

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**Worksheet author****Ruth Guinsburg****Date Submitted for review: October 3, 2009****Clinical question.****In apneic neonates suspected of narcotic depression (P), does naloxone (I) when compared to effective ventilation without naloxone (C) improve outcome (O)?****Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy****State if this is a proposed new topic or revision of existing worksheet: Revision****Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

Search strategy (including electronic databases searched).

Strategy for searches without any limit of period:

1. Medline - ("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND "infant, newborn"[MeSH Terms]: 189 references.
2. Medline - ("narcotic antagonists"[MeSH Terms] OR ("narcotic"[All Fields] AND "antagonists"[All Fields]) OR "narcotic antagonists"[All Fields] OR "narcotic antagonists"[Pharmacological Action]) AND "infant, newborn"[MeSH Terms]: 312 references
3. Embase - 'naloxone'/exp/mj AND [newborn]/lim AND [embase]/lim: 331 references
4. SciELO (www.scielo.br) - Naloxone [Term] in all indexes (regional): 35 references
5. NICHD Cochrane Neonatal – Naloxone [Term]: 5 references
6. ECC Master library: “naloxone” and “infant” [Terms in Abstract]: 21 references
7. Eligible articles in reference lists of all articles that met inclusion criteria

• State inclusion and exclusion criteria

Inclusion criteria:

1. Case reports, case series, cross-sectional, prospective or retrospective cohorts, clinical trials, systematic reviews and meta-analysis that analyzed the use of naloxone in the delivery room for depressed infants at birth and/or for infants of mothers that received opioids prior to delivery.
2. Animal studies that evaluate effects and side-effects of naloxone with neonatal models.
4. Human studies that evaluate possible side effects of naloxone in pediatrics

Exclusion criteria:

Naloxone studies in any age groups beyond neonatal period (except for possible side effects) and comments or personal opinions.

• Number of articles/sources meeting criteria for further review:

The following studies about naloxone use were retrieved:

- 12 studies of narcotic exposed infants but they were not necessarily depressed or apneic at birth. These included 2 meta-analyses (the same meta-analysis published both in Cochrane review and Arch Dis Child Fetal Neonatal Ed)
- 7 studies on depressed infants or animals at birth not exposed to narcotics prior to delivery. These included 1 meta-analysis, 2 clinical and 4 animal studies.
- 3 studies with infants exposed to maternal opioids and depressed at birth. All 3 studies were observational studies about frequency of naloxone use for neonatal resuscitation in the delivery room.
- 1 experimental study with animals not exposed to maternal opioids and not depressed at birth.
- 6 studies about possible side effects of naloxone use in pediatric patients: 3 case reports, 1 cohort and 2 animal studies.
- 1 in vitro study regarding the effect of naloxone on immature endothelial cells.
- 1 systematic review of available information on possible benefits of Naloxone use in neonatal resuscitation in the delivery room resulting from 2005 ILCOR evidence review process.

Observation: Literature search of all databases was done again at October 1st, 2009 with the same strategy described above but restricted to the six months. 2 new studies were retrieved but none had relevant information to be added.**Therefore, 31 studies are included in the evaluation process.**

Summary of evidence

Evidence Supporting Clinical Question:

Good					[Wiener, 1977, 228-9]*E [Wiener, 1977, 229-31]*E <i>[Chernick and Craig, 1982, 1252-3]**E</i> <i>[Ting and Pan, 1994, 359-64]**E</i>
Fair					[Hodgkinson, 1978, 294-8]*E [Brice, 1979, 356-61]*E <i>[Chernick, 1980, 357-9]</i>
Poor					[Evans, 1976, 1098-100]*E [Gerhardt, 1977, 1009-12]*E
	1	2	3	4	5
Level of evidence					

E = Other endpoint; *Italics* = *Animal studies*

* narcotic exposed infants or animals, but not necessarily depressed at birth

** depressed infants or animals at birth not exposed to narcotics prior to delivery

Evidence Neutral to Clinical Question

Good					[McGuire and Fowlie, 2002, CD003483]*E [McGuire and Fowlie, 2003, F308-11]*E [McGuire, 2004, CD003955]**E <i>[Van Woerkom, 2004, 147-51]^{&} E</i>
Fair					[Herschel, 2000, 831-4]***E
Poor					
	1	2	3	4	5
Level of evidence					

E = Other endpoint; *Italics* = *Animal studies*

* narcotic exposed infants or animals, but not necessarily depressed at birth

** depressed infants or animals at birth not exposed to narcotics prior to delivery

*** depressed infants or animals at birth and exposed to narcotics prior to delivery

**** not depressed infants or animals at birth and exposed to narcotics prior to delivery

& other

Evidence Opposing Clinical Question

Good					<p>[Bonta, 1979, 102-5]*E [Laudenbach, 2001, 457-66]**E [Chernick, 1988, 519-25]**E <i>[de-Castro, 1993, 747-51]*****E</i> [Gill and Colvin, 2007, 795-8]***E [Box and Cochran, 2006, 1083-6]***E <i>[Padbury, 1987, 590-3]*****E</i> <i>[Martinez, 1988, 343-7]*****E</i></p>
Fair					<p>[Dick, 1978, 95-110]*E [Welles, 1984, 617-9]*E <i>[Young, 1984, 52-6]**E</i></p>
Poor					<p>[Deshpande and Gill, 2009, 115-7] *****E [Gibbs, 1989, 159-60]*E [Johnson, 1995, 356-7]*****E [Prough, 1984, 485-6]*****E [Hasan, 2003, 1587-92]*****E</p>
	1	2	3	4	5
Level of evidence					

E = Other endpoint; *Italics* = *Animal studies*

* narcotic exposed infants or animals, but not necessarily depressed at birth

** depressed infants or animals at birth not exposed to narcotics prior to delivery

*** depressed infants or animals at birth and exposed to narcotics prior to delivery

**** not depressed infants or animals at birth and exposed to narcotics prior to delivery

***** non-newborn infants with side effects related to naloxone administration

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Since the last revision [Guinsburg and Wyckoff, 2006, 121-32, viii] no substantial studies were added to the literature. There are no studies comparing neonatal outcomes after the administration of naloxone versus positive pressure ventilation for newborn infants apneic at birth. There is not a single study evaluating the efficacy of naloxone in reversing respiratory depression at birth in babies exposed to opioids prior to delivery.

Evidence does exist to indicate that for infants with good respiratory effort despite maternal opiate exposure, subtle measures of respiration are increased at least for a short period of time after administration of naloxone with enhanced alveolar ventilation in the first 30 minutes after drug administration and improved CO₂ response curves (**LOE 5**) [Brice, Moreland, 1979, 356-61] [Chernick and Craig, 1982, 1252-3] [Chernick, Madansky, 1980, 357-9] [Evans, Hogg, 1976, 1098-100] [Gerhardt, Bancalari, 1977, 1009-12] [Wiener, Hogg, 1977, 229-31] [Wiener, Hogg, 1977, 228-9]. But, there are no studies that address clinically relevant endpoints such decreased need for prolonged ventilation in the delivery room and/or admission to the neonatal intensive care unit [McGuire and Fowlie, 2002, CD003483] [McGuire and Fowlie, 2003, F308-11]. On the other hand, some observational studies show a steady decrease in naloxone use in the delivery room for narcotic exposed newborn infants without concurrent increase in morbidity (**LOE 5**) [Box and Cochran, 2006, 1083-6] [Gill and Colvin, 2007, 795-8].

Although there is some evidence of improved short term behavioral assessment in narcotic exposed neonates that receive naloxone at birth, these effects do not last long and their clinical relevance is questionable (**LOE 5**) [Hodgkinson, Bhatt, 1978, 294-8] [McGuire, Fowlie, 2004, CD003955].

Animal data and sparse case reports in neonates and pediatric patients raise concerns about direct myocardial depression [Deshpande and Gill, 2009, 115-7] or catecholamine surge after the use of high doses of naloxone, increasing sympathetic nervous system activity, which may result in cardiac arrhythmias, hypertension and non-cardiogenic pulmonary edema (**LOE 5**) [Martinez, Padbury, 1988, 343-7] [Padbury, Agata, 1987, 590-3] [Hasan, Benko, 2003, 1587-92] [Johnson, Mayer, 1995, 356-7] [Prough, Roy, 1984, 485-6].

Some very limited animal information raises questions about long term effects of naloxone regarding the potential to increase neuronal and/or white matter and/or endothelial damage in asphyxiated patients (**LOE 5**) [Laudenbach, Calo, 2001, 457-66] [Van Woerkom, Beharry, 2004, 147-51], and regarding modifications in pain responsiveness during life (**LOE 5**) [de-Castro, Cabral-Filho, 1993, 747-51].

The concern for precipitating seizures due rapid withdrawal is based on one case report (**LOE 5**) [Gibbs, Newson, 1989, 159-60].

Acknowledgements:

Citation List

1. Bonta BW, Gagliardi JV, Williams V, Warshaw JB. Naloxone reversal of mild neurobehavioral depression in normal newborn infants after routine obstetric analgesia. *J Pediatr.* 1979 Jan;94(1):102-5.

Research notes:

LOE 5 opposing; randomized control trial; the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

2. Box D, Cochran D. Safe reduction in administration of naloxone to newborn infants: an observational study. *Acta Paediatr.* 2006 Sep;95(9):1083-6.

Research notes:

LOE 5 opposing; retrospective and prospective cohort study; the study does not compare naloxone and PPV; the study addresses practices and not outcomes.

3. Brice JE, Moreland TA, Walker CH. Effects of pethidine and its antagonists on the newborn. *Arch Dis Child.* 1979 May;54(5):356-61.

Research notes:

LOE 5 supporting; randomized control trial with some methodological problems; the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

4. Chernick V, Craig RJ. Naloxone reverses neonatal depression caused by fetal asphyxia. *Science.* 1982 Jun 11;216(4551):1252-3.

Research notes:

LOE 5 supporting; animal study that does not compare naloxone and PPV; depressed newborns were not exposed to opioids before birth.

5. Chernick V, Madansky DL, Lawson EE. Naloxone decreases the duration of primary apnea with neonatal asphyxia. *Pediatr Res.* 1980 Apr;14(4 Pt 1):357-9.

Research notes:

LOE 5 supporting; animal study that does not compare naloxone and PPV; depressed newborns were not exposed to opioids before birth.

6. Chernick V, Manfreda J, De Booy V, Davi M, Rigatto H, Seshia M. Clinical trial of naloxone in birth asphyxia. *J Pediatr.* 1988 Sep;113(3):519-25.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; depressed newborns were not exposed to opioids before birth.

7. de-Castro RM, Cabral-Filho JE, Costa JA, Costa FB, Gallindo MA, Hecksher CA. Neonatal treatment with naloxone causes permanent hyperalgesia in rats. *Braz J Med Biol Res.* 1993 Jul;26(7):747-51.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; newborn animals were not exposed to opioids before birth and were not depressed/apneic at birth.

8. Deshpande G, Gill A. Cardiac arrest following naloxone in an extremely preterm neonate. *Eur J Pediatr.* 2009 Jan;168(1):115-7.

Research notes:

LOE 5 opposing; case report of a premature infant that had serious side effects after naloxone use to reverse morphine overdosing.

9. Dick W, Knoche E, Traub E. Clinical investigations of the influence of various naloxone doses on the newborn. *J Perinat Med.* 1978;6(2):95-110.

Research notes:

LOE 5 opposing; randomized control trial with some methodological problems; the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

10. Evans JM, Hogg MI, Rosen M. Reversal of narcotic depression in the neonate by naloxone. *Br Med J.* 1976 Nov 6;2(6044):1098-100.

Research notes:

LOE 5 supporting; case series? The study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

11. Gerhardt T, Bancalari E, Cohen H, Rocha LF. Use of naloxone to reverse narcotic respiratory depression in the newborn infant. *J Pediatr.* 1977 Jun;90(6):1009-12.

Research notes:

LOE 5 supporting; case series? The study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

12. Gibbs J, Newson T, Williams J, Davidson DC. Naloxone hazard in infant of opioid abuser. *Lancet.* 1989 Jul 15;2(8655):159-60.

Research notes:

LOE 5 opposing; case report of an infant born to an opioid abuser mother that had seizures after naloxone administration.

13. Gill AW, Colvin J. Use of naloxone during neonatal resuscitation in Australia: compliance with published guidelines. *J Paediatr Child Health.* 2007 Dec;43(12):795-8.

Research notes:

LOE 5 opposing; retrospective and prospective cohort study; the study does not compare naloxone and PPV; the study addresses practices and not outcomes.

14. Guinsburg R, Wyckoff MH. Naloxone during neonatal resuscitation: acknowledging the unknown. *Clin Perinatol.* 2006 Mar;33(1):121-32, viii.

Research notes:

Systematic review regarding evidence retrieved for 2005 ILCOR Consensus on Science. LOE not attributed since it was not used either to refute or to support the clinical question.

15. Hasan RA, Benko AS, Nolan BM, Campe J, Duff J, Zureikat GY. Cardiorespiratory effects of naloxone in children. *Ann Pharmacother.* 2003 Nov;37(11):1587-92.

Research notes:

LOE 5 opposing; cohort of pediatric patients reporting effectiveness and safety of naloxone treatment.

16. Herschel M, Khoshnood B, Lass NA. Role of naloxone in newborn resuscitation. *Pediatrics.* 2000 Oct;106(4):831-4.

Research notes:

LOE 5 neutral; retrospective and prospective cohort study; the study does not compare naloxone and PPV; the study addresses practices and not outcomes

17. Hodgkinson R, Bhatt M, Grewal G, Marx GF. Neonatal neurobehavior in the first 48 hours of life: effect of the administration of meperidine with and without naloxone in the mother. *Pediatrics.* 1978 Sep;62(3):294-8.

Research notes:

LOE 5 supporting; randomized controlled clinical trial; The study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

18. Johnson C, Mayer P, Grosz D. Pulmonary edema following naloxone administration in a healthy orthopedic patient. *J Clin Anesth.* 1995 Jun;7(4):356-7.

Research notes:

LOE 5 opposing; case report of a teenager female healthy patient that had serious side effects after post-operative naloxone use.

19. Laudенbach V, Calo G, Guerrini R, Lamboley G, Benoist JF, Evrard P, et al. Nociceptin/orphanin FQ exacerbates excitotoxic white-matter lesions in the murine neonatal brain. *J Clin Invest.* 2001 Feb;107(4):457-66.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; depressed newborn animals were not exposed to opioids before birth.

20. Martinez A, Padbury J, Shames L, Evans C, Humme J. Naloxone potentiates epinephrine release during hypoxia in fetal sheep: dose response and cardiovascular effects. *Pediatr Res.* 1988 Apr;23(4):343-7.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; sympathoadrenal response in hypoxic newborn lambs with naloxone use.

21. McGuire W, Fowlie PW. Naloxone for narcotic-exposed newborn infants. *Cochrane Database Syst Rev.* 2002(4):CD003483.

Research notes:

LOE 5 neutral; meta-analysis, but comprises studies that do not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

22. McGuire W, Fowlie PW. Naloxone for narcotic exposed newborn infants: systematic review. Arch Dis Child Fetal Neonatal Ed. 2003 Jul;88(4):F308-11.

Research notes:

LOE 5 neutral; meta-analysis, but comprises studies that do not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth. Same meta-analysis as above published in a different place.

23. McGuire W, Fowlie PW, Evans DJ. Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. Cochrane Database Syst Rev. 2004(1):CD003955.

Research notes:

LOE 5 neutral; meta-analysis, but comprises studies that do not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth, but were not exposed to opioids before at labor or delivery.

24. Padbury JF, Agata Y, Polk DH, Wang DL, Callegari CC. Neonatal adaptation: naloxone increases the catecholamine surge at birth. Pediatr Res. 1987 Jun;21(6):590-3.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; sympathoadrenal response in hypoxic newborn lambs with naloxone use.

25. Prough DS, Roy R, Bumgarner J, Shannon G. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology. 1984 May;60(5):485-6.

Research notes:

LOE 5 opposing; case report of two teenager patients that had serious side effects after naloxone use.

26. Ting P, Pan Y. The effects of naloxone on the post-asphyxic cerebral pathophysiology of newborn lambs. Neurol Res. 1994 Oct;16(5):359-64.

Research notes:

LOE 5 supporting; animal study that does not compare naloxone and PPV; depressed newborn animals were not exposed to opioids before birth.

27. Van Woerkom R, Beharry KD, Modanlou HD, Parker J, Rajan V, Akmal Y, et al. Influence of morphine and naloxone on endothelin and its receptors in newborn piglet brain vascular endothelial cells: clinical implications in neonatal care. Pediatr Res. 2004 Jan;55(1):147-51.

Research notes:

LOE 5 neutral; in vitro study with immature cultured endothelial cells; it does not compare naloxone and PPV.

28. Welles B, Belfrage P, de Chateau P. Effects of naloxone on newborn infant behavior after maternal analgesia with pethidine during labor. Acta Obstet Gynecol Scand. 1984;63(7):617-9.

Research notes: LOE 5 opposing; randomized clinical trial (powerless); the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

29. Wiener PC, Hogg MI, Rosen M. Effects of naloxone on pethidine-induced neonatal depression. Part I-- Intravenous naloxone. Br Med J. 1977 Jul 23;2(6081):228-9.

Research notes:

LOE 5 supporting; randomized clinical trial (powerless); the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

30. Wiener PC, Hogg MI, Rosen M. Effects of naloxone on pethidine-induced neonatal depression. Part II-- Intramuscular naloxone. Br Med J. 1977 Jul 23;2(6081):229-31.

Research notes:

LOE 5 supporting; randomized clinical trial (powerless); the study does not compare naloxone and PPV; neonates were not necessarily depressed/apneic at birth.

31. Young RS, Hessert TR, Pritchard GA, Yagel SK. Naloxone exacerbates hypoxic-ischemic brain injury in the neonatal rat. Am J Obstet Gynecol. 1984 Sep 1;150(1):52-6.

Research notes:

LOE 5 opposing; animal study that does not compare naloxone and PPV; depressed newborn animals were not exposed to opioids before birth.