment, were assessed based on the Bayley's Scale III. A score of <70 is known to be severe impairment, however, after the caffeine therapy the score was improved to a score of <85 (mild impairment). Lastly, an 11 year follow up study found that the caffeine group performed better than the placebo group in fine motor coordination, visuospatial integration, visuospatial organization and visual perception. Neurobehavioral outcomes were similar for both groups.

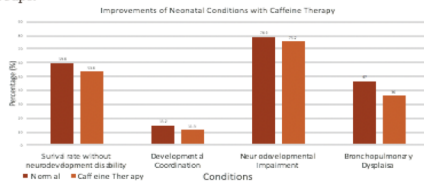
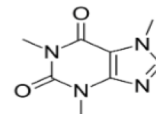


Figure 1: The improvements on different neonatal conditions with and without the application of Caffeine Therapy

## Conclusion

Neonatal caffeine citrate therapy is one of the most common therapies in neonatal medicine, however, it is unclear what the long-term risks or benefits of caffeine therapy are, especially in regard to neurodevelopment. Studies have shown that caffeine therapy for apnea in low birth weight infants improves rate of survival without neurodevelopmental disability. Although these findings are promising, they still do not address the long-term effects of therapy on neurodevelopment. Mürner-Lavanchy et al. attempted to fill this gap in the literature by conducting a large cohort study to determine the neurobehavioral outcomes 11 years after neonatal caffeine therapy for apnea in preterm neonates. They found that caffeine therapy had no adverse effects on general intelligence, attention and behavior. However, the study had an ascertainment rate of 78% for the neurobehavioral outcomes. This ascertainment bias challenges the accuracy of the results found since it is uncertain whether the outcomes of the entire cohort were reflected. Further randomized control trials and long-term cohort studies are needed to assess the safety and efficacy of caffeine therapy, including its long-term effects on neurodevelopment. Additionally, the current body of literature fails to distinguish the effects of early vs late caffeine therapy or the most effective dosage and duration of treatment.



Caffeine Citrate

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