UiT The Arctic University of Norway

Faculty of Health Sciences

Caffeine for treating apnea in premature babies

- A literary review

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Figure 1: Premature baby. The Royal Women's Hospital, Melbourne, Australia, 'Shutterstock'

Preface

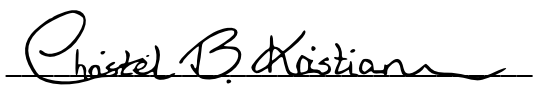
Identifying a topic to compose my master's thesis upon was a thought-provoking exercise.

During my second-year assignment I completed a quantitative survey and worked with statistical analysis and interpretations. Conversely, this year, I knew I wanted to do a literary review to improve my research and writing skills on scientific and evidence-based medicine. By conducting a literary review, I intend to develop and master my understanding of recognized medical databases, like Cochrane, Embase and Medline, which upon completion, should prove to become a significant asset when I come to treat my own patients in the future.

To achieve this, I desired a topic that challenged me, I knew little about and most importantly, fascinated me, because this was something I would be pursuing for almost a year. I recall while on exchange in Melbourne, Australia at The Royal Women's Hospital last year, the pediatricians mentioned caffeine for treating apnea in premature babies. The treatment was said to help their immature lungs develop faster. Prior to my exchange, I understood pregnant women should restrict their caffeine intake as too much could damage the fetus or lead to miscarriage. I found this to be a bit conflicting and perplexing to me. In this, I discovered an interesting topic. I determined I wanted to direct further research into this caffeine treatment to check for benefits and possible side effects in comparison with any placebo and/or other available treatments.

My thesis has not required any financial support nor needed any request to REK (Regional Committees for medical and Health Research Ethics) as this is a literary review.

Acknowledgements:
I want to express my deepest gratitude to my supervisor Marko Lukic for being uttermost supportive, and for providing me with all necessary instructions to pull this through. Thanks to Eirik Reierth, a senior academic librarian at The UiT – Science and Health Library, for stipulating how to do a proper systematic search. I also need to mention my best friend Marte Ramskjell, a hospital pharmacist at the University Hospital of North Norway, both for your expertise and fantastic support. Many thanks to my good friend William Spence, a general practice lawyer from New Zealand, for helping me with a little English grammar. Last but not least, a special thanks my family and friends for your patience and understanding, especially my little sister, Margrethe B. Kristiansen.



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Fauske, Norway, 1st of June 2021

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Summary

Introduction:
Premature infants with pulmonary complications is becoming a substantial health care problem. AOP being one of the biggest challenges that may end in death with no or wrongful treatment. Non-invasive respiratory support has been the favorable alternative, and caffeine citrate has been the drug of choice since the 1970s. The aim of this study is to explore how effective caffeine is for treating apnea in premature babies, but also to assess possible side effects.

Material and method:
A systematic literature search was performed in PubMed, Embase, MEDLINE and Cochrane around mid-August of 2020. The search was based around a PICO format with the use of MeSH-terms. To begin with, 455 articles were identified, but after removing duplets and screening with advanced options (only full-text, language and year), 76 articles remained. These were skimmed superficially by the abstract, and eventually 30 articles were included in the review.

Results:
Caffeine is effective in reducing and eliminating apnea episodes. It reduced BPD in VLBW preterm infants with AOP, the need of supplemental oxygen and the need for positive airway pressure. It improved survival rates without neurodevelopmental disability at 18-21 months in infants with VLBW. Caffeine therapy reduced the incidence of cerebral palsy, death and survival rates with neurodevelopmental disability. Neonates receiving caffeine at an earlier stage stayed shorter in the NICUs and were less likely to need ventilation. A side effect was temporarily reduced weight gain. Some studies showed that caffeine increased heart rate.

Conclusion and consequences:
In preterm infants, caffeine is effective in reducing AOP, the need for ventilation and enhances the success of extubation. As caffeine has been the golden standard for four decades, it is safe to say it has a respected benefit risk ratio. However, additional larger studies are needed to discover potentially rarer adverse side effects.

Key words:
Premature infant; caffeine; apnea of prematurity.

Clarification of Key Words and Abbreviations

- **Apnea**: A transient absence of spontaneous respiration.
- **AOP = Apnea of Prematurity**
- **BP = Blood Pressure**
- **BPD = Bronchopulmonary Dysplasia**: A chronic lung disease developed after oxygen inhalation therapy or mechanical ventilation, usually occurring in certain premature infants, or newborn infants with respiratory distress syndrome. Histologically, it is characterized by the unusual abnormalities of the bronchioles, such as metaplasia, decrease in alveolar number, and formation of cysts.
- **Caffeine**: A methylxanthine naturally occurring in some beverages and also used as a pharmacological agent. Caffeine's most notable pharmacological effect is as a central nervous system stimulant, increasing alertness and producing agitation. It also relaxes smooth muscle, stimulates cardiac muscle, stimulates diuresis, and appears to be useful in the treatment of some types of headache.
- **CAP = Caffeine for treating Apnea of Prematurity**
- **CPAP = Continues Positive Airway Pressure**
- **EET = Endo Tracheal Tube**
- **FDA = United States Food and Drug Administration:** An agency of the PUBLIC HEALTH SERVICE concerned with the overall planning, promoting, and administering of programs pertaining to maintaining standards of quality of foods, drugs, therapeutic devices, etc.
- **GA = Gestational Age**: The age of the conceptus, beginning from the time of fertilization. In clinical obstetrics, the gestational age is often estimated as the time from the last day of the last menstruation which is about 2 weeks before ovulation and fertilization.
- **GW = Gestational Week**
- **Infant**: A child between 1 and 23 months of age
- **NICU = Neonatal Intensive Care Units:** Hospital units providing continuing surveillance and care to acutely ill newborn infants.
- **NEC = Necrotizing Enterocolitis**
- **NNT = Numbers Needed to Treat**
- **PDA = Patent Ductus Arteriosus:** A congenital heart defect characterized by the persistent opening of fetal DUCTUS ARTERIOSUS that connects the PULMONARY ARTERY to the descending aorta allowing unoxygenated blood to bypass the lung and flow to the PLACENTA. Normally, the ductus is closed shortly after birth.
- **PMA = Post Menstrual Age:** Gestational age plus chronological age
- **PPV = Positive Pressure Ventilation**
- **Premature birth**: Childbirth before 37 weeks of pregnancy (259 days from the first day of the mother's last menstrual period, or 245 days after fertilization).
- **ROP = Retinopathy of prematurity**
- **VLBW = Very Low Birth Weight**: An infant whose weight at birth is less than 1500 grams (3.3 lbs), regardless of gestational age.

Most terms are obtained directly from PubMed.
https://www.ncbi.nlm.nih.gov/mesh/

1 Introduction

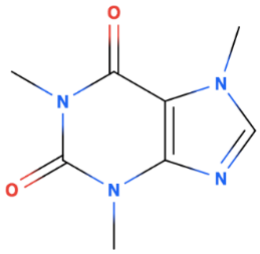


Figure 2: The chemical structure of caffeine

1.1 Background: Caffeine

Caffeine, also known as 1,3,7-trimethylxanthine, is a stable alkaloid and a mild stimulant of the central nervous system. It originated from Africa more than a millennium ago, and has ever since been used to improve people's mood (1, p. 10). The active ingredient has been added to a wide variety of products like soft and energy drinks, chocolate, hair as well as skin care products, and many medications; particularly for treating pain, headache and apnea of prematurity (AOP).

The US Food and Drug Administration (FDA) consider a daily amount of about 400 mg of caffeine (4-5 cups of coffee), as being a safe amount for healthy adults. For pregnant women 200 mg apply (1-2 cups of coffee) (2). Studies have shown that by increasing the dose to 300 mg, the risk of miscarriage increases by 37%, and at 600 mg the risk increases exponentially by 250% (3).

The mean half-life of caffeine is found to be 5 hours in adults (4). In preterm babies however it is significantly longer. In a study done by Doyle et al in 2016, the authors found that for preterm infants at 35 ± 1 week postmenstrual age (PMA), caffeine had a half-life of 87 ± 25 h (5). Caffeine has been the gold-standard treatment in the neonatal intensive care unit for the past 40 years (6), and is thought to be safe and effective in treating apneas.

1.2 Definitions

- **Apnea**: a period of not breathing.

  In premature babies this accounts for pauses lasting longer than 20 seconds.

  Symptoms: - Bradycardia (heart rate less than 80-100 bpm)
  - Cyanosis (bluish discoloration of skin or mucous membranes)
  - Low oxygen saturation (< 85% SaO_2 without receiving excess O_2) (7)
- **Preterm babies**: born before 37 weeks of gestation (8)

1.3 Epidemiology of babies with apnea

For term-born infants, only 1-2% are born with apnea (9). For late preterm neonates (34-36 weeks' gestation) the incidence is a little higher, 4-7%. Contrariwise, ≥ 84% with fetal weight < 1000 grams / gestational age (GA) <29 weeks, are born with AOP. The same is true for 54% of babies between 30-31 weeks' GA, and 15% of babies at 32-33 weeks' GA (10). This demonstrates that the incidence of AOP is inversely proportional with GA and birth weight.

1.4 Lung development and physiology

Lung development is divided into three phases (11)

Phase	Period	Development
1) Embryonic	4-7 weeks GA	Specifies lung organogenesis with two lungs. Formation of major airways and pleura.
2) Fetal (divided into three stages):		
Pseudoglandular	5-17 weeks GA	Formation of airways with bronchial tree and respiratory parenchyma. Start of the acinus.
Canalicular	16-26 weeks GA	Finishes formation of acini (operative part for gas exchange) due to epithelial differentiation. The most distal airways are being completed with air-blood barrier. Surfactant appears.
Saccular	24-38 weeks GA	Further progression of upcoming airspaces.
3) Postnatal	36-weeks GA to 4 years	Continuation of alveolar proliferation. Establishing secondary septa, resulting in the foundation of the alveoli.

Table 1: Lung Development and Physiology

It is important to notice that surfactant, produced by type 2 alveolar epithelial cells, is essential to reduce surface tension and for gas exchange to take place. It is produced starting around week 23 of gestation (11). Near the end of this canalicular phase, initial gas exchange may occur and it is possible for prematurely born babies to survive. Other important factors for lung development is adequate space, fetal breathing movements and sufficient amniotic fluid. Maturation can be stimulated by glucocorticoids, beta-adrenergic agonists & thyroid hormones, as well as caffeine citrate (12).

1.5 Caffeine citrate - mechanism of action

Caffeine works by inhibiting adenosine A1 and A2 receptors (the resting/sleep receptors) and stimulates catecholamine release. This in turn leads to a feeling of well-being, better mood, more energy, increased ability to stay focused and delays the need of sleep. Caffeine may also improve certain cognitive functions (13). Nonetheless, it is classified as a doping substance by the International Olympic Committee as it increases physical endurance, with the upper limit of urine concentration being 12 µg / ml (14).

The lethal dose is estimated to be around 5-10 grams. However, with a chronic intake of more than 500 mg daily (approx. 1 L of coffee), intoxication can occur. Intoxication is associated with anxiety, irritability, chronic insomnia, anorexia and low grade fever. Caffeine can also aggravate symptoms that people with cardiac arrhythmias (tachyarrhythmia) and dyspepsia experience (14).

Another mechanism of action with higher dosages is inhibition of phosphodiesterase. This in turn leads to inactivation of cAMP (the 2nd messenger for activating adrenoceptors) and increases intracellular cAMP. The result enhances adrenoceptor activity and thus bronchodilation. They can also produce anti-inflammatory effects by inhibiting the signaling protein TNF-alpha (tumor necrosis factor alpha) (15).

Caffeine also stimulates peripheral chemoreceptors, which in turn initiate normal breathing. It may also enhance clearance of ciliary mucosa and increase drive of the diaphragm muscle. The active ingredient is both water and fat soluble, meaning it can cross the blood-brain barrier. Absorption takes place in the small intestine, entering the bloodstream via the liver where it is broken down by cytochrome P450 oxidases, especially CYP1A2 (16).

Caffeine is also shown to increase sensitivity due to high levels of carbon dioxide in the bloodstream, leading to elevated metabolic rate, decreased muscle fatigability, and escalate diuresis via tubular adenosine A1 receptors (17).

1.6 The use of caffeine citrate at The University Hospital of North Norway

At the University Hospital of North Norway (UNN), Caffeine citrate (Peyona®) is being used as first line treatment for AOP. It works by increasing respiration response to pCO_2, and has a positive effect on respiratory muscles by increasing CNS excitation. Following a bolus dose, increased diaphragmatic activity and greater tidal volume is seen in preterm infants. Compared to theophylline, caffeine has a greater distance to toxic levels (> 250 micromol/L). Moreover, it can be dosed once daily (due to longer half-life), has more reliable enteral absorption, gives less side effects, and requires no routine of monitoring serum levels (18).

Administration of Caffeine citrate at UNN (19)	
Loading dose:	20 mg/kg
Maintenance dose:	5-10 mg/kg.
Side effects	Not common, but might give tachycardia. If pulse reaches > 180 bpm, then they lower the dose.
Discontinuation	- Usually at postmenstrual age +/- 34 weeks. - Or when the baby is on CPAP and been 5-7 days without significant apnea. Can be used longer if needed

Table 2: Caffeine Administration at UNN

1.7 Aim of current study

The incidence of preterm babies is increasing globally (20), so is the number of survivors (21). As a consequence, a rising number of newborns are growing up with pulmonary complications, which are potentially long-term. In fact, it is becoming a substantial health care problem (22). AOP is one of the biggest challenges, as this may lead to respiratory failure and the need for mechanical ventilation. Ventilation itself could give rise to bronchopulmonary dysplasia (BPD), a chronic lung disease.

Premature infants on ventilation can also develop neurological impairments that can eventually lead to death (23). This is why non-invasive respiratory support is the favorable treatment. Caffeine citrate has been the drug of choice since the 1970s (24). The aim of this study is to explore how effective caffeine is for treating apnea in premature babies, but also to assess potential side effects.

2 Material and Method

2.1 PICO search

A search strategy was based on the following PICO:

Population:	Preterm babies with apnea
Intervention:	Caffeine
Comparison:	No treatment, placebo, other treatments
Outcome	Primary outcome: Beneficial effects of caffeine on treating AOP, including reduced events of AOP, fewer days on ventilation and shorter stays at the NICUs.
	Secondary outcome: Side effects, including neurodevelopmental occurrences, increased heart rate, necrotizing enterocolitis, reduced weight gain, need of ventilation or CPAP.

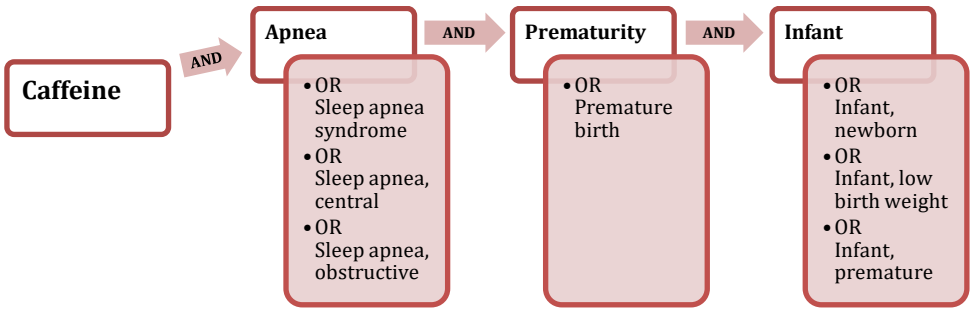
Table 3: Pico Search Format

I decided to include all full-text papers in English published after the year of 2000, regardless of study design. Exclusion criteria were anything that did not fit the PICO criteria above or did not provide an answer to the research question. Thus, RCTs, cohort studies (prospective and retrospective) and reviews were included.

2.2 MeSH terms

To include as many articles as possible, a systematic search was prepared operating MeSH (Medical Subject Headings) terms.

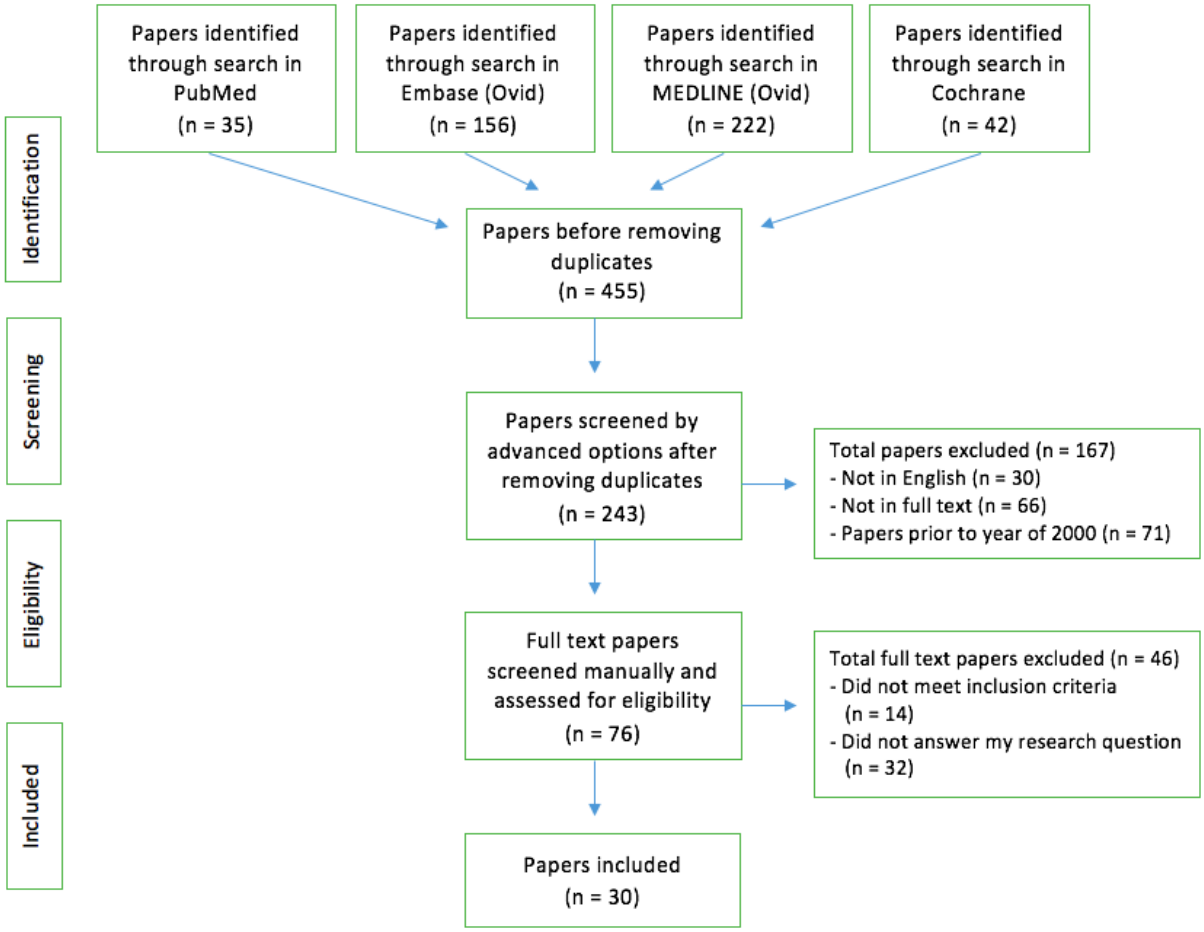
Figure 3: MeSH terms



2.3 Prisma Flow Chart

Four databases were used in this systematic literary search; PubMed, Embase, Medline and Cochrane. Initially, a total of 455 articles were found using the MeSH terms 'caffeine', 'apnea', 'prematurity' and 'infant'. After removing duplicates, 243 articles remained. By filtering for English language and full-text-only articles published after the year of 2000, 76 articles were left. These were manually skimmed by reading the abstract to check if they met the inclusion criteria and gave answer to the research question. Finally, 30 articles remained of interest, and thus were included in the literary review. Reference lists were also hand searched.

Figure 4: Prisma Flow Chart of systematic literature search



3 Results

3.1 The CAP trial

A study by Schmidt et al (25), one of the largest randomized multicenter placebo-controlled trial study on the subject, included a total of 2006 infants weighing in between 500-1250 g at birth. They were randomized within the first 10 days of life to receive either caffeine (n = 1006) or saline placebo (n = 1000) until therapy was no longer needed. The caffeine group received a loading dose of 20 mg/kg at median 3 days of age, and a maintenance dose of 5-10 mg/kg until therapy weaned off, which happened before reaching 35 weeks post menstrual age (PMA).

The authors found that at PMA of 36 weeks, only 36% (of n = 963, still alive) in the caffeine group received supplemental oxygen vs 47% (of n = 954, still alive) in the placebo group ($p < 0.001$). Also, the caffeine group discontinued positive airway pressure 1 week earlier than the placebo group, 31 weeks being the median PMA vs 32 weeks PMA ($p < 0.001$). Further, co-interventions with either Doxapram (a respiratory stimulant), postnatal corticosteroids, and/or red-cell transfusions were all less frequently used in the caffeine group ($p < 0.001$ for each comparison).

A side effect of caffeine therapy was temporarily reduced weight gain, being largest two weeks into therapy with a mean difference of -23 grams ($p < 0.001$). Death rates, brain injuries measured with ultrasonography, and necrotizing enterocolitis (NEC) did not differ significantly between the two groups at their first discharge home.

A post-hoc analysis showed that the infants in the caffeine group were significantly less likely to undergo surgery to close a patent ductus arteriosus (PDA) vs the placebo group. Since their study protocol did not mandate serial echocardiography in all study patients, it is uncertain whether caffeine promoted the closure of a patent ductus arteriosus and this would need further studies.

The authors conclusion was that caffeine reduced bronchopulmonary dysplasia (BPD) in very low birth weight (VLBW) preterm infants with AOP, which they defined as not needing supplemental oxygen at 36 weeks PMA. Caffeine did not seem to cause any short-term side effects except for the temporary reduction in weight gain. When the FDA approved caffeine citrate for treating apnea of prematurity, a warning stated that there might be a possible association between methylxanthines and development of NEC. The absenteeism of any detectible effect of caffeine on NEC in this study is reassuring.

In November 2007 Schmidt et al (26) published a follow-up from their first study. This time they were observing possible long-term side effects as the babies turned 18-21 months. In total, 937 babies in the caffeine group and 932 in the placebo group had adequate data and were eligible for follow-up. Primary outcomes were death, deafness, blindness, cerebral palsy, or cognitive delay. Just over 40% of the participants in the caffeine group died or survived with a neurodevelopmental disability, which was significantly fewer compared with the placebo group; 46.2% ($p = 0.008$). The number needed to treat (NNT) AOP with caffeine to avoid one adverse outcome at 18 months was 16 (95% CI 9-56).

Furthermore, caffeine significantly reduced the incidence of cerebral palsy; only 4.4% in the caffeine group compared to 7.3% in the placebo group ($p = 0.009$). Further, there was a significant difference in the incidence of cognitive delay, 33.8% in the caffeine group vs 38.3% in the placebo group ($p = 0.04$). Early cessation of any positive airway pressure in the caffeine group justified 49% of the beneficial long-term effect.

The death rates, deafness, and blindness and the mean percentiles for height, weight, and head circumference at follow-up did not differ significantly between the two groups. However, a post-hoc analysis showed reduced incidence of severe eye disease, retinopathy, in the caffeine group. Overall, they concluded that caffeine therapy for apnea of prematurity improves survival rate without neurodevelopmental disability at 18 - 21 months in infants with VLBW.

In 2010, Davis et al published a study (27) to assess if the benefits of caffeine maybe varied in subgroups, looking at the participants in the CAP trial. They divided subgroups according

to indication for receiving caffeine, being either to prevent or treat apnea, or to facilitate removal of an endotracheal tube (EET). They also looked into the levels of respiratory support; no support, none-invasive support or ventilation via ETT. Furthermore, they viewed the time for commencing the drug; mean PMA being 3 days, early group being before 3 days and late being 3 days and beyond.

A total of 1869 infants (93,2%) were included. There was little evidence of a differential treatment effect of caffeine. There was, however, indication of heterogeneity of caffeine effect for the outcomes death or major disability (p = 0.03) and cognitive delay (P = 0.02). Infants receiving respiratory support at the time of randomization appeared to derive greater long-term neurological benefits from caffeine than those who did not. The differences in PMA at last endotracheal intubation (p = 0.04) and PMA at last positive pressure ventilation (PPV) (p = 0.03) were statistically significant. Infants whose treatment commenced before 3 days of age appeared to derive greater short-term respiratory benefits from caffeine than infants commencing treatment at $\geq$ 3 days. That is, starting caffeine early resulted in larger reductions in days on respiratory support.

PMA at the time of discontinuing PPV was shorter with earlier treatment (p = 0.01). Mean differences in odds ratio (95% CI) were: early, 1.35 weeks (0.90-1.81); and late 0.55 weeks (0.11-0.99). Therefore, the authors concluded that there was evidence of beneficial effects of caffeine. Infants receiving respiratory support appeared to derive more neurodevelopmental benefits from caffeine than infants not receiving support, and earlier initiation of caffeine might have been associated with a greater reduction in time on ventilation.

In 2012, a 5-year follow-up was conducted in order to assess long lasting effects (28).
A total of 1640 children (84.9%) had adequate data for the main outcomes at 5 years of age (n= 833 in the caffeine group, n = 807 in the placebo group). The main outcomes were death or survival with or without cognitive impairment, behavior problems, health issues, deafness and/or blindness. Results showed a lower percentage of death in the caffeine group, although borderline not statistically significant (p = 0.09). Most of the other outcomes were not significantly different between the two groups.

Gross motor impairment was less severe in caffeine-treated children than in controls, and they showed better motor coordination and visual perception. The incidence of cognitive impairment was strikingly lower at 5 years than 18 months, although still similar in both groups (p = 0.89). Nonetheless caffeine had a small continuous favorability. The conclusion was that at 5 years of age, neonatal caffeine therapy could no longer be said to have a significantly improved survival rate without disability, and that the benefits on survival rates without disability at 18 months mitigated during childhood development.

In 2014, a 5-year follow-up randomized controlled trial was conducted by Doyle et al (29), exploring developmental coordination disorder (DCD), i.e. motor performance below the 5th percentile in children with full scale Intelligence Quotient (IQ) > 69, without being diagnosed with cerebral palsy (CP). The rate of DCD was significantly lower in the caffeine group (11.3%) compared to the placebo group (15.2%) (p = 0.032), concluding that neonatal caffeine therapy for AOP reduced the risk of DCD at 5 years' age.

Motor dysfunction with or without CP is more common in children born prematurely or with low birth weight compared to those born to term. This is important not only for the motor impairment per se, but also due to associated problems like cognitive shortages, lower academic performance, behavior problems, poor social skills, and self-esteem issues.

In 2017, an 11-Year follow-up (30) of the CAP trial was conducted to evaluate whether or not neonatal caffeine therapy was associated with improved functional outcomes 11 years later. 920 children had adequate data for the follow-up outcomes; academic performance, motor impairment and behavioral problems. Their results showed that caffeine therapy was associated with a significantly reduced risk of motor impairment compared with placebo (p = 0.009). There was however no difference in academic performance nor behavioral problems.

In 2018, another 11-year follow-up double-blind randomized placebo-control study (31) was conducted to investigate further long term effects. Measurements were fixed on general intelligence, attention, executive function, visuomotor integration and perception, and behavior, including up to 870 children. The caffeine group performed significantly better than placebo in fine motor coordination (p = 0.01) as well as in visuomotor integration (p =

0.05), visual perception (p = 0.02) and visuospatial organization (p = 0.003). General neurobehavioral outcomes were similar in both groups. None of the secondary outcomes reported were adversely affected by caffeine. This highlights the long-term safety of caffeine therapy going forward into middle school age.

Taking most of the aforementioned articles into account, neonatal caffeine therapy appears to have a lasting beneficial effect on motor function, both at 18 months, 5 and 11 years of age. Of preterm infants the NNT with caffeine to prevent one case of moderate to severe motor impairment at 11 years of age, was found to be approximately 13.

3.2 Effectiveness of caffeine for treating AOP

In 2000, Erenberg et al (32) published a multicenter parallel randomized, double-blind, placebo-controlled trial with open-label rescue (caffeine citrate rescue arm as the safety net for the placebo group). They included 82 preterm infants, 28–32 weeks' post-conception. 45 of whom received caffeine citrate solution, 37 received placebo, and both completed 10 days of double-blind therapy. The caffeine group received 20 mg loading dose followed by 5 mg/kg/day.

Caffeine citrate was significantly more effective in reducing apnea episodes, by at least 50% after 6 days compared to placebo ($p < 0.05$), and approached statistical significance after 3 days ($p < 0.10$). It was also significantly better than placebo in eliminating apnea in 5 days ($p < 0.05$), and approached significance ($p < 0.10$) after 2 days.

Results showed that 68,9% in the caffeine group vs 43,2% in the placebo group experienced a ≥ 50% reduction in apnea episodes (p = 0.02) for an aggregate of 7–10 days of treatment. Elimination of apnea happened to 24,4% in the caffeine group vs zero in the placebo group (p = 0.005).

To summarize, caffeine citrate in the right given dose is safe and effective for treating apnea of prematurity in infants 28–32 weeks postconception. No clinically significant differences were found between groups in vital signs, body weight, or laboratory values. In both groups,

the increase in mean daily weight was similar during the study. Adverse events were not significantly different between the groups.

3.3 Pharmacodynamical effects

In 2016, Yu et al (33) did a retrospective observational study on 115 preterm infants from January 2006 to October 2011. Their aim was to explore the relationship between caffeine intake and pharmacodynamics effects on heart rate, respiratory rate, episodes of apnea and/or other adverse effects. The infants median age was 29 weeks and birth weight 1230 grams. Caffeine citrate was given at postnatal age of 1 (1-3) day and therapeutic drug monitoring (TDM) was performed at 15 (10-24) days postnatally. No direct correlation was found between caffeine serum concentrations and respiratory rate or apneic episodes. Though, heart rate and caffeine concentrations were significantly correlated ($p < 0.05$).

The severity of recorded tachycardia was mostly mild to moderate from 170 – 212 bpm. The authors found a significant correlation between caffeine citrate and heart rate ($p < 0.05$). The physiological effect was however minor. The regimen 40/5 mg/kg q12h led to significantly higher percentage of patients experiencing tachycardia than the standard regimen ($p < 0.001$). No direct correlation between caffeine citrate concentration and respiratory rate or apneic episodes was found.

Apneic episodes and onset of adverse events that happened on the same day as TDM were measured. None of the neonates died or had any severe reaction under current dosing regimens. Out of 115 patients, a total of 27 patients (23.4 %) were re-intubated onto a mechanical ventilator during the entire course of caffeine therapy, of which 10 patients (8,6 %) were re-intubated secondary to worsening symptoms of apnea.

Ulanovsky et al (34) explored caffeine´s effect on the autonomic nervous system with regards to treating premature infants with apnea. They prospectively studied 21 preterm infants and focused on their heart rate variability. They did not find any changes in heart rate, blood pressure nor tone of the autonomic nervous system following caffeine

administration. They found no short term detrimental effects on heart rate variability.

Rossor et al (35) studied 26 premature infants to determine if caffeine therapy in premature infants could increase ventilator response. They found that caffeine administration significantly increased ventilatory response to hypercarbia (n=14, mean difference 41ml/kg/min/% CO_2, 95% CI 26–57, p = 0.001). CO_2 sensitivity was significantly lower after discontinuing caffeine therapy. Furthermore, an initial weaker ventilatory response to hypercarbia was associated with the subsequent development of apnea requiring treatment with caffeine.

3.4 Caffeine on brain activity

In 2000, Dani et al published a study (36) looking at hemodynamic changes in the brain of preterm infants after maintenance dose of caffeine or aminophylline therapy for treating apnea of prematurity. They were measuring cerebral blood flow non-invasively with near-infrared spectroscopy (NIRS) and cerebral Doppler ultrasonography on 40 infants < 32 GW and birth weight < 1500 g. Half received caffeine and the other half aminophylline.

They found that caffeine did not significantly affect brain hemodynamics, including cerebral blood flow, heart rate, mean systemic arterial pressure, arterial oxygen saturation, transcutaneous carbon dioxide tension nor hemoglobin. While aminophylline induced a transient increase in oxygenated and deoxygenated hemoglobin concentration (hence O_2Hb and HHb) and cerebral blood flow velocity (CBV) in similar extent as caffeine.

In 2014, Hassanein et al published a prospective observational study (37) on 33 preterm infant below 34 weeks GA, in Egypt. Their aim was to investigate caffeine's effect on preterm infants' respiratory functions and brain cortical activity, using conventional-integrated electroencephalography (cEEG) and aEEG (amplitude-integrated). Together with cardiopulmonary and sleep state, they recorded 20 preterm infants before, during and 2 hours after intravenous caffeine infusions, and they were controlled against 13 non-caffeinated preterm infants. They were also measured at 36 weeks' post-menstrual age as an outcome parameter.

They found significant differences between the groups when it came to increasing heart rate ($p < 0.001$), mean arterial BP ($p < 0.001$) and capillary SaO_2 ($p = 0.003$) after 30 minutes. They didn't find any differences in clinical seizures nor any difference in cEEG, but a significant increase in aEEG continuity was detected starting half an hour after caffeine administration compared to before ($p = 0.002$). Furthermore, at 36 weeks' control, they found significantly longer NICU stays in the controls not receiving caffeine ($p = 0.022$). They concluded that caffeine increases cerebral cortical activity and result in maturation at 36 weeks, without risk of seizures.

From December 2015 to September 2016, Dix et al included 34 preterm infants (< 32 GA) in an observational study (38) at a Wilhelmina children's hospital Utrecht in the Netherlands. The babies were neuromonitored using NIRS for surveilling regional cerebral oxygen saturation ($rScO_2$) and fractional tissue oxygen extraction (FTOE), using the anterior cerebral artery (ACA) and internal carotid artery (ICA) 10 minutes prior to receiving caffeine, 30 minutes during, and every hour up to 6 hours after receiving caffeine.

They found that caffeine increased oxygen extraction in the brain, which suggested a transient stimulating effect on brain metabolism, because cerebral oxygen saturation decreased. This could however be due to a decrease in cerebral blood flow or cerebral vasoconstriction which might have been pCO_2 induced. They also found significant decrease in pCO_2. Furthermore, they found a significant increase in heart rate and mean arterial blood pressure.

No changes were found with regards of brain perfusion nor electrical activity of the brain, neither was there any changes in respiration rate (RR) nor SaO_2 over time. In the ACA, there was a significant decrease in peak systolic velocity (PSV) and Doppler-measured resistance-index (RI), while end-diastolic velocity (EDV) did not change significantly. No changes in Doppler variables were measured in the ICA after caffeine intake.

In 2015, Maitre et al (39) did a study on 45 infants. Their aim was to assess whether or not caffeine had an impact on improving cortical differentiation on complex speech sounds. They find an improvement in auditory processing probably due to improved

neurodevelopmental outcomes. Normally preterm infants show reduced speech sound discrimination when compared to term babies. This study however, revealed that preterm infants receiving low dose caffeine had a similar perception to that of a more mature infant not exposed to caffeine, which suggests that caffeine might improve cortical processing of auditory stimuli. Their finding has also been supported from a previous study done by Chen et al in 94. (40)

3.5 Caffeine's effect on premature babies' sleep

Curzi-Dascalova et al (41) studied 15 preterm infants regarding caffeine's influence on sleep. 10 infants received caffeine, and 5 were controls receiving no caffeine therapy. In both caffeine- and non-caffeine-treated babies, the various sleep variables, including wakefulness, active and quiet sleep, and total sleep time, were similar before and after the caffeine dose ($p > 0.2$). Oxygen saturation in arterial blood did not drop below 85% in any of the infants and healthily altered between 90-97%. They found no significant differences in sleep organization between 33- and 34-week PMA infants receiving maintenance-dose caffeine citrate (5 mg/kg/day) by matching with control infants.

In 2014, Marcus et al (42) published a double-blind, randomized, controlled clinical trial. They included 201 ex-preterm children aged 5–12 years old, 98 of whom had received caffeine, and 103 had gotten placebo. This was yet another prospective follow-up study of the CAP trial. The hypothesis was that caffeine therapy for AOP would result in long-term abnormalities in sleep patterns and breathing during sleep. The children underwent actigraphy (recording motor activity), polysomnography, and caregivers fulfilled sleep questionnaires. Investigators and families remained blinded as to whether or not the child had received caffeine or placebo as a neonate.

A large proportion of children in both groups had obstructive sleep apnea syndrome (OSAS), 8.2% of the caffeine group and 11.0% of the placebo group. Furthermore, 24% of the caffeine group and 29% of the placebo group had either an elevated apnea hypopnea index (AHI – being the number of pauses or almost pauses per hour) and/or a history of adenoidectomy/tonsillectomy (standard treatment for childhood OSAS). Results showed

that sleep questionnaire scores were within the natural range, and did not differ amongst the groups, including sleep onset latency and sleep efficiency. No difference was found in the restless legs syndrome either.

From 2013 – 2015, the authors from a Finnish study recruited 21 preterm infants at 35,7 mean GW (43). The aim of the study was to explore the effects of caffeine and supplemental oxygen on periodic breathing (PB, consisting of short apnea episodes separated by hyperpnoeic episodes) and apnea of prematurity during sleep and NREM (non-rapid eye movement) sleep, using polysomnography. Most cases of PB and AOP happened during NREM and caused intermittent hypoxia.

The authors found that oxygen supplementation decreased PB time by 99% and caffeine by 91% ($p < 0.001$). Further, they observed that a reduction in AOP, from 1.4 per hour at baseline to 0.4 with oxygen ($p = 0.03$) and 0.3 with caffeine ($p = 0.07$). They concluded that preterm infants might likely benefit from a prolonged caffeine treatment to prevent intermittent hypoxia.

3.6 Early vs late administration

A Canadian retrospective observational cohort study on 5517 neonates (approximately same gestational age, < 31 GW) by Lodha et al (17) was conducted between 2010-2012. They divided neonates from 29 different Canadian neonatal intensive care units (NICUs) into two groups; 74.6% receiving early caffeine treatment (within the 2nd day after birth), and 25.4% receiving it later (after or on the 3rd day following birth).

The study demonstrated that neonates in the early group had lower odds of composite death or BPD with an adjusted odds ratio (AOR) = 0.81, 95% CI 0.67-0.98, as well as PDA, AOR = 0.74, 95% CI, 0.62-0.89. No adverse impact on any other outcomes was observed, such as NEC, severe neurological injury nor severe retinopathy of prematurity. Furthermore, the neonates in the late group stayed longer in the NICUs and they were more likely to receive surgical intervention such as mechanical ventilation, high-frequency ventilation, and

needed oxygen for a longer time period.

3.7 High vs low dose

In 2015, Mohammed et al (44) published a randomized, pilot, double-blinded, prospective study, comparing two different dose regimens of caffeine citrate in preterm infants in Egypt. They compared high-dose (loading 40 mg/kg/day and maintenance of 20 mg/kg/day) vs low-dose (loading 20 mg/kg/day and maintenance of 10 mg/kg/day) caffeine citrate in preterm infants <32 weeks' gestation, presented with AOP within the first 10 days of life. A total of 120 neonates (60 in each group) were enrolled.

High-dose caffeine was associated with a significant reduction in extubation failure in mechanically ventilated preterm infants (10 out of 30 infants (33 %) vs 13 out of 35 infants (37 %) in the high vs low dose caffeine groups, respectively; RR 0.89, 95 % CI 0.46-1.7, $p < 0.05$), frequency of apnea ($p < 0.001$), and days of documented apnea ($p < 0.001$). High-dose caffeine was associated with a significant reduction in the duration of oxygen therapy. Nonetheless, high-dose caffeine was associated with a significant increase of tachycardia episodes (23 vs 8 %, $p < 0.05$), but without significant impact on physicians decision to withhold caffeine.

The use of higher than current standard dose of caffeine may decrease the chance of extubation failure in mechanically ventilated preterm infants and the frequency of AOP without significant side effects, giving fewer apnea episodes and less days of documented apnea. No significant difference was noted in neonatal mortality, BPD, NEC, IVH, ROP, or length of hospital stay between the groups.

3.8 Caffeine vs other Methylxanthines

In 2017, Khurana et al (45) published a study on 79 children observing long-term neurodevelopment outcome at 18 to 24 months of corrected age, after receiving either caffeine or aminophylline therapy for AOP ≤34 weeks of gestational age. 43 of whom had received caffeine and 36 aminophylline. Cognitive, language and motor deficits were assessed by Bayley Scale of Infant and toddler Development (BSID –III). Postnatal

characteristics such as hearing and visual impairments during NICU visit were noted and followed up.

Infants allocated to the caffeine group showed 84% lower risk of acquiring cognitive impairment (RR 0.16, CI 95% 0.02-1.36), 50% lower risk of developing motor deficits (RR 0.50, CI 95% 0.12-1.95) and 24% lower risk of developing language problems (RR 0.76, CI 95% 0.36-1.58). Infants received caffeine had 40% lesser risk of developing visual abnormalities (RR – 0.60, CI 95% 0.34-1.04). However, in all the neurodevelopment fields, the differences between the groups were not statistically significant, including development of hearing impairments. Nevertheless, the clinical significance of caffeine over aminophylline cannot be overlooked.

Risk of mortality in the caffeine group was 9% lower than in the aminophylline group, although statistically non-significant (RR – 0.92, CI 95% – 0.45-1.84, p = 0.81). Incidence of mortality was found to be 11.2% in caffeine treated infants where against 12.2% in aminophylline group. Physical growth parameters were found to be similar.

In 2009 Skouroliakou et al (46) published a randomized controlled trial viewing differences in effect between caffeine and theophylline for treating apnea of prematurity. They enrolled 70 neonates < 33 weeks' GA, of whom 33 received caffeine and 37 theophylline. Treatment was started if an infant had $\geq$ 3 apneic attacks requiring vigorous intervention within 24 h. If < 3 apnea episodes were recorded, prophylaxis was initiated. Therapy with either methylxanthine reduced apneic events, most in the caffeine group (p = 0.005), but also in the theophylline group (p = 0.012).

Analysis of the caffeine data showed a significant decrease in the number of apneic events per day after caffeine administration on days 1–3 (p = 0.001) and 4–7 (p = 0.001). Analysis of combined (treatment plus prophylaxis) data showed a significant decrease in apnea frequency only in those infants receiving caffeine (p = 0.001). There was, however, no sustained benefit of caffeine over theophylline beyond the first week of therapy.

In 2017, Shivakumar et al (47) published a single-center randomized controlled trial from

India, comparing the efficacy and safety of caffeine and aminophylline for treating apnea of prematurity. They included 240 preterm infants < 34 weeks GA. Half received caffeine and the other half aminophylline. Primary outcome was frequency of apneic episodes (number of apnea spells per 24 hour) at an interval of 1 to 3 day, 4 to 7 day and 8 to 14 day of therapy.

The results showed that apneic episodes during 4-7 days of therapy was found to be significantly higher in caffeine group ($p = 0.03$), although, complete perseverance of apnea was attained after median of 6 days in either group. They found no difference in median length hospital stay at the NICU between the groups. Furthermore, there was no significant difference in the risk of developing feed intolerance (17% vs 22.8%, RR 0.74, 95% CI 0.39-1.40), jitteriness (8% vs 9%, RR 0.87, 95% CI 0.31-2.49) or glucose abnormality (3% vs 3%, RR 1.02; 95% CI 0.21-4.92).

Persistent desaturation in caffeine group was higher than that of aminophylline during first 3 days of therapy ($p = 0.006$). However, in the second week of therapy, aminophylline group reported higher desaturation episodes ($p < 0.001$). Additionally, aminophylline group had higher mean HR on the 2nd day ($p = 0.007$) and the 3rd day ($p = 0.002$). Risk of developing tachycardia was lower in caffeine vs aminophylline-treated infants (RR 0.30, 95% CI 0.15-0.60).

In 2018, Shivakumar et al (48) published yet another randomized study trial by looking at hemodynamic effects on caffeine vs aminophylline therapy in 185 preterm neonates ≤ 34 weeks, using echocardiography. Results showed that heart rate was significantly and exclusively higher in the aminophylline-treated neonates than the caffeine-treated ones ($p < 0.001$). End-systolic volume was higher in both caffeine ($p < 0.001$) and aminophylline group ($p = 0.001$) compared to pretreatment values. End-diastolic volume was also significantly higher in both groups ($p = 0.01$).

In 2000, Gannon et al (49) compared the use of caffeine citrate with theophylline. They concluded that caffeine was the desired drug of choice given its longer half-life, once a day dosing interval, fewer side effects, easier monitoring and earlier onset of action. Moreover,

it has almost 100% bioavailability given orally, a wider therapeutic window and fluctuates less in plasma concentrations compared with theophylline. See table 4 for further comparison, and table 5 for additional effects of Methylxanthines (24).

Comparison of Caffeine and Theophylline

Variable	**Caffeine**	**Theophylline**
- Efficacy	+++	+++
- Peripheral side effects	+/-	+++
- Drug clearance	Very slow ($T_{1/2}$ = 100 hours)	Slow ($T_{1/2}$ = 30 hours)
- Plasma level at steady state	Stable	Fluctuating
- Need for drug monitoring	+/-	+++
- Dosing interval	Once daily	1-3 times a day

Table 4: Theophylline or caffeine: which is best for AOP?

Major Effects of Methylxanthines ↑= increases ↓= decreases

- Regularized breathing pattern
- ↑ ventilator drive
- ↑ chemoreceptor sensitivity to carbon dioxide
- ↓ REM sleep
- ↑ Blood glucose
- Enhanced diaphragmatic contractility
- Stimulus of CNS
- ↑ renal blood flow and ↑ diuresis
- Augmentation of the basal metabolic rate
- Stimulation of gastric secretion and ↓ esophageal sphincter tone

Table 5: Major effects of methylxanthines

In 2006, Natarajan et al published an observational study (50) on 101 premature neonates regarding drug monitoring of caffeine plasma concentration. They showed that monitoring of plasma concentrations of caffeine is unnecessary, even in extremely premature infants with renal or hepatic dysfunction. This was due to the fact that the overwhelming majority attained goal plasma levels with current dosing regimens with concentrations in the range of 5 - 20 mg/L. However, monitoring of plasma levels may be prudent in cases without clinical effect, because higher doses may be attempted.

3.9 Prophylactic treatment

In 2001, Henderson-Smart, DJ and Steer, PA reviewed the evidence (51) on prophylactic use of caffeine to prevent apnea, including cyanosis and bradycardia in ex-preterm infants who underwent general anaesthesia just before surgery. They included three eligible trials, each of which showed that caffeine-treated infants had fewer apnea/bradycardia episodes. The estimate for absolute risk difference was -0.58 (95% CI -0.74 - -0.43), i.e. less than two infants had to be treated with caffeine to prevent one having postoperative apnea. Caffeine also reduced bradycardia and oxygen desaturation after general anaesthesia. The clinical importance of this is however unclear given the small population sizes. No adverse effects of caffeine were mentioned.

In 2016, Armanian et al (52) published a single-center randomized double-blinded placebo-control clinical trial study to investigate the preventive effects of caffeine on apnea incidence in higher-risk neonates. A total of 52 infants with a birth weight below 1200 g were eligible for enrollment. 26 were given caffeine, and 26 infants were controls. The preventive effect of caffeine on apnea was significant in these infants. Only 4 infants (15.4%) in the caffeine group developed apnea, compared with 16 (61.5%) in the control group ($p = 0.001$).

In the caffeine group, two (7.7%) of the neonates developed bradycardia and five (19.2%) developed cyanosis, compared to 16 infants (61.5%) that did not receive caffeine ($p < 0.05$). No difference in medication side effect, like tachycardia, was reported in the neonates ($p > 0.99$). Only four infants (15.4%) in the caffeine group developed chronic lung disease (CLD; defined as dependent on oxygen at 28 days of life), compared to 11 (44.0%) in the placebo group ($p = 0.025$). In conclusion, it appears that less mature infants will have greater benefits of prophylactic caffeine on the incidence and severity of apnea.

In 2019, Jain et al published their results from a randomized double blinded trial (53).
Their aim was to evaluate weather caffeine given in bolus dose of 20 mg/kg followed by 5 mg/kg would reduce the age of the first successful extubation for ventilated infants.
They enrolled 110 infants between 23-30 weeks GA requiring mechanical ventilation the first 5 days of life. The intervention group received early caffeine with a loading dose of 20 mg/kg

followed by a 5 mg/kg maintenance dose. The control group received normal saline bolus and maintenance dose.

The patients were followed until 36 weeks GA or until discharge or death, whichever came first. The trial was stopped early at 75% enrollment (goal 80% power) with 83 infants enrolled, due to a persistent, although nonsignificant trend of higher mortality in the early caffeine group. They concluded that caffeine given prophylactically does not reduce the age of first successful extubation after mechanically ventilation as there were no significant outcome differentiation between the two groups. A larger multicenter trial is necessary to detect minimal clinically important differences in mortality. Trials terminated early may be difficult to interpret. Although ethically appropriate, it can reduce power to detect clinically important differences in outcomes.

In 2003, Steer et al (54) published a double-blind randomized dose response trial. The primary outcome measure was extubation failure, defined as neonates who were unable to be extubated within 48 h of caffeine loading or who required re-ventilation or Doxapram within 7 days of caffeine initiation. Continuous recordings of oxygen saturation and heart rate were commenced in a subgroup of enrolled infants.

A total of 127 babies were enrolled into the study trial, with 42, 40 and 45 being randomized to the 3 mg, 15 mg and 30 mg dose groups of caffeine, respectively. The extubation failure rates were found to be 19 (45%), 10 (25%) and 11 (24%), respectively ($p = 0.06$). The 3 mg group had significantly more documented apnoea per group over the 7-day trial than the other two dose groups ($p < 0.01$). The numbers of infants experiencing tachycardia (defined as a HR > 200 bpm for four consecutive hourly interval recordings) was 1, 5 and 8 infants in the 3 mg, 15 mg and 30 mg groups, respectively, but these differences were not statistically significant ($p = 0.07$).

Infants on the two highest doses of caffeine (15 and 30 mg/kg) recorded a significantly higher mean HR and mean SpO_2 ($p = 0{,}001$ for both). No difference was demonstrated in the numbers of infants with major neonatal morbidity (Grade 3 or 4 intraventricular haemorrhage, necrotizing enterocolitis, culture proven sepsis, patent ductus arteriosus,

pulmonary air leak).

Infants in the two higher dose groups had statistically significantly less documented apnea than the lowest dose group ($p = 0.01$). Of the 37 neonates with continuous pulse oximetry recordings, those on higher doses of caffeine recorded a statistically significantly higher mean heart rate, oxygen saturations and less time with oxygen saturations <85%.

This trial indicated there were short-term benefits of decreased apnea in the urgent peri-extubation period for ventilated infants born <32 weeks' gestation receiving higher doses of caffeine. They conclude that a dose of 3 mg/kg per day of caffeine citrate is less effective than 15 mg/kg or 30 mg/kg per day for preventing apnoea in infants <32 weeks' gestation in the week following extubation.

4 Discussion

4.1 Summary of main results

The main purpose of this review was to summarize the available evidence on how effective caffeine is for treating AOP, and at the same time look for possible side effects. The most important findings were that caffeine reduced BPD in VLBW preterm infants with AOP, the need of supplemental oxygen and the need for positive airway pressure. A side effect of caffeine therapy was temporarily reduced weight gain (25).

Caffeine citrate was significantly more effective in reducing apnea episodes, by at least 50% in 6 days compared to placebo, and approached statistical significance in 3 days. It was also significantly better than placebo in eliminating apnea in 5 days, and approached significance after 2 days (32).

Furthermore, caffeine therapy for AOP improved the survival rate without neurodevelopmental disability at 18 - 21 months in infants with VLBW. Caffeine also reduced the incidence of cerebral palsy, death and survival rates with neurodevelopmental disability. The incidence of cognitive delay was likewise lower in the caffeine group (26). At 5 years follow-up it was a lower percentage of death in the caffeine group, although not statistically significant (28). Furthermore, neonatal caffeine therapy for AOP reduced the risk of DCD in 5-years-old (29). It appears to have a lasting beneficial effect on motor function, both at 18 months, 5 and 11 years of age (30).

When it comes to heart rate, studies conclude differently. A retrospective observational study discovered a significant correlation between caffeine citrate and heart rate (33). However, the severity was mostly mild to moderate from 170 – 212 bpm, and the physiological effect was minor. Other studies did not find any differences in heart rates (34) (55). Yet another study found significant results after 30 minutes of administration in the caffeine group on increasing heart rate, mean arterial BP and capillary SaO_2 (37).

High-dose caffeine was associated with a significant reduction in extubation failure in mechanically ventilated preterm infants, frequency of apnea, and days of documented apnea. Further, it was associated with a significant reduction in the duration of oxygen therapy. Nonetheless, high-dose caffeine was associated with an increase of tachycardia, but noteworthy without impact on physicians decision to withheld caffeine therapy (44).

Regarding the effect of caffeine and brain activity, no differences were found in clinical seizures nor in cEEG, but a significant increase in aEEG continuity was detected starting half an hour after caffeine administration. At 36 weeks' control, at significantly longer NICU stays in the controls not receiving caffeine was found in one study. The authors concluded that caffeine increased cerebral cortical activity and resulted in maturation at 36 weeks, without risk of seizures (37).

Neonates receiving caffeine early had lower odds of composite death, BPD and PDA. No adverse impact on any other outcomes was observed, like NEC, severe neurological injury nor severe ROP. Furthermore, the neonates in the early group stayed shorter in the NICUs and, they were less likely to receive surgical intervention like mechanical ventilation, high-frequency ventilation, and also needed shorter periods of oxygen (17).

4.2 Comparison with other studies and reviews

Other literary reviews support the findings from this review, including Henderson-Smarts´ "Methylxanthine treatment for apnoea in preterm infants (Review)", published in 2010 (56), and Moscino et al's more recent study "Caffeine in preterm infants: where are we in 2020?" (23). These reviews together with this one allow for a more precise understanding of the effects in these related, but different populations.

The incidence as well as the severity of the clinical apnea is greatest in infants born at earlier gestational ages, and therefore it would be expected that they would benefit more from treatment (55). The same is true for treating AOP prophylactically (52). McCallum at Edinburgh University in Scotland did a clinical review on WHO guidelines behind using caffeine for treating AOP prophylactically in otherwise healthy premature infants, and its

association with bradycardia and hypoxia. He found fewer episodes of apnea and bradycardia in the treated groups at term age compared to the controls. However, his conclusion was that bigger studies would be required before supporting the use of caffeine prophylactically.

Although a few studies found increased heart rate as a side effect to caffeine for treating AOP, a Cochrane review in 2004 (57) of two randomized controlled studies found no significant change between caffeine and no-caffeine group in the terms of tachycardia and the use of positive airway pressure ventilation.

Gregory D. Funk, a professor at the Department of Physiology at University of Alberta is nonetheless losing sleep over the "caffeination" of prematurity, he writes in 2009 (58). He worries about the long term side effects caffeine might have on infants, referring to a study done by Montandon et al on rats (59). They discovered that a regimen of orally distributed caffeine of 15 mg/kg/day from postnatal age 3-12, changed the rats sleep architecture, e.g. a 50% latency to sleep onset. It also changed their respiratory control in adulthood with a reduced response to increased CO_2.

On the other hand, another study concluded that therapeutic neonatal administration of caffeine had no long-term side effects on sleep duration nor sleep apnea during childhood. However, ex-preterm infants are in general at risk for developing obstructive sleep apnea. A limitation with this study was that only a small portion of patients agreed to join the study. Henceforth, it is possible that parents with concerns about their child's sleep may have been more ready to consent. Nevertheless, no differences were noted between the caffeine and placebo groups (42).

4.3 Biological mechanisms

The biological proposed mechanism of caffeine's effect on AOP include amongst other things; stimulation of the respiratory center, increased sensitivity to CO_2, increased tonus of skeletal muscle tone, enhanced contractility of the diaphragm, as well as increased minute ventilation, metabolic rate and oxygen consumption. Furthermore, caffeine stimulates the

cardiovascular and central nervous system and enhance secretion of catecholamines. It has a diuretic effect and alters glucose homeostasis (13) (60). Some overlap is therefore expected in the way caffeine affects both primary and secondary outcomes of this review.

The proposed mechanism of temporary weight gain was thought to be increased oxygen consumption with methylxanthines (25). Further, caffeine increased oxygen extraction in the brain, which suggests a transient stimulating effect on brain metabolism, because cerebral oxygen saturation decreases. This could, however, be due to a decrease in cerebral blood flow or cerebral vasoconstriction which might have been pCO_2 induced. They also found significant decrease in pCO_2 (38).

4.4 Strengths

There are several benefits to this study. A total of 30 articles have been included from a wide range of sources, and consequently knowledge on the topic has been summarized. The task has been clearly defined and many different variables have been looked at. Further, only new articles from the years after 2000 have been included. The study design is modest in the way that it uses already existing data, not collecting raw data, as this is a literary review. Besides, the study is less resource-intensive when it comes to planning, since most work is based around the systematic search and reading articles.

While a lot of the articles included in this review have smaller sample sizes, most can be applied to a bigger population. RCTs usually have lesser external validity, but since the population studied here is so narrow, that is premature babies with apnea, they too provide a higher external validity. Further, most studies included are RCTs with superior quality compared to for example case control studies.

Even though this study may not provide a complete answer to the research question, it will hopefully be of great help and value for others going further into investigation on the same subject. The study has been cautiously written with the ignorant reader in mind. Thus, the transparency of this review makes it simple to recreate. Moreover, being “systematic” offers a sense of thoroughness.

4.5 Limitations

Writing a literary review brings some disadvantages on its own. They are very much restricted to the accessibility of sources. It is thus an inevitable chance to overlook important "grey" literature. While MeSH terms are a great way to include a vast amount of articles, chances are not all articles of interest will appear in a search.

The possible lack of quality in each article included in this review, provides further disadvantages to the finishing review. All study designs were included in the systematic search, most of them were RCTs, and only a few were purely observational, with RCTs being the gold standard, and observational studies lowers the overall quality.

As the infant's lungs and central respiratory control mature, AOP most often resolves on its own, which makes it more of a developmental disorder rather than a disease (61). AOP is also increasingly more common in premature infants, and compulsorily improves with age, even without treatment. With this in mind, studies are of lesser value without controls. Subsequently, all of the studies in this review had controls.

4.6 Summary of GRADE evaluation

Many articles have accounted for most of the checklist questions, making it easier to grade them – from very low to high quality based on their study designs. It was a criterion of writing the master thesis to grade at least five articles (see attachments). Four of the studies chosen were RCTs and one was a cohort. The RCTs start with high initial quality while the cohort starts with low. Of the four RCTs, one article remained high grade, two were downgraded to moderate and one to low.

Some of the reasons for downgrading were small population sizes, lack of follow-up data, missing detail information and in general not enough information and transparency. The cohort studied remained of a low quality. It had a large study population, but did not mentioned basic details about background of study-infants, it had some inconsistency in the protocol of early caffeine use, potential variations in the maintenance dose, and it did not mention long-term neurobehavioral outcomes.

5 Conclusion

Caffeine has played an important role over the past four decades going from invasive to non-invasive support treating AOP. In preterm infants, caffeine is effective in reducing AOP, the need for ventilation and given early reduces the time stayed at the NICUs. Caffeine-treated preterm babies have lower rates of BPD, IVH and PDA, and have optimistic long-term outcomes on neurodevelopment and respiratory functions. Few adverse events have been identified to cause long-term adverse effects.

Additional larger studies are necessary to detect less common adverse effects, although the ones included are adequate to show the effect on AOP. Moreover, longer follow-up studies than 11 years would be of great value for possibly long-standing adverse effects. In order to indicate which infants are most likely to benefit from this treatment, there is need for stratification by for example GA and birth weight and other risk factors for future studies.

As caffeine has been the golden standard for the past four decades, it is safe to say it has a respected benefit risk ratio.

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7 Summary of GRADE Evaluations

GRADE 1: Reference #17

Reference:
Lodha A, Seshia M, McMillan DD, Barrington K, Yang J, Lee SK, et al.
Association of early caffeine administration and neonatal outcomes in very preterm neonates.
JAMA pediatrics. 2015;169(1):33-8.

Study design: Cohort study, retrospective observational

Grade - Quality: ⊕⊕○○ LOW

Purpose

To determine the effect of early initiation of caffeine therapy on neonatal outcomes in very preterm infants born in Canada.

Conclusion

In very preterm neonates, early (prophylactic) caffeine use was associated with a reduction in the rates of death or bronchopulmonary dysplasia and patent ductus arteriosus. No adverse impact on any other outcomes was observed.

Country

Canada

Year of data collection

2010 - 2012

Material and method

Population:
5517 eligible preterm neonates, all born at less than 31 weeks' gestation, from a total of 29 participating Canadian Neonatal Network NICUs. Divided into 2 groups based on the following timing of caffeine initiation: within the first 2 days after birth (early) and ≥ 3rd day following birth (late).

Cohorts:

Early caffeine	Late caffeine
3806 neonates (76,4%). BW 1070 (850–1310) g. GA 28 (26–29) weeks.	1295 neonates (25,4%). BW 1050 (790–1360) g. GA 28 (26–30) weeks.

Main outcome:
A composite of death or bronchopulmonary dysplasia (defined as needing supplemental oxygen at 36 weeks PMA or at discharge from the NICU).

Statistical methods:
SAS version 9.2 software package (SAS Institute Inc).
- Pearson $\chi 2$
- t test
- Wilcoxon rank test
- Multivariable logistic regression analysis

Results

Main findings:

Benefits of early caffeine
- Reduction in BPD or death (AOR 0.81, 95% CI 0.67-0.98).
- Reduced incidence of PDA (40.5% versus 46.2%) and of surgical treatment for PDA (13.3% versus 25%). (AOR 0.74, 95% CI 0.62-0.89).
- Reduced duration of MV, HFV and CPAP on day 2; reduction in the use of postnatal steroids.

Drawbacks or no effect of early caffeine:
- No difference in mortality (AOR 0.98, 95% CI 0.70-1.37).
- No difference in NEC ≥ stage 2 (AOR 0.88, 95% CI 0.65-1.20), ROP ≥ stage 3 (AOR 0.78, 95% CI 0.56-1.10), severe neurological injury (presence of parenchymal echolucency, periventricular echogenicity or PVL) (AOR 0.80, 95% CI 0.63-1.01)

Additional findings
The total duration of exposure to caffeine was longer in the early group. More neonates in the late group received postnatal steroids, and stayed longer in the NICU and were more likely to receive mechanical ventilation, high-frequency ventilation, and oxygen for a longer period of time.

Table 3. Comparison of Resource Use Between Preterm Infants Administered Caffeine Either Within (Early Group) or After (Late Group) the First 2 Days of Life

Variable	Caffeine Group, Median (IQR) Early (n = 3806)	Late (n = 1295)	*P* Value
Discharged receiving oxygen, No. (%)	931 (24.5)	323 (24.9)	.73
Duration of oxygen requirement, d	9 (1-43)	8 (1-49)	.67
Duration of mechanical ventilation, d	2 (1-9)	4 (1-23)	<.01
Duration of noninvasive respiratory support, d	1 (1-5)	1 (1-5)	.02
Length of stay, d	52 (27-88)	49 (21-88)	.48
Discharged receiving caffeine, No. (%)	1386 (35.4)	475 (36.7)	.87

Discussion / comments / checklist

Checklist:
- **Is the purpose clearly stated?** – Yes
- **Are the groups recruited from the same population/population group (selection bias)?** – Yes
- **Were the groups comparable in relation to important background factors? (selection bias)** – Yes, maternal and infant demographic characteristics and perinatal risk factors were compared. There was no difference in weight or gestational age at birth between the groups.
- **Were the exposed individuals representative of a defined population group / population?** – Yes
- **Were exposure and outcome measured equally and reliably (validated) in the two groups? (Classification bias)** – Yes
- **Is the person who evaluated the results (endpoints) blind to group affiliation?** Unclear, not mentioned.
- **Was the study prospective?** – No, retrospective.
- **Were enough people in the cohort followed up? (Attrition bias / follow-up bias).** – Unclear, not mentioned.
- **Have dropout analyzes been performed? (Eval. Attrition bias)** – Not applicable
- **Was the follow-up time long enough to detect positive and / or negative outcomes?** – Not applicable
- **Have important confounding factors been taken into account in the design / implementation / analyzes?** – Yes, they have used Adjusted OR, meaning they have taken into account various clinically significant predictors of neonatal morbidity and mortality including gestational age, small for gestational age, antenatal steroid exposure, intubation on day 2 after birth, site, outcome of death or BPD, SNAP-II severity scores, and the use of surfactants.
- **Do you believe in the results? (Bradford Hills criteria (time sequence, dose-gradient response, biological plausibility, consistency).** – Yes
- **Can the results be transmitted to the general population?** – Yes
- **Other literature that strengthens / weakens the results?** Lack of evidence from RCTs, but is supported by a single center study of 140 neonates by Patel et al. and also by Dobson et al.
- **What do the results mean for changing practice?** It may be more beneficially to give caffeine early on prophylactically to preterm infant < 31 weeks GA.

What do the authors discuss as:
- **Strength:**
Large, multicenter national cohort study using recent data collected following standard definitions. Data entry at each center was carried out by trained data abstractors. Analyses were adjusted for sites, all-important clinical variables, and significant.

- **Weakness:**
Its retrospective observational nature, missing detailed information about racial/ethnic backgrounds, variations and inconsistency in the protocol for early caffeine use at various centers, potential variations in the maintenance dose of caffeine, and the inability to determine specific indications for caffeine use, as well as the absence of long-term neurobehavioral data from the neonates who received caffeine in the early group. Long-term neurodevelopmental outcomes of patients who received early caffeine are important to identify any potential untoward consequences.

GRADE 2: Reference #25

Reference: Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. **Caffeine therapy for apnea of prematurity.** The New England journal of medicine. 2006;354(20):2112-21.			**Study design:** RCT **Grade - Quality** ⊕⊕⊕⊕ HIGH
Purpose	**Material and method**	**Results**	**Discussion / comments / checklist**
To study the short- and long-term efficacy and safety of methylxanthine therapy in infants with very low birth weight. **Conclusion** *Caffeine therapy for apnea of prematurity reduces the rate of BPD in infants with very low birth weight.* **Country** America, Canada, Australia, the United Kingdom, Ireland, Switzerland, Sweden, Germany, Israel and the Netherlands. **Year of data collection** 1999 - 2004	Recruitment participants: 2006 infants Inclusion criteria: Infants with a birth weight of 500-1250 g were eligible for enrollment if their clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life. Exclusion criteria: Dysmorphic features or congenital abnormalities likely to affect life expectancy or neurologic development (n=242). Unlikely to be available for long-term follow-up (n=425). Previously treated with a methylxanthine (n=277). Unknown reasons (n=33) Outcomes: Primary outcome: a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 21 months. Short-term outcomes after the completion of recruitment and the initial hospitalization of the study infants, include BPD, ultra-sonographic signs of brain injury, NEC, ROP, and growth. Exposure variables: Caffeine 20 mg per kg loading dose and 5mg/kg daily (1006 infants) vs placebo - normal saline (1000 infants) commenced at an average of 3 days. Important confounding factors: They adjusted for center in the analysis to eliminate the bias caused by the variability of practice among the clinical sites, using Odds Ratio. Statistical methods: - Logistic-regression model. - 95% CI for the treatment effect expressed as an OR. - z-test statistic for the null hypothesis of no treatment effect - Student's t-test - Fisher's exact test	Main findings: Of 963 infants who were assigned to caffeine and who remained alive at a PMA of 36 weeks, 350 (36%) received supplemental oxygen, as did 447 of the 954 infants (47%) assigned to placebo (AOR 0.63, 95% CI 0.52-0.76, P<0.001). Positive airway pressure was discontinued 1 week earlier in the infants assigned to caffeine (median PMA, 31.0 weeks, interquartile range, 29.4-33.0) than in the infants in the placebo group (median PMA, 32.0 weeks; interquartile range, 30.3-34.0; P<0.001). Side effects - other important endpoints: - Caffeine reduced weight gain temporarily. The mean difference in weight gain between the groups receiving caffeine vs placebo was greatest after 2 weeks (mean difference, −23 g, 95% CI, −32 - −13, P<0.001). - The rates of death, ultrasonography signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups.	Checklist: • **Is the purpose clearly stated?** – Yes • **Who is included / excluded? (selection / generalizability)** – 4315 eligible infants, 1628 lacked parental consent and 681 were not approached. Moderate risk of selection bias. • **Were the groups close to the start? (selection?, did the randomization work?)** – Yes, birth characteristics of mothers and infants in the caffeine and placebo groups were similar in multiple centers in various countries. Antenatal corticosteroids 88% vs 87%, chorioamnionitis 14% vs 13%, caesarean section 62% vs 63%. • **Randomization procedure?** – Computer-generated randomization. • **Were participants / study staff blinded to group affiliation?** – Blinding of intervention in 90.5%. Concealment of randomization (on site in pharmacy). An external safety committee reviewed the study data every four to six months during the enrollment phase. • **Were the groups treated equally beyond the "intervention"?** – Yes. • **Primary endpoint - validated? (Classified bias?)** – Yes. • **Were the participants accounted for at the end of the study? (attrition/follow-up bias)** – Follow-up 96% for perinatal outcomes, also follow-up to 18-21months. Blinding of outcome assessment, check. • **What are the results? Precision?** – Good, due to narrow CI and a large population. • **Can the results be transferred to practice?** – Yes • **Were all outcome measures assessed?** – Yes • **Are the benefits worth the disadvantages / costs?** – Yes • **Other literature that strengthens the results?** – Yes. Previously data have stablished that methylxanthines reduces the frequency of apnea. Henderson-Smart DJ, Steer P. Methyl-xanthine treatment for apnea in preterm infants. Cochrane Database Syst Rev 2001;3:CD000140. What do the authors discuss as: - **Strength:** It was a large, multicenter, randomized, placebo-controlled trial. "Gold" standard for interventions. Control for bias by randomization procedures. - **Weakness:** The study protocol did not mandate serial echocardiography in all study patients. Therefore, it is uncertain whether caffeine promoted the closure of a patent ductus arteriosus or whether the clinical staff were more likely to look for and close a patent ductus arteriosus in the placebo group than in the caffeine group because the infants in the placebo group required positive air-way pressure and supplemental oxygen for a longer period than did infants assigned to caffeine. May have ethical implications. **Do the results have plausible explanations?** Yes

GRADE 3: Reference #32

Reference:
Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA.
Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study.
Pharmacotherapy. 2000;20(6):644-52.

Study design: RCT

Grade - Quality ⊕○○○ LOW

Purpose	Material and method	Results	Discussion / comments / checklist
To evaluate the efficacy and safety of caffeine citrate for treatment of apnea of prematurity. **Conclusion** *20 mg/kg caffeine citrate intravenously followed by 5 mg/kg/day caffeine citrate) either intravenously or orally for 10 days is safe and effective for treating apnea of prematurity in infants 28–32 weeks post-conception.* **Country** America **Year of data collection** Unclear, 1999?	Recruitment participants: 87 preterm infants; 45 received caffeine and 37 placebo. Inclusion criteria: 28-32 weeks PMA and less than 24 hours of age with six or more apnea episodes (>20 seconds duration) in 24 hours. Exclusion criteria: - Secondary apnea (CNS, lung disease, anemia, infection, shock), Hemoglobin < 10 g/dL, cardiovascular abnormalities or abnormal temperature, including distinctive abnormal lab findings. Outcomes: Failure = <50% reduction in apnea (>20 seconds), use of IPPV (provided by author), death by 30 days. Exposure variables: Caffeine citrate 20 mg/kg IV and 5 mg/kg daily vs placebo (citric acid/sodium citrate). They compared the occurrence of apnea episodes in these infants for up to 10 days. The secondary objective was to obtain plasma concentrations of caffeine citrate in premature infants receiving the agent for up to 12 days. Statistical methods: - χ^2 - t-test - Fisher's exact test	Main findings: - Caffeine citrate was significantly more effective than placebo in reducing apnea episodes by at least 50% in 6 days ($p<0.05$), and approached statistical significance ($p<0.10$) in 3 days. - Caffeine was significantly better than placebo in eliminating apnea in 5 days ($p<0.05$), and approached significance ($p<0.10$) in 2 days. - The number of infants with an aggregate of 7–10 days of at least a 50% reduction in apnea events / elimination of apnea, was significantly higher in the caffeine citrate than in the placebo group. Side effects - other important endpoints: - Adverse events did not differ significantly between groups. - No correlations were found between success and mean daily plasma concentrations or baseline characteristics. - Volume of distribution and clearance increased with weight, supporting weight-adjusted dosing of caffeine citrate. Table 4. Percentages of Most Frequently Reported Adverse Events Treatment Group Adverse Event — Caffeine Citrate — Placebo Injection site reaction — 8.7 — 12.8 Perinatal disorder (trace aspirates, feeding intolerance) — 8.7 — 5.1 Constipation — 17.4 — 20.5 Gastrointestinal disorder (gastroesophageal reflux, dilated loops of bowel) — 4.3 — 7.7 Anemia — 6.5 — 17.9 Hyponatremia — 0 — 5.1 Rash — 8.7 — 7.7	Checklist: • **Is the purpose clearly stated?** – Yes • **Who is included / excluded? (selection / generalizability)** – Two placebo infants never received the study drug and therefore were excluded from all analyses. Three infants had fewer than six apnea events during the baseline observation and was excluded from the efficacy analysis (n = 82), but included in the safety analysis (n = 85). • **Were the groups close to the start? (selection? did the randomization work?)** – Some differences between the groups at baseline; more males and Caucasians in the placebo group and they had overall higher weight at entry compared to the caffeine group, moderate risk. • **Randomization procedure?** – After obtaining signed, written, informed consent from parents or legal guardians, infants were randomized to treatment with caffeine citrate or placebo using computer-generated random numbers in blocks of six. • **Were participants / study staff blinded to group affiliation?** – Not mentioned. • **Were the groups treated equally beyond the "intervention"?** – Unclear • **Primary endpoint - validated? (Classified bias?)** – Yes, but not secondary. • **Were the participants accounted for at the end of the study? (attrition/follow-up bias)** – Follow-up information was obtained for 20 infants randomized to caffeine citrate and 10 randomized to placebo who had a 50% or greater reduction in the number of apnea events on completion of 10 days of double-blind therapy. • **What are the results? Precision?** – Small, mostly due to small population size. • **Can the results be transferred to practice?** – Yes • **Were all outcome measures assessed?** – No, because only four infants received more than 10 days of therapy, analysis of success beyond 10 days were not conducted. • **Are the benefits worth the disadvantages / costs?** – No • **Other literature that strengthens the results?** – Yes, other studies have shown that caffeine decrease the number and/or frequency of apnea events. What do the authors discuss as: - **Strength**: Multicenter, parallel, randomized, double-blind, placebo-controlled trial with open-label rescue - **Weakness:** Small population size, imbalanced groups, unclear blinding, not mentioned secondary outcomes, poor follow-up data. **Do the results have plausible explanations?** – Yes.

GRADE 4: Reference #44

Reference:
Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N.
High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial.
Eur J Pediatr. 2015;174(7):949-56.

Study design: RCT

Grade - Quality ⊕⊕⊕◯ MODERATE

Purpose	Material and method	Results	Discussion / comments / checklist
To compare the efficacy and safety of high versus low-dose caffeine citrate on AOP and successful extubation of preterm infants from mechanical ventilation.	Recruitment participants: 120 neonates (60 in each group) were enrolled. Inclusion criteria: Infants with a gestational age <32 weeks, who exhibited apnea of prematurity within the first 10 days of life. Exclusion criteria: Major congenital malformations and chromosomal anomalies. Outcome: Extubation failure in mechanically ventilated infants (need of re-intubation within72 h of extubation from mechanical ventilation). Exposure variables: They compared high-dose (loading 40 mg/kg/day and maintenance of 20 mg/kg/day) versus low-dose (loading 20 mg/kg/day and maintenance of10 mg/kg/day). Statistical methods: SPSS statistical soft-ware - Student t test - Mann–Whitney U test - Chi-square test - Fisher exact test - Kolmogorov–Smirnov test - Kaplan–Meier	Main findings: High-dose caffeine was associated with a significant reduction in extubation failure in mechanically ventilated preterm infants ($p<0.05$), a reduction in the frequency of apnea ($p<0.001$), and a reduction of days of documented apnea ($p<0.001$). Side effects - other important endpoints: - High-dose caffeine was associated with significant increase in episodes of tachycardia ($p = 0.04$) without a significant impact on physician decision to withhold caffeine. - No difference in the incidence of BPD (Bronchopulmonary dysplasia). - No difference in the incidence of ROP (Retinopathy of prematurity), IVH (intraventricular hemorrhage), PVL (Periventricular leukomalacia) or LOS (Length of hospital stay). **Table 4** Side effects of caffeine Characteristics | High-dose caffeine ($n=60$) | Low-dose caffeine ($n=60$) | RR (95 % CI) | p value Tachycardia | 14 (23 %) | 5 (8 %) | 1.94 (1.09–4.17) | 0.04* Hypertension | 2 (3 %) | 1 (2 %) | 1.51 (0.30–7.57) | 1.0 Time to reach full enteral feeding (days) | 12.2±5.6 | 13.8±6.3 | | 0.19 Caffeine withhold for suspected side effects | 6 (10 %) | 2 (3 %) | 3.22 (0.61–16.6) | 0.27 Weight gain (g/kg/day) | 11.3±4.3 | 12.1±3.6 | | 0.37 Data expressed as mean±SD or number (percentage)	Checklist: • **Is the purpose clearly stated?** – Yes • **Who is included / excluded? (selection / generalizability)** – During the study period, 218 preterm infants of GA <32 weeks were admitted to the NICU. Forty-seven of the 167 infants eligible for the study were excluded before enrolment due to failure to approach for consent and non-documented apnea. • **Were the groups close to the start? (selection? did the randomization work?)** – Yes, baseline characteristics were broadly similar. • **Randomization procedure?** – Enrolled infants were assigned randomly to treatment groups using internet-based random table technique with cards in opaque sealed envelopes. A designated pharmacist was responsible for the randomization of the selected infants and the preparation of caffeine dose; the investigators, nursing staff and family were blinded to patient´s group. • **Were participants / study staff blinded to group affiliation?** – Yes. • **Were the groups treated equally beyond the "intervention"?** – Unclear • **Primary endpoint - validated? (Classified bias?)** – Yes • **Were the participants accounted for at the end of the study? (attrition/follow-up bias)** –Yes • **What are the results? Precision?** – Difficult to assess because of missing CI. • **Can the results be transferred to practice?** – Yes. • **Were all outcome measures assessed?** – Yes • **Are the benefits worth the disadvantages / costs?** – Unclear, significantly more patients in the high-dose caffeine group experienced tachycardia (23% vs 8% (p = 0.04). Caffeine therapy was withheld owning to a physician concern of a significant side effect in 6 infants in the high- and 2 infants in the low-dose group. • **Other literature that strengthens the results?** – Yes. Steer P, Flenady V, Shearman A, Charles B, Gray PH, Henderson-Smart D, Bury G, Fraser S, Hegarty J, Rogers Y, Reid S, Horton L, Charlton M, Jacklin R, Walsh A (2004) High dose caffeine citrate for extubation of preterm infants: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed 89:F499–F503. What do the authors discuss as: - **Strength**: Single-center, randomized, pilot, double-blinded, prospective study. - **Weakness:** Small sample size. This pilot study was not powered to definitively address the targeted outcome. Therefore, a larger prospective trial upon appropriately powered sample size should be conducted to definitively address the efficacy and safety of high-dose caffeine. Serum level of caffeine was not measured in the study which could further prove or disprove a dose-response relationship. Also, long-term follow-up of neonatal outcome is warranted. **Do the results have plausible explanations?** – Yes.
Conclusion *The use of higher, than current standard, dose of caffeine may decrease the chance of extubation failure in mechanically ventilated preterm infants and frequency of AOP without significant side effects.*			
Country Egypt			
Year of data collection 2011 - 2012			

GRADE 5: Reference #54

<table>
<tr><td colspan="3">Reference:
Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG.
Periextubation caffeine in preterm neonates: a randomized dose response trial.
Journal of paediatrics and child health. 2003;39(7):511-5.</td><td colspan="2">Study design: RCT
Grade - Quality ⊕⊕⊕○ MODERATE</td></tr>
<tr><td>Purpose</td><td>Material and method</td><td>Results</td><td colspan="2">Discussion / comments / checklist</td></tr>
<tr><td>To compare the effectiveness of three dosing regimens of caffeine for preterm infants in the periextubation period.
Conclusion
This trial indicated there were short-term benefits of decreased apnea in the immediate periextubation period for ventilated infants born < 32 weeks' gestation receiving higher doses of caffeine.
Country
Australia
Year of data collection
1993 - 1995</td><td>Recruitment participants:
A total of 127 babies were enrolled into the study
Inclusion criteria:
- Neonates <32 GW
- Ventilated for >48 h
Exclusion criteria:
Major congenital abnormality, infection (sepsis confirmed by blood culture), major neurological condition, grade 3/4 intraventricular hemorrhage, mechanical ventilation for a period greater than 28 days, or previous exposure to methylxanthine therapy.
Outcomes:
Extubation failure, defined as neonates who were unable to be extubated within 48 h of caffeine loading or who required re-ventilation or Doxapram dose within 7 days of caffeine loading.
Exposure variables (validated / not validated):
42, 40 and 45 neonates receiving 3, 15, and 30 mg/kg, respectively, validated.
Statistical methods:
- ANOVA with the Bonferroni multiple comparison test
- Wilcoxon rank sum test
- Chi-square / Fishers exact test</td><td>Main findings:
No statistically significant difference was demonstrated in the incidence of extubation failure between dosing groups (19, 10, and 11 infants in the 3, 15, and 30 mg/kg groups, respectively), however, infants in the two higher dose groups had statistically significantly less documented apnea than the lowest dose group.

Side effects - other important endpoints:
Of the 37 neonates with continuous pulse-oximetry recordings, those on higher doses of caffeine recorded a statistically significantly higher mean heart rate, oxygen-saturations and less time with oxygen saturations < 85%. There was an increase in the number of infants with feed intolerance in the15 mg and 30 mg groups compared to the 3 mg group, although this did not reach statistical significance.
No difference was demonstrated in the numbers of infants with major neonatal morbidity (Grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, culture proven sepsis, patent ductus arteriosus, pulmonary air leak).</td><td colspan="2">Checklist:
• Is the purpose clearly stated? – Yes
• Who is included / excluded? (selection / generalizability) – A total of 240 infants (80 infants in each of the three-dose groups) was required using an α level of 0.05, and statistical power of 80%. 127 (67%) were enrolled into the trial; the main reason for not enrolling eligible infants was parental refusal. Furthermore 8 infants were excluded due to the failing of giving them caffeine. A further nine infants did not complete the planned 7-day course of caffeine, due to a decision by the attending neonatologist to commence aminophylline therapy for apnoeic episodes of concern.
• Were the groups close to the start? (selection? did the randomization work?) – Yes, infants in the three study groups were similar in gestational age, birthweight, principal diagnosis, exposure to antenatal steroids, exposure to exogenous surfactant and postnatal age at study entry.
• Randomization procedure? – Infant were allocated to one of the three caffeine regimens 24 h prior to a planned extubation or within 6 hours of an unplanned extubation using a computer-generated list of random numbers by a hospital pharmacist.
• Were participants / study staff blinded to group affiliation? – Unclear, not mentioned.
• Were the groups treated equally beyond the "intervention"? – Unclear
• Primary endpoint - validated? (Classified bias?) – No. This pragmatic trial was not designed to study the long-term outcome of preterm infants' exposure to caffeine therapy. Also, this trial was terminated prior to achieving the target sample size.
• Were the participants accounted for at the end of the study? (attrition/follow-up bias) – Unclear
• What are the results? Precision? – Fairly good. Apnea was assessed in this trial by nursing record. Nurse recordings of apnea have been shown to be inaccurate in earlier studies.
• Can the results be transferred to practice? – Yes
• Were all outcome measures assessed? – No
• Are the benefits worth the disadvantages / costs? – The lack of availability in Australia at the time of the study of a cheap, commercially available caffeine product, made long-term dosing with caffeine impossible.
• Other literature that strengthens the results? – The result of one small trial suggested that extremely low birthweight infants may benefit from higher than standard doses. Scanlon JE, Chin KC, Morgan ME, Durbin GM, Hale KA, Brown SS. Caffeine or theophylline for neonatal apnoea? Arch.Dis. Child. 1992; 67 (4 Spec. No.): 425–8.

What do the authors discuss as:
- Strength
single center, double-blind clinical trial. In this blinded randomized trial, any bias should be avoided and the nurse record, regardless of accuracy against formal computer analysis, is often the critical information used by clinicians in clinical decision management, (e.g. the need for a change in therapeutic support).
- Weakness
Single center. Small sample size. Further studies with larger numbers of infants assessing longer-term outcomes are necessary to determine the optimal dosing regimen of caffeine in preterm infants.

Do the results have plausible explanations? – Yes.</td></tr>
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