



CODEN [USA]: IAJPBB

ISSN : 2349-7750

## INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.7445196>Available online at: <http://www.iajps.com>

Research Article

### OVERVIEW OF CAFFEINE CITRATE ROLES IN NEONATAL APNEA

<sup>1</sup>Amaal basrwan\*,<sup>2</sup>-Raghdah Nuri shaban,<sup>3</sup>-Dhaifallah abdulaziz alzhahrani,<sup>4</sup>-Hussein Abdul Mohsen Al-Maqati,<sup>5</sup> Khaled Ali babalghith,<sup>6</sup>-Ehab ayman soqaty,<sup>7</sup>-Ahmed Hassan Alhadri,<sup>8</sup>-Nany Mohammed Nawwar,<sup>9</sup>-Ebtissam Mohammad Badawoud,<sup>10</sup>-Abdullah Ibrahim Zakri,

<sup>1</sup>Pediatric consultant, Heraa General Hospital

<sup>2</sup>Pharmacist, Heraa General Hospital

<sup>4</sup>Pharmacy technician, Alnoor specialist hospital

<sup>3</sup>Pharmacist, Alnoor specialist hospital

<sup>5</sup>Pharmacy technician, Heraa General Hospital

<sup>6</sup>Pharmacy technician, Poison Control and Forensic Chemistry Center - makkah

<sup>7</sup>General Directorate of quality & patient safety – MOH, Bsc. Pharm.

<sup>8</sup>Msc in Biochemistry, General Directorate of quality & patient safety - MOH

<sup>9</sup>General Directorate of Quality and Patient Safety, MOH, MSc. Pharmaceutical Economics and Policy, Diploma of Total Quality Management, BSc. Pharm.

<sup>10</sup>General Directorate of quality & patient safety – MOH, MSC. Healthcare and Hospital Administration

**Article Received:** November 2022    **Accepted:** November 2022    **Published:** December 2022

#### Abstract:

*Caffeine is the most commonly administered drug in neonatal critical care units. It is used for the prevention and treatment of apnea, despite being linked to a decreased risk of bronchopulmonary dysplasia (BPD) in infants aged 18 to 21 months. We conducted a comprehensive search of EMBASE, the Cochrane Database of Systematic Reviews (CDSR), and PubMed from inception to January 2022 using variations of the key phrases "apnea," "caffeine," "intensive care, neonatal," and "baby, newborn" to discover relevant literature. However, its influence on BPD and neurodevelopmental outcomes may be mediated by its anti-inflammatory mediator, white matter protection, and induction of surfactant protein B effects. Despite the fact that long-term studies have demonstrated the safety of caffeine as it is currently administered, it is evident that additional research is required to determine the optimal dosage, as well as the timing of initiation and cessation.*

#### Corresponding author:

**Amaal basrwan,**

*Pediatric consultant, Heraa General Hospital*

QR code



Please cite this article in press Amaal basrwan et al, *Overview Of Caffeine Citrate Roles In Neonatal Apnea., Indo Am. J. P. Sci.*, 2022; 09(12).

**INTRODUCTION:**

Apnea of prematurity (AOP) is a common developmental complication in preterm infants that may have various causes, primarily constituting two different types of AOP: a central apnea due to no or insufficient respiratory drive due to the immaturity of the brain stem, and an obstructive apnea due to obstruction of the infants' (upper) airways. Based on these, the possibility of mixed apnea also exists [1]. Additional causes of neonatal apnea include brain tissue damage, respiratory disease, infection, gastrointestinal reflux, cardiac issues, and metabolic disorders [2]. This can result in hypoxemia and reflex bradycardia, which may necessitate active resuscitative efforts if prolonged.

Caffeine, theophylline, and aminophylline have been used for AOP for over four decades as respiratory stimulants. Since the mid-1970s, caffeine, a methylxanthine derivative, has been used in the neonatal intensive care unit (NICU) to treat AOP [3, 4]. According to the Caffeine for Apnea of Prematurity (CAP) trial, caffeine reduced duration of ventilation and oxygen dependence and improved disability and survival without disability [5]. At the age of 11 years, the CAP trial revealed a significant advantage for the caffeine group in terms of motor skills compared to the placebo group [6].

The incidence of apnea of prematurity increases with decreasing gestational age, from 7% of neonates born between 34 and 35 weeks to nearly 100% of those born before 29 weeks [7]. This significantly extends the length of hospitalization [8]. Severe apnea (lasting longer than 20 s) is typically accompanied by bradycardia or desaturation, which may result in cerebral hemodynamic disturbances, subsequently affecting neurodevelopment [7,8]. Moreover, in a post-hoc analysis of data from extremely premature neonates, prolonged hypoxemic episodes during the first three months after birth were associated with a variety of adverse outcomes, such as increased mortality after 36 weeks, motor impairment, cognitive or language delay, severe hearing loss, and bilateral blindness [9].

Methylxanthine therapy is the cornerstone of pharmacologic treatment for prematurity apnea [9]. Both caffeine citrate and theophylline have comparable efficacy, although caffeine citrate is associated with a more favorable safety profile and a lower incidence of adverse effects [10]. Moreover, compared to theophylline, caffeine citrate has a longer half-life and does not require drug-level monitoring; therefore, it is generally preferred [10] according to

guidelines. However, the majority of the evidence supporting these therapy recommendations come from very small, older research, with only one big, long-term follow-up investigation [11,12].

**DISCUSSION:**

A 2018 systematic review and meta-analysis (SRMA) conducted by Chen *et al.* [13] compared the efficacy and safety of high (10–20 mg/kg daily) versus low (5–10 mg/kg daily) caffeine citrate maintenance dosages for the treatment of apnea in premature infants. This analysis comprised 13 randomized controlled trials (RCTs) involving 1515 infants. Compared to the low-dose group, the high-dose group had a higher rate of successful treatment (risk ratio [RR] 1.37, 95% confidence interval [CI] 1.18–1.60) and success rate for ventilator removal (RR 1.74, 95% CI 1.04–2.40). In addition, the high-dose group had a lower extubation failure rate (RR 0.5, 95% CI 0.35–0.71), frequency of apnea (weighted mean difference [WMD] 1.55, 95% CI 2.72 to 0.39), apnea duration (WMD 4.85, 95% CI 8.29 to 1.39), and incidence of bronchopulmonary dysplasia (BPD) However, the incidence of tachycardia was higher (RR 2.02, 95% CI 1.30–3.12) None or moderate heterogeneity was observed across all evaluated outcomes. There were no significant differences between groups in adverse events such as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL), or in-hospital mortality.

Henderson-Smart *et al.* [14] conducted a Cochrane review to determine the effect of caffeine versus theophylline treatment on the risk of apnea in preterm infants with recurrent apnea. Included were a total of five trials with 108 infants. The treatment failure rate (less than 50% reduction in apnea/bradycardia) and the mean apnea rate did not differ between groups following 1–3 days and 5–7 days of treatment, respectively. Change in dose due to tachycardia or feed intolerance was significantly reduced in the caffeine group (RR 0.17, 95% CI 0.04–0.75).

Another study [15] by the same authors compared the effectiveness of doxapram and methylxanthines in preterm infants with recurrent apnea. This review included 91 infants with recurrent apnea across four trials. Without heterogeneity, there were no differences in the incidence of treatment failure within 48 hours (RR 0.91, 95% CI 0.45–1.85) between groups. In the trials, no infants were exposed to MV regardless of treatment. Moreover, none of the studies provided safety information.

Another Cochrane review [16] conducted by the same research team evaluated the effects of methylxanthine treatment on the incidence of apnea. Significantly fewer treatment failures and less use of intermittent positive pressure ventilation were observed with theophylline and caffeine compared to placebo. There was no significant difference between the methylxanthines and the control group in terms of the low rate of death before discharge. Two infants in the theophylline group exhibited tachycardia, according to one study. Age at the time of last endotracheal tube use (MD 0.60 weeks, 95% CI 1.03 to 0.17) and age at the time of last positive pressure ventilation (MD 0.90, 95% CI 1.04 to 0.48) were all lower in the caffeine group.

Vliegenthart et al. [17] compared a high versus a standard caffeine treatment regimen in infants with a gestational age of 32 weeks, with loading doses of 10–80 mg/kg versus 10–30 mg/kg and maintenance dosages of 5–30 mg/kg versus 2.5–10 mg/kg/day, respectively. This analysis included six RCTs with 620 infants. A meta-analysis revealed a significant reduction in BPD (RR 0.72, 95% CI 0.54–0.97), the combined outcome BPD or mortality (RR 0.76, 95% CI 0.59–0.98), and failure to extubate [typical relative risk (TRR) 0.51, 95% CI 0.37–0.70] in infants assigned to a higher caffeine dose. There were no differences between the groups regarding the adverse events NEC, spontaneous intestinal perforation, hyperglycemia, ROP, and IVH. There was observed heterogeneity due to the inconsistent definition of high and low caffeine dosages.

The most recent SRMA [18] included six randomized controlled trials (including 816 preterm infants) that compared high- and low-dose caffeine, with loading doses of over versus under 20 mg/kg and maintenance doses of over versus under 10 mg/kg/day, respectively. There was no statistically significant difference in mortality between the two groups (RR 0.85, 95% CI 0.53–1.38). At high heterogeneity, however, high-dose caffeine was associated with fewer instances of extubation failure (RR 0.51; 95% CI 0.36–0.71), apneas (MD 5.68; 95% CI 6.15 to 5.22), and BPD (RR 0.76; 95% CI 0.60–0.96), as well as a shorter duration of mechanical ventilation (MD 1.69; 95% CI 2.15 to Other studies [13, 17] reported no differences in the incidence of serious adverse events; however, a higher incidence of tachycardia was observed with the higher dose, but this did not result in the discontinuation of caffeine treatment in infants. The greater caffeine dose was also perhaps associated with an increase in cerebellar hemorrhage; however, this association was

only observed when the high dose was administered early.

#### **Theophylline compared to caffeine:**

Caffeine is currently the most frequently utilized xanthine treatment, accounting for 96% of all methylxanthines used in clinical practice despite not being globally accessible. This is the outcome of multiple decades of comparative research. In a double-blind research, Bairam et al. found that although both theophylline and caffeine were beneficial, the former tended to have more side effects, while the latter shown more pharmacologic stability, allowing for a single daily maintenance dose. This has led to the widespread agreement that therapeutic drug monitoring of caffeine when used to treat apnea of prematurity is often ineffective and unnecessary [19]. Interestingly, neonates may methylate theophylline into caffeine [20]. This may contribute to its efficacy, raising doubts about whether plasma concentrations of both xanthines should be evaluated in infants treated with theophylline.

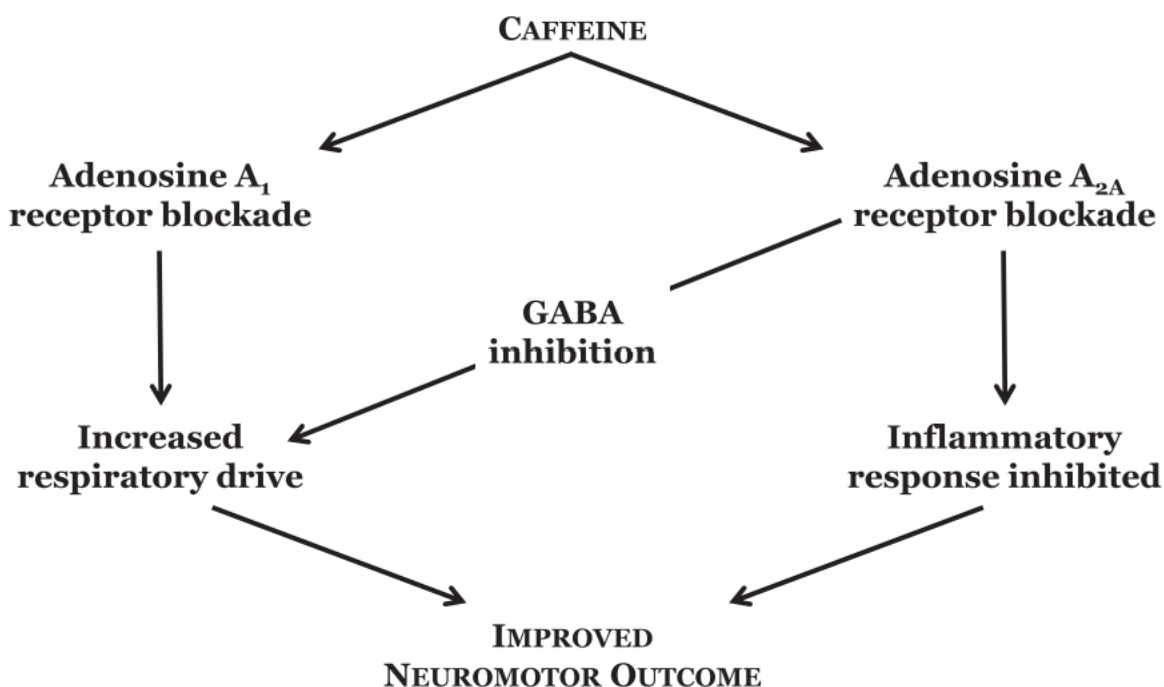
#### **Physiologic/biologic mechanisms of action:**

There is little doubt that xanthines boost respiratory neuronal output, and it appears that this effect is most pronounced in neonates [21]. (Fig. 1). The strong effect on respiratory control in neonates may be attributable to neurodevelopmental maturational variations and/or the comparatively high circulation amounts of caffeine administered to preterm newborns, both of which are poorly understood. There are both central and peripheral mechanisms involved. The former comprises the reversal of adenosinergic inhibition (described later) of inspiratory neurons in the brainstem, an increase in CO<sub>2</sub> responsiveness, and perhaps a decrease in hypoxic depression of breathing [22,23]. Animal studies [24,25] have also suggested an influence of xanthines on peripheral chemosensitivity. For caffeine or aminophylline to improve ventilation and reverse hypoxic respiratory depression, peripheral chemoreceptors must be functional.

The hypothesis of diaphragmatic fatigue as a cause of respiratory failure appears to have gotten less attention in recent years. Theophylline increased transdiaphragmatic pressures in adult patients with chronic obstructive pulmonary disease via an influence on cellular calcium metabolism, as reported in an adult rodent model [26]. While newborn studies failed to establish an impact of aminophylline on diaphragm contraction in a softly breathing piglet [27], Parikka et al. found an increase in diaphragmatic electrical activity 30 minutes after a caffeine-loading

dosage [28]. The benefits of bronchodilator medication in the neonatal intensive care unit (NICU) are mixed, despite the fact that increased airway responsiveness is a key long-term concern for former premature newborns. Xanthines can serve as bronchodilators, and a group of infants with bronchopulmonary dysplasia (BPD) had improved respiratory performance after receiving caffeine [29]. Using adenosine receptor activation, persistent hypoxia causes periventricular white matter damage in

neonatal animals. This suggests that caffeine may provide a protective effect by inhibiting adenosine receptors. Caffeine prevented hypoxia-induced aberrant oligodendrocyte development in newborn mice [30]. Since adenosine production generated by hypoxia may, in theory, also have a neuroprotective effect, it is debatable whether caffeine directly induces white matter protection in premature newborns [31].



**Fig. 1.** Proposed pathways by which neonatal caffeine therapy results in improved longer-term outcomes.

Randomly assigning 18 newborns to a treatment or control group for 15 days [32]. The nine neonates who received caffeine citrate experienced a significant decrease in apnea from baseline on the first day of treatment; those in the control group did not experience any improvement in apnea throughout the duration of the research. In a second study, 85 neonates were randomly assigned to receive caffeine citrate or a placebo for up to 10 days. Caffeine citrate was again associated with a rapid improvement in apnea, with the difference between the caffeine citrate treatment and the placebo treatment approaching significance within two days [33].

The Caffeine for Apnea of Prematurity (CAP) research, in which almost 2,000 newborns were randomized to receive caffeine citrate or a placebo [34] followed these relatively small early

investigations. During the first three weeks after randomization, neonates receiving caffeine citrate gained significantly less weight than those in the placebo group, as measured by a drop in mean weight from baseline. In fact, failure to thrive and feeding intolerance are recognized as adverse effects of caffeine citrate (although their incidence is unknown), and one study suggests that long-term administration of caffeine in preterm neonates is associated with an increase in oxygen consumption and a subsequent decrease in weight gain [35,36]. The current study's bodyweight statistics are therefore particularly comforting, as the majority of newborns gained weight between the baseline and Visit 3 (Week 2), and all neonates gained weight between Visits 3 and 4.

The primary objective of the current trial, change from baseline in the number of apnea occurrences following the initial loading dosage, was evaluated in the entire population, all of whom had had at least four apnea

events within 24 h. Such newborns are at risk for a variety of unfavorable long-term outcomes, including neurological development [4]. The CAP trial, in which participants were followed for 11 years, is one of the few trials assessing the long-term advantages of caffeine citrate in neonates. Those who took caffeine citrate as neonates had better expiratory flow and a lower risk of motor impairment at follow-up compared to those who did not [35,36].

Concerns concerning safety included known side effects, such as tachycardia and potential diuresis, but were primarily centered on the behavioral and metabolic implications of xanthine therapy. Despite the clear stimulating effect of coffee in later life, sleep organization appeared unaffected in premature infants, given the limitations of available monitoring techniques; this view holds to this day. Unsurprisingly, a higher respiratory drive may be related with a higher metabolic rate [37]. In the CAP Trial, a delay in weight gain between caffeine-exposed and placebo-exposed neonates verified this. However, this weight loss trend was not maintained, and the benefits of caffeine appeared to prevail. Historically, this issue prompted efforts to keep xanthine levels as low as feasible. A third issue has been a potential effect on cerebral blood flow; nevertheless, multiple investigations applying non-invasive techniques on neonates have yielded inconclusive results with no discernible adverse effect on outcome [38].

### CONCLUSION:

In the first few months of life, the use of caffeine for the prevention and treatment of apnea of prematurity has been associated with a decreased incidence of bronchopulmonary dysplasia (BPD). Although the neurodevelopmental advantage was no longer statistically significant at 5 years of age, caffeine was associated with sustained improvement in coordination and less gross motor impairment than placebo. Due to the low number and quality of relevant evidence, it is not possible to draw definitive conclusions regarding the comparative efficacy and safety of different administration times and doses of caffeine. To confirm the varied elements of caffeine use in newborn apnea, particularly the optimal dosage regimen, larger and longer-term studies are required.

### REFERENCES:

- Finer NN, Barrington KJ, Hayes BJ, Hugh A. Obstructive, mixed, and central apnea in the neonate: physiologic correlates. *J Pediatr.* 1992;121(6):943–950.
- Kondamudi NP, Wilt AS. *Infant apnea*. Florida: StatPearls Publishing; 2020. [
- Aujard Y. Caffeine in the treatment of apnea in premature infants. *Arch Fr Pediatr.* 1990;47(10):763.
- Kreutzer K, Bassler D. Caffeine for apnea of prematurity: a neonatal success story. *Neonatology.* 2014;105(4):332–336.
- Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine therapy for apnea of prematurity. *N Engl J Med.* 2006;354(20):2112–2121.
- Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG, Dewey D, D’Ilario J, Doyle LW, Grunau RE. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: an 11-year follow-up of the CAP randomized clinical trial. *JAMA Pediatr.* 2017;171(6):564–572.
- Zhao J, Gonzalez F, Mu D. Apnea of prematurity: from cause to treatment. *Eur J Pediatr.* (2011) 170:1097–105. 10.1007/s00431-011-1409-6.
- Theobald K, Botwinski C, Albanna S, McWilliam P. Apnea of prematurity: diagnosis, implications for care, and pharmacologic management. *Neonatal Netw.* (2000) 19:17–24.
- Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *JAMA.* (2015) 314:595–603.
- Eichenwald EC, American Academy of Pediatrics Committee on Fetus and Newborn . Apnea of prematurity. *Pediatrics.* (2016) 137:e20153757.
- Sims ME, Yau G, Rambhatla S, Cabal L, Wu PY. Limitations of theophylline in the treatment of apnea of prematurity. *Am J Dis Child.* (1985) 139:567–70. 10.1001/archpedi.1985.02140080037028.
- Murat I, Moriette G, Blin MC, Couchard M, Flouvat B, De Gamarra E, et al. The efficacy of caffeine in the treatment of recurrent idiopathic apnea in premature infants. *J Pediatr.* (1981) 99:984–9.
- Chen J, Jin L, Chen X. Efficacy and safety of different maintenance doses of caffeine citrate for treatment of apnea in premature infants: a systematic review and meta-analysis. *Biomed Res Int.* 2018;2018:9061234.
- Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev.* 2010(1).
- Henderson-Smart DJ, Steer PA. Doxapram versus methylxanthine for apnea in preterm

- infants. *Cochrane Database of Systematic Reviews* 2000(4).
16. Henderson-Smart DJ, De Paoli AG: Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst. Rev.* 2010(12).
  17. Vliegenthart R, Miedema M, Hutten GJ, van Kaam AH, Onland W. High versus standard dose caffeine for apnoea: a systematic review. *Arch Dis Child Fetal Neonatal Ed.* 2018;103(6):F523–F529.
  18. Brattström P, Russo C, Ley D, Bruschetti M. High-versus low-dose caffeine in preterm infants: a systematic review and meta-analysis. *Acta Paediatr.* 2019;108(3):401–410.
  19. Natarajan G, Botica M-L, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007;119:936e40.
  20. Boutroy MJ, Vert P, Royer RJ, Monin P, Royer-Morrot MJ. Caffeine, a metabolite of theophylline during the treatment of apnea in the premature infant. *J Pediatr* 1979;94:996e8.
  21. Atik A, Harding R, De Matteo R, et al. Caffeine for apnea of prematurity: effects on the developing brain. *Neurotoxicology* 2017;58:94e102.
  22. Julien CA, Joseph V, Bairam A. Caffeine reduces apnea frequency and enhances ventilatory long-term facilitation in rat pups raised in chronic intermittent hypoxia. *Pediatr Res* 2010;68:105e11.
  23. Herlenius E, Lagercrantz H, Yamamoto Y. Adenosine modulates inspiratory neurons and the respiratory pattern in the brainstem of neonatal rats. *Pediatr Res* 1997;42:46e53.
  24. Blanchard PW, Cot A, Hobbs S, Foulon P, Aranda JV, Bureau MA. Abolition of ventilatory response to caffeine in chemodenervated lambs. *J Appl Physiol* 1986;61:133e7.
  25. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. *N Engl J Med* 1984;311:349e53.
  26. Maycock DE, Standaert TA, Watchko JF, Woodrum DE. Effect of aminophylline on diaphragmatic contractility in the piglet. *Pediatr Res* 1990;28:196e8.
  27. Parikka V, Beck J, Zhai Q, Leppasalo J, Lehtonen L, Soukka H. The effect of caffeine citrate on neural breathing pattern in preterm infants. *Early Hum Dev* 2015;91:565e8.
  28. Davis JM, Bhutani VK, Stefano JL, Fox WW, Spitzer AR. Changes in pulmonary mechanics following caffeine administration in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1989;6:49e52.
  29. Back SA, Craig A, Luo NL, et al. Protective effects of caffeine on chronic hypoxia-induced perinatal white matter injury. *Ann Neurol* 2006;60: 696e705.
  30. Rivkees SA, Wendler CC. Adverse and protective influences of adenosine on the newborn and embryo: implications for preterm white matter injury and embryo protection. *Pediatr Res* 2011;69:271e8.
  31. Murat I, Moriette G, Blin MC, Couchard M, Flouvat B, De Gamarra E, et al.. The efficacy of caffeine in the treatment of recurrent idiopathic apnea in premature infants. *J Pediatr.* (1981) 99:984–9. 10.1016/S0022-3476(81)80038-
  32. 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) 20:644–52.
  33. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al.. Caffeine therapy for apnea of prematurity. *N Engl J Med.* (2006) 354:2112–21. 10.1056/NEJMoa054065.
  34. Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG, et al.. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity. *JAMA Pediatr.* (2017) 171:564.
  35. Chiesi Limited *Peyona (Caffeine Citrate) 20 mg/ml Solution for Infusion and Oral Solution: Summary of Product Characteristics.* (2017). Available online at: <https://www.medicines.org.uk/emc/medicine/26467>.
  36. Bauer J, Maier K, Linderkamp O, Hentschel R. Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. *Pediatrics.* (2001) 107:660–3. 10.1542/peds.107.4.660
  37. Carnielli VP, Verlato G, Benini F, et al. Metabolic and respiratory effects of theophylline in the preterm infant. *Arch Dis Childh Fetal Neonatal Ed* 2000;83:F39e43.
  38. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112e21.