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## ***What We Know or Don't Know About Neonatal Pain and Sedation Management***

### **References**

Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med.* 1987 Nov 19;317(21):1321-9. doi: 10.1056/NEJM198711193172105. PMID: 3317037.

Andropoulos DB. Effect of Anesthesia on the Developing Brain: Infant and Fetus. *Fetal Diagn Ther.* 2018;43(1):1-11. doi: 10.1159/000475928. Epub 2017 Jun 7. PMID: 28586779.

Bellù R, Romantsik O, Nava C, de Waal KA, Zanini R, Bruschettini M. Opioids for newborn infants receiving mechanical ventilation. *Cochrane Database Syst Rev.* 2021 Mar 17;3(3):CD013732. doi: 10.1002/14651858.CD013732.pub2. PMID: 33729556; PMCID: PMC8121090.

Campo-Soria C, Chang Y, Weiss DS. Mechanism of action of benzodiazepines on GABAA receptors. *Br J Pharmacol.* 2006 Aug;148(7):984-90. doi: 10.1038/sj.bjp.0706796. Epub 2006 Jun 19. PMID: 16783415; PMCID: PMC1751932.

COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE. Prevention and Management of Procedural Pain in the Neonate: An Update. *Pediatrics.* 2016 Feb;137(2):e20154271. doi: 10.1542/peds.2015-4271. Epub 2016 Jan 25. PMID: 26810788.

Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: A systematic review of observational studies. *Eur J Pain.* 2016 Apr;20(4):489-98. doi: 10.1002/ejp.757. Epub 2015 Jul 29. PMID: 26223408.

Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, et al; GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet.* 2016 Jan 16;387(10015):239-50. doi: 10.1016/S0140-6736(15)00608-X. Epub 2015 Nov 4. Erratum in: *Lancet.* 2016 Jan 16;387(10015):228. doi: 10.1016/S0140-6736(16)00054-4. PMID: 26507180; PMCID: PMC5023520.

de Tristan MA, Martin-Marchand L, Roué JM, Anand KJS, Pierrat V, et al. Association of Continuous Opioids and/or Midazolam During Early Mechanical Ventilation with Survival and Sensorimotor Outcomes at Age 2 Years in Premature Infants: Results from the French Prospective National EPIPAGE 2 Cohort. *J Pediatr.* 2021 May;232:38-47.e8. doi: 10.1016/j.jpeds.2020.12.069. Epub 2021 Jan 1. PMID: 33395567.

DiMaggio C, Sun LS, Ing C, Li G. Pediatric anesthesia and neurodevelopmental impairments: a Bayesian meta-analysis. *J Neurosurg Anesthesiol.* 2012 Oct;24(4):376-81. doi: 10.1097/ANA.0b013e31826a038d. PMID: 23076225; PMCID: PMC3475986.

Duerden EG, Guo T, Dodbiba L, Chakravarty MM, Chau V, et al. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. *Ann Neurol.* 2016 Apr;79(4):548-59. doi: 10.1002/ana.24601. Epub 2016 Feb 15. PMID: 26754148.



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García-Valdivieso I, Yáñez-Araque B, Moncunill-Martínez E, Bocos-Reglero MJ, Gómez-Cantarino S. Effect of Non-Pharmacological Methods in the Reduction of Neonatal Pain: Systematic Review and Meta-Analysis. *Int J Environ Res Public Health.* 2023 Feb 12;20(4):3226. doi: 10.3390/ijerph20043226. PMID: 36833919; PMCID: PMC9959594.

Mangat AK, Oei JL, Chen K, Quah-Smith I, Schmölzer GM. A Review of Non-Pharmacological Treatments for Pain Management in Newborn Infants. *Children (Basel).* 2018 Sep 20;5(10):130. doi: 10.3390/children5100130. PMID: 30241352; PMCID: PMC6210323.

McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, et al; GAS Consortium. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. *Lancet.* 2019 Feb 16;393(10172):664-677. doi: 10.1016/S0140-6736(18)32485-1. Epub 2019 Feb 14. Erratum in: *Lancet.* 2019 Aug 24;394(10199):638. doi: 10.1016/S0140-6736(19)31958-0. PMID: 30782342; PMCID: PMC6500739.

Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev.* 2017 Jan 31;1(1):CD002052. doi: 10.1002/14651858.CD002052.pub3. PMID: 28141899; PMCID: PMC6464963.

Portelli K, Kandraju H, Ryu M, Shah PS. Efficacy and safety of dexmedetomidine for analgesia and sedation in neonates: a systematic review. *J Perinatol.* 2024 Feb;44(2):164-172. doi: 10.1038/s41372-023-01802-5. Epub 2023 Oct 16. PMID: 37845426.

Puia-Dumitrescu M, Comstock BA, Li S, Heagerty PJ, Perez KM, et al; PENUT Consortium. Assessment of 2-Year Neurodevelopmental Outcomes in Extremely Preterm Infants Receiving Opioids and Benzodiazepines. *JAMA Netw Open.* 2021 Jul 1;4(7):e2115998. doi: 10.1001/jamanetworkopen.2021.15998. PMID: 34232302; PMCID: PMC8264640.

Sanders RD, Xu J, Shu Y, Januszewski A, Halder S, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. *Anesthesiology.* 2009 May;110(5):1077-85. doi: 10.1097/ALN.0b013e31819daedd. PMID: 19352168.

Sun LS, Li G, Miller TL, Salorio C, Byrne MW, et al. Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. *JAMA.* 2016 Jun 7;315(21):2312-20. doi: 10.1001/jama.2016.6967. PMID: 27272582; PMCID: PMC5316422.

Sun L. Early childhood general anaesthesia exposure and neurocognitive development. *Br J Anaesth.* 2010 Dec;105 Suppl 1(Suppl 1):i61-8. doi: 10.1093/bja/aeq302. PMID: 21148656; PMCID: PMC3000523.

Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician.* 2008 Mar;11(2 Suppl):S133-53. PMID: 18443637.

Tucker MH, Tiwari P, Carter BS. The physiology, assessment, and treatment of neonatal pain. *Semin Fetal Neonatal Med.* 2023 Aug;28(4):101465. doi: 10.1016/j.siny.2023.101465. Epub 2023 May 20. PMID: 37236846.



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Velasco B, Mohamed E, Sato-Bigbee C. Endogenous and exogenous opioid effects on oligodendrocyte biology and developmental brain myelination. *Neurotoxicol Teratol*. 2021 Jul-Aug;86:107002. doi: 10.1016/j.ntt.2021.107002. Epub 2021 Jun 12. PMID: 34126203; PMCID: PMC8277740.

Weng Y, Zhang J, Chen Z. Effect of non-pharmacological interventions on pain in preterm infants in the neonatal intensive care unit: a network meta-analysis of randomized controlled trials. *BMC Pediatr*. 2024 Jan 3;24(1):9. doi: 10.1186/s12887-023-04488-y. PMID: 38172771; PMCID: PMC10765718.

Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology*. 2009 Apr;110(4):796-804. doi: 10.1097/01.anes.0000344728.34332.5d. PMID: 19293700; PMCID: PMC2729550.