Clinical question. In apneic newborns 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: Review of an existing worksheet

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).
“NEWBORN RESUSCITATION” AND “NALOXONE” OR “NARCAN” OR “OPIATE ANTAGONIST” as MeSH (heading) AND “Neonatal” OR “Newborn” OR “Infant” PubMed (85 hits), EMBASE (54 hits), Medline (87 hits), Cochrane Library (2 hits), SCOPUS (99 hits), AHA Endnote Database (29 hits), hand review of references of articles of relevance (2)

• State inclusion and exclusion criteria
Inclusion: English language, human and animal, neonatal or neonatal model studies, editorials and review articles included but only used for hand-searching for further references
Exclusion: Adult studies, abstract only, single case reports

• Number of articles/sources meeting criteria for further review:
40 articles reviewed
19 met inclusion criteria
21 excluded due to poor quality, reviews only, single case reports, or information not specific enough to the proposed PICO question
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Evidence Supporting Clinical Question</th>
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| Good              | <br> | <br> | <br> | <br> | Belfrage, 1981 p43<sup>E</sup>  
|                   | Brice, 1979 p356<sup>E</sup>  
|                   | Evans, 1976 p1098<sup>E</sup>  
|                   | Gerhardt, 1977 p1009<sup>E</sup>  
|                   | Hodgkinson, 1978 p294<sup>E</sup>  
|                   | Weiner, 1977 p228<sup>E</sup>  
|                   | Weiner, 1977 p229<sup>E</sup>  |
| Fair              | <br> | <br> | <br> | <br> | |
| Poor              | 1 | 2 | 3 | 4 | 5 |

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*italics = Animal studies*
### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
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<th>McGuire, 2002 pCD003483(^E)</th>
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| Fair | | | | | Bonta, 1979 p102\(^E\)  
|      | | | | | Dick, 1978 p95\(^E\)  
|      | | | | | Dick, 1978 p97\(^E\)  
|      | | | | | Moreland, 1980 p609\(^E\)  
|      | | | | | Stile, 1987 p454\(^E\)  |
| Poor | | | | |  |

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*Italicics* = Animal studies

### Evidence Opposing Clinical Question

| Good | | | | | Box, 2006 p1083\(^E\)  
|------|------|------|------|------|------------------|
|      | | | | | Herschel, 2000 p831\(^E\)  
| Fair | | | | | Gill, 2007 p795\(^E\)  
|      | | | | | Singh, 2006 p385\(^E\)  
|      | | | | | Gerhardt, 1977 p971\(^E\)  
|      | | | | | Welles, 1984 p617\(^E\)  |
| Poor | | | | |  |

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

*Italicics* = Animal studies
Although naloxone has long been in use for neonates exposed to maternal narcotics during labor, there is no evidence that naloxone will improve outcomes compared to continued effective ventilation without naloxone for apneic newborns suspected of narcotic depression. There are no studies that directly address this issue. All randomized trials of naloxone excluded the very babies for which we consider its use. For newborns who are vigorous in the delivery room despite their mother having received opioids, naloxone subtly increases ventilation parameters (such as increased alveolar ventilation and improved CO2 response curves) for a short period of time but the clinical relevance of these observations is questionable {NOTE: Belfrage1981 p43\textsuperscript{E}, Brice-1979 p356\textsuperscript{E}, Evans-1976 p1098\textsuperscript{E}, Gerhardt-1977 p1009\textsuperscript{E}, Hodgkison-1978 p298\textsuperscript{E}, Wiener 1977 p228\textsuperscript{E}, Wiener 1977 p229\textsuperscript{E}} LOE 5. Several other studies found no difference between vigorous naloxone treated and placebo or no drug treated newborns as far as pH, PCO2, Apgars, and neurologic outcomes {Bonta-1979 p102\textsuperscript{E}, Dick 1978 p95\textsuperscript{E}, Dick 1978 p97\textsuperscript{E}} LOE 5. Several studies have shown that when naloxone is available to providers in the delivery room, it is frequently misused due to lack of provision of effective ventilation prior to administration {Herschel 2000 p831\textsuperscript{E}, Box 2006 p1083\textsuperscript{E}, Singh 2006 p385\textsuperscript{E}, Gill 2007 p795\textsuperscript{E}} LOE 4. Thus, there is no evidence of benefit and substantial evidence of risk. Consequently, naloxone should not be recommended during delivery room resuscitation.

Acknowledgements: None

Citation List

**Belfrage, 1981 p43\textsuperscript{E}**

**Level of Evidence**: 5-(did not study newborns with respiratory depression and dose was only 60% of that previously recommended by ILCOR)

**Quality**: Fair- Randomized (no methodology given), non-blinded, no sample size determinations

**Supportive/Neutral/Opposing**: Supportive-infants exposed to naloxone had higher respiratory rates than placebo

**Industry Funding**: None reported

**Comments**: Participants: Enrolled infants were SVD deliveries with non-complicated pregnancies and labor of term infants with single narcotic exposure within 3 hours of delivery that did NOT have respiratory depression (All with Agpars > 8 at one minute). Intervention/Comparator: At ~ 40 minutes of life, randomized to either 60 mg IM naloxone \((n=18)\) or placebo \((n=10)\)

**Outcomes (E-other)**: Apgars, time from birth to sustained respiration, at 20 minutes of life continuous monitoring of RR, HR, plasma concentrations of naloxone in umbilical artery and vein, maternal cubital vein, and 70 minute of life CBG.

**Findings**: When Opiate was given less than 1 hour prior to delivery the time to spontaneous respiration was shorter \((23 \pm 8 \text{ versus } 35 \pm 15 \text{ sec})\). Following naloxone at 40 min of life, 40% had increased respiratory rate compared to 10% of placebo. no data given as to the clinical significance of increase in RR noted (no means or SD), not given in the DR

**Bonta, 1979 p102\textsuperscript{E}**
Level of Evidence: 5-(did not study infants with respiratory depression and dose was only 20% of that previously recommended by ILCOR)
Quality: Fair- Randomized and blinded but no a priori sample size determination.
Supportive/Neutral/Opposing: Neutral- no improvement in 5 minute Apgar or pCO2, but no detrimental effects of naloxone noted either
Industry Funding: None reported
Comments: Participants: Infants with narcotic exposure within 6 hrs of delivery. Enrolled infants did NOT necessarily have respiratory depression (All with Apgars > 6 at one minute). Excluded breech, cesarean delivery and infants with Apgar score < 6 at one min. Intervention/Comparator: 0.02 mg/kg IM naloxone (n=22) versus placebo (n=21). Outcomes (E-other): Apgars, CBG 1,5,10,30,60, and 120 min, Scanlon neurobehavioral exam at 1,4 and 24 hrs. Findings: naloxone exposed infants were more alert and responded better to sound. No difference found in APGARS or pCO2 at 1, 60, 120 or 240 minutes.

Box, 2006 p1083

Level of Evidence: 4-retrospective and prospective data regarding naloxone use in the delivery room in a general delivery population
Quality: Good
Supportive/Neutral/Opposing: Opposing
Industry Funding: None reported
Comments: Participants: All infants born during 2 study periods were examined for use of naloxone in the delivery room. Intervention: Good Practice Guidelines used to educate staff as to when naloxone is really indicated, dosage and route, and appropriate monitoring. Dosage used was 0.1mg/kg when used. Comparator: Before and after the education intervention. Outcome: Naloxone use frequency when used in a manner consistent with resuscitation guidelines. Findings: If guidelines are followed, the use of naloxone can be drastically reduced without evidence of harm. Naloxone is rarely needed in newborns.

Brice, 1979 p356

Level of Evidence: 5-(Did not study newborns with respiratory depression and dose only 10-20% of that previously recommended by ILCOR)
Quality: Fair- Randomized (methodology not described), non-blinded except to Scanlon examiner, no a priori sample size determination
Supportive/Neutral/Opposing: +/- Supportive (higher CO2 output at 15 min)
Industry Funding: None reported
Comments: Participants: Infants with narcotic exposure within four hours of delivery, (excluded if abnormal pregnancy or abnormal labor and delivery, excluded if cord pH<7.25,or did not respond to simple resuscitative efforts, or any anomalies. Intervention/Comparator: 0.01 mg/kg (n=14) or 0.02 mg/kg IV (n=12) (n=26 total) vs no drug (n=24). Outcomes (E-Other): Time to sustained respiration, measures of alveolar ventilation up to 24 hours of life, Brazelton Score, Scanlon Score within first 24 hours of life. Findings: No difference in time to sustained respiration or behavioral scores, narcan infants had statistically higher expired CO2 output at 15 minutes (of unknown clinical significance) and higher alveolar ventilation (? Statistical and clinical significance).

Dick, 1978 p95

Part A (p.95)
Level of Evidence: 5-Infants with respiratory depression were not studied, authors do not specify exactly when naloxone was given although presumably right at time of delivery
Quality: Fair- Randomized (methodology not described), non-blinded, no sample size calculations
Supportive/Neutral/Opposing: Neutral-no clear benefit or harm
Industry Funding: Not reported
Comments: Participants: 40 newborns of unspecified gestation, whose mothers had been given IV pethidine in labor. Intervention/Comparator: IV naloxone 0.02 mg/kg (n=10) versus 0.03 mg/kg (n=10) versus 0.04 mg/kg (n=10) versus no drug (n=10). Outcome (E-Other): CBG at 1,5,10,30,60, and 120 min. Findings: no difference in pH or pCO2 between the 4 groups. 2 of the naloxone groups PCO2 values decreased more markedly when compared to control at 20 and 60 min but all were in normal range.

Part B (p.97)
Level of Evidence: 5-Infants with respiratory depression were not studied, authors do not specify exactly when naloxone was given although presumably right at time of delivery
Quality: Fair- Randomized (methodology not described), double-blinded, no sample size calculations
Supportive/Neutral/Opposing: Neutral
Industry Funding: Not reported
Comments: Participants: 30 newborns of birth weight 3247-3338g, whose mothers had been given IV pethidine in labor within 2 hours of birth. Intervention/Comparator: IV naloxone 0.04 mg/kg (n=10) versus IV naloxone 0.04 mg total (n=10) versus placebo (n=10). Outcomes (E-Other): CBG at 1,5,10,30,60,120 min. Findings: No difference in pH or pCO2 between the 3 groups

Evans, 1976 p1098

Level of Evidence: 5- Not looking at infants with respiratory depression despite BMV, not looking at meaningful outcomes and naloxone dose used only 40% of that previously recommended by ILCOR
Quality: Fair- Randomized (methodology not described), non-blinded, no sample size calculations
Supportive/Neutral/Opposing: ± Favorable
Industry Funding: Not reported
Comments: Participants: Only healthy newborns with no respiratory depression enrolled. Controls were exposed to epidural anesthesia and no naloxone versus Pethidine exposed versus Pethidine exposed who also received naloxone. Do not say how long before delivery the Pethidine was given. Intervention/Comparator: Naloxone 0.04 mg/kg versus no drug versus control. Outcomes (E-Other): Compared alveolar PCO2, alveolar ventilation and ventilatory rate at 10 and 30 minutes. Findings: Naloxone treated neonates were comparable with epidural group although the effects of naloxone were diminishing at 30 minutes. No difference in RR.

Gerhardt, 1977 p1009

Level of Evidence: 5- Infants did not have respiratory depression in DR and dose of naloxone used is 10% of the previously recommended dose from ILCOR
Quality: Fair- Randomized (methodology not described), non-blinded, not powered
Supportive/Neutral/Opposing: ± Supportive
Industry Funding: None reported

Comments: Newborns of mothers who received pethidine within 3 hours of delivery.

Intervention/Comparator: Dose of naloxone 0.01 mg/kg IM versus placebo 30 minutes after birth at time of study. Outcomes (E-Other): respiratory rate, tidal volume, minute ventilation, end-tidal CO2, ventilatory response to inhalation of 4% CO2.

Findings: RR, TV in normal range prior to medication but there was decreased CO2 response curve which improved following naloxone. Differences don’t appear to be clinically meaningful.

Gerhardt, 1977 p971E

Level of Evidence: 5- Prospective cohort study examining effect of maternal opiate anesthesia on infant respiratory status at birth (no naloxone exposure)

Quality: Fair- Retrospective observational data, convenience sample

Supportive/Neutral/Opposing: Opposing- Merperidine exposed infants did not have respiratory depression thus naloxone unlikely to have benefit

Industry Funding: None reported

Comment: Participants: 24 term infants exposed to maternal meperidine IV within one hour prior to delivery.

Intervention/Comparator: None (Observational Study) Outcomes (E-Other): Apgar scores, RR, TV minute ventilation, end-tidal CO2, and ventilatory response to 4% CO2 and dynamic compliance 20-30 minutes after birth. Findings: Meperidine does not significantly alter Apgar scores, TV, minute ventilation, RR or ETCO2. The extent of respiratory center depression could be determined only by decreased ventilatory response to CO2.

Gill, 2007 p795E

Level of Evidence: 4- retrospective case series (large)

Quality: Fair

Supportive/Neutral/Opposing: Opposing (naloxone is most frequently NOT being used in the way that was recommended by ILCOR)

Industry Funding: None

Comments: Participants: Infants who received naloxone in the delivery room in certain regions of Australia.

Intervention/Comparator: Received naloxone in the delivery room Outcomes: Was naloxone given in compliance with ILCOR guidelines a)to infants with in utero exposure to opiate within 4 hours of delivery b) who had respiratory depression despite what would otherwise appear to be effective positive pressure ventilation, c) was the recommended dose and route used, d) was appropriate NICU monitoring provided after naloxone administration. Findings: ~20% of those infants given naloxone were not even exposed to in utero opiates, ~40% were given naloxone before any positive pressure ventilation was even tried, the dose was frequently correct but the route was IM which has the least evidence of efficacy, 80% of those who received naloxone received no monitoring after drug administration.

Herschel, 2000 p831E

Level of Evidence-4- Case series part prospective and part retrospective of 28 infants who received naloxone in the DR.
**Quality-Good**

**Supportive/Neutral/Opposing: Opposing**

**Industry Funding:** None

**Comments:** Purpose: To determine if naloxone is used according to AAP guidelines for newborn resuscitation. Findings: Over 50% of the time it was not used as recommended. No difference in Apgar scores between those exposed and not-exposed to opiates. Author’s raise the question that as there are no studies proving efficacy and we often use it not according to guidelines-should we be using it at all?

**Hodgkinson, 1978 p294**


**Level of Evidence:** 5-Naloxone given to mother’s prior to delivery rather than to a opiate-exposed newborn with respiratory depression

**Quality:** Fair-randomized, blinded trial but no a priori power calculations

**Supportive/Neutral/Opposing:** Supportive

**Industry Funding:** None

**Comments:** Participants: Term infants whose mothers delivered under general anesthesia

Intervention/Comparator: Group 1 (n=28) no maternal narcotic and no naloxone during labor, Group 2 (n=33) mothers received meperidine and no naloxone during labor, Group 3 (n=40) mothers received meperidine and 0.4 mg IV naloxone about 15 minutes prior to delivery.

Outcomes (E-Other): Early neonatal neurobehavioral scales at 2,4 and 24 hours of age

Findings: Higher scores in infants whose mother’s received naloxone in addition to opiate for approximately two hours.

**McGuire, 2002 pCD003483**


**Level of Evidence:** 5-Meta-analysis that found little actual data to support or refute current recommendation

**Quality:** Good

**Supportive/Neutral/Opposing:** Neutral

**Industry Funding:** None

**Comments:** Cochrane review of naloxone for narcotic-exposed newborn infants. The findings of the trials are of limited relevance in the clinical context for which naloxone has been recommended by NRP, AAP and ILCOR

**Moreland, 1980 p609**


**Level of Evidence:** 5-Observational cohort study assessing naloxone pharmacokinetics in term newborns

**Quality:** Fair

**Supportive/Neutral/Opposing:** Neutral-provides evidence that naloxone gets absorbed but does not speak to efficacy or harm

**Industry Funding:** None reported

**Comments:** Participants: Term infants (37-42 weeks) with narcotic exposure within four hours of delivery and normal pregnancy, labor and delivery (informed consent obtained)

Intervention/Comparator: IV naloxone 35 μg (n=6), IV naloxone 70 μg (n=6), IM naloxone 200 μg (n=17) given at 1 minute following birth
Outcomes (E-Other): Plasma Narcan levels over a period of 6-36 hours (that's what they say)

Findings: Both IV doses resulted in peak levels at 40 minutes and 3 hour half-life. IM Narcan resulted in peak level at .5-2 hours and then biphasic decline with levels declining rapidly between 1-4 hours and then slowly from four hours onward. Note: Methodology is confusing. Report sampling at 6-36 hours but mention data and levels at 5 and 40 minutes (also seem to have some babies as another report from Brice, JE-1979 but different drug levels reported). Included infants did not have respiratory depression at birth.

Singh, 2006 p385E

Level of Evidence: 5-appropriate naloxone use data extracted from paper looking at benefit of practical newborn resuscitation training programs for mid-wives-retrospective cohort data
Quality: Fair
Supportive/Neutral/Opposing: Opposing-Another paper documenting that over 50% of the time naloxone is given inappropriately (and that educational interventions can improve this)

Industry Funding: None
Comments: Participants: Newborns in a delivery room database from 3 different epochs, 1 before introduction of the resuscitation training course and 2 after. Intervention/Comparator: Mid-wife newborn resuscitation training course. Outcome (E-Other): Appropriate use of naloxone in the delivery room. Findings: Training course decreased the incidence of inappropriate use of naloxone; however, majority of naloxone is still given in the delivery room outside of guidelines.

Stile, 1987 p454E

Level of Evidence: 5- Observational cohort study assessing naloxone pharmacokinetics in preterm newborns
Quality: Fair-small sample size
Supportive/Neutral/Opposing: Neutral-provides evidence that naloxone gets absorbed but does not speak to efficacy or harm

Industry Funding: None
Comments: Participants: Premature infants (n=10) BW 1328 ± 402g and EGA 29.4 ± 2.8 weeks on day 4.5 ± 3.2 days of life. Intervention: 0.4 mg/kg naloxone IV bolus. Outcomes (E-Other): serum concentrations at 0, 5,15,30,60,120,240 minutes and at 12 hours. Findings: Half-life-70 ± 35 minutes. Note: Naloxone not given in the DR, the premature infants studied did not have respiratory depression, used 4X the dose previously recommended by ILCOR.

Welles, 1984 p617E

Level of Evidence: 5-Infants did not have respiratory depression and naloxone was given after arrival to the NICU (not in the delivery room).
Quality: Randomized (procedure not described), blinded, no sample size calculations
Supportive/Neutral/Opposing: Opposing

Industry Funding: None
Comments: Participants: Vigorous term infants (38-42 weeks) whose mothers received pethidine during labor, excluded if one minute Apgar < 8, five minute Apgar score < 9. Intervention/Comparator: 0.1 mg IM naloxone
(n=14) versus placebo (n=13) given at one hour of age. Outcome (E-Other): Behavioral scores at 12-24 hours and 72 hours. Findings: No differences found on Brazelton scores, Broussard scores were worse in naloxone exposed infants per mothers.

**Weiner, 1977 p228**


**Level of Evidence:** 5-only vigorous infants were included, dose was only 40% of that previously recommended by ILCOR

**Quality:** Fair-Randomized (methodology not described), blinded but no sample size calculation.

**Supportive/Neutral/Opposing:** Neutral

**Industry Funding:** None

**Comments:** Participants: Infants of mothers who received pethidine during labor at any time. Had to be term, SVD or easy forceps, Apgar >7 at one minute and cord UVC pH >7.25 (how did they know?). Intervention/Comparator: Dose of naloxone 0.04 mg total IV via UVC at one minute of life (n=10) versus placebo (n=18). Outcomes (E-Other): 0.5,4,8,12,24 and 48 hours Peak alveolar CO2, CO2 excretion, alveolar ventilation, feeding behavior, habituation to a sound stimulus. Findings: Alveolar CO2 lower and alveolar ventilation higher at 0.5 hours in naloxone group but not different at any other time point and no difference in other outcomes

Note: Opiate given any time during delivery, not depressed infants, dose different

**Weiner, 1977 p229**


**Level of Evidence:** 5- only vigorous infants were included, IM dose was not what was previously recommended by ILCOR

**Quality:** Fair-Randomized (methodology not described), blinded. No sample size calculation

**Supportive/Neutral/Opposing:** Neutral

**Industry Funding:** None

**Comments:** Participants: Infants of mothers who received pethidine during labor at any time. Had to be term, SVD or easy forceps, Apgar >7 at one minute and cord UVC pH >7.25 (how did they know?). Interventions: Naloxone 0.2 mg total IM at one minute of life (n=15) versus placebo (n=15). Outcomes (E-Other): 0.5,4,8,12,24 and 48 hours- Peak alveolar CO2, CO2 excretion, alveolar ventilation, feeding behavior, habituation to a sound stimulus. Findings: Naloxone infants had statistically significant reduction in mean alveolar CO2 tension and an increase in CO2 excretion and mean alveolar ventilation at all times up to 48 hours of birth (of questionable clinical relevance as both groups were in normal clinical range). The mean rate of habituation to a repeated auditory stimulus, sucking frequency, sucking pressure and consumption of milk were all higher in the naloxone infants up to 48 hours after birth. Notes: All CO2 were in normal range (38-42 mmHg in placebo and 32-33 mmHg in the narcan group, dose different but closer to current) *1980 letter to BMJ reports that at age 10-16 month follow-up no difference on Denver developmental screen and neurologic exam

**Other Publications Not Included**


**AAP Committee on Drugs-1980 Critique**

No controlled trials regarding the clinical scenario for which they recommend Narcan

**AAP Committee on Drugs-1990 Critique**
Dose change supported by Weiner’s 1977 paper that used higher IM dose to get sustained changes in ventilatory parameters and by wide range of doses 0.005 to 0.4 mg/kg that have been given without obvious short term ill effects. Still no controlled trials regarding the clinical scenario for which they recommend naloxone.

**Clark, 1976 p570**

**Level of Evidence-5** (data collected on giving naloxone to mother prior to delivery)
Quality: Poor- Non-randomized, non-blinded, no placebo group
Supportive/Neutral/Opposing: Neutral- Little difference in study infants and controls in blood gas values or neurobehavioral examination
Industry Funding: None reported
Comments: Participants: Laboring mothers who received merperidine during labor. Excluded preterm, breech pregnancies. Intervention/Comparator: Mothers were given various doses of naloxone (0.008-0.06 mg/kg) prior to delivery (not randomized). No control group for comparison. Outcomes (E-Other): Compared Apgar scores, blood gas values, neurobehavioral scores of newborn EXCLUDED due to poor quality design

**Deshpande, 2009 p115**

**Level of Evidence: 5**
Quality: Poor-single case report
Supportive/Neutral/Opposing: Opposing-caused harm
Industry Funding: None
Comment: Naloxone given to premature infant to reverse the effects of morphine overdose but resulted in immediate cardiac arrest.

**Fahnenstich, 2000 p836**

**Level of Evidence: 5-** observation from prospective series on Fentanyl administration in neonates so not the population we are really interested in but does show naloxone reversing the effects of opiates in neonates
Quality: Fair
Supportive/Neutral/Opposing: ± Favorable
Industry Support: None reported
Comments: Prospective case series, observational study. Participants: 8 of 89 preterm and term infants who received fentanyl for perioperative analgesia or procedures had complications of chest-wall rigidity or laryngospasm. Intervention: All were immediately reversed with naloxone 0.02-0.04 mg/kg IV (no comparison group). Outcome (E-Other): Relief of chest-wall rigidity or laryngospasm. Findings: Naloxone provided relief EVIDENCE EXCLUDED as not close to study population of interest to answer the PICO question
Fischer, 1974 p849E

**Level of Evidence:** 5- Study did not take place in the DR so these were not in utero opiate exposed newborns and dose used was 10% of that previously recommended by ILCOR

**Quality:** Poor  Non-randomized, non-blinded, no sample size calculations (very small numbers),

**Supportive/Neutral/Opposing:** Favorable

**Industry Funding:** None reported

**Comments:** Participants: Infants undergoing intubation for surgery. Controls received no opiate, no naloxone (n=5) however another group did receive opiate and no naloxone (n=5) versus a third group who received opiate and naloxone (n=6) at dose of 0.01 mg/kg IV. **Intervention:** Dose of naloxone was 0.01 mg/kg IV.

**Outcomes (E-Other):** tidal volume, minute volume. **Findings:** Opiate exposed infants who received naloxone had increased minute volume due to increased tidal volume (not rate) but all groups were within normal range.

EVIDENCE EXCLUDED due to poor quality

Gibbs, 1989 p159E

**Level of Evidence:** 5

**Quality:** Poor—single case report

**Supportive/Neutral/Opposing:** Opposing—caused harm

**Industry Funding:** None

**Comment:** Single case report of seizure in infant of opioid abuser who was given naloxone

Greer, 1995 p845E

**Greer, 1995 p845 Critique**
Non-randomized, non-blinded animal trial

IP Fentanyl resulted in naloxone-reversible, dose dependent decrease in frequency and amplitude of breathing of unanesthetized neonatal rats

Guinsburg, 2006 p121

**Guinsburg, 2006 p121 Critique**

Review article highlighting the evidence behind the 2005 ILCOR guidelines regarding use of naloxone for infants with in utero opioid exposure and respiratory depression. No new data is presented.

Handal, 1983 p438

**Level of Evidence:** 5- Provides naloxone pharmacokinetics in adults including onset of action IV versus SQ or IM
**Quality:** Fair - Collective review of naloxone use in emergency medicine  
**Supportive/Neutral/Opposing:** Supportive  
**Industry Funding:** None reported  
**Comments:** Provides adult data for IV, SQ and IM naloxone  
Data EXCLUDED-population too different from that of the PICO question

**McGuire, 2003 pF308**  

*McGuire, 2003 pF308 Critique*  
Rehash of Cochrane Collection findings therefore not included.

**Menahem, 2008 p467**  

*Menahem, 2008 p467 Critique*  
Letter to the editor advocating that naloxone be left available in the delivery room because some babies might really need it-no data provided. Authors of study being critiqued responded that the clinical perception that infants benefit has never been rigorously assessed and there is growing evidence of potential negative effects. Thus they feel the risks outweigh the benefits. No new data to support this contention either. Therefore this publication was not included.

**Refstad, 1980 p265**  

*Refstad, 1980 p265 Critique*  
Randomized trial of maternal pethidine versus pentazocine during labor. Noted that 4 pethidine versus 2 pentazocine exposed infants were depressed at delivery and received BMV followed by naloxone before 15 minutes of life (cord gases not suggestive of asphyxia). No information on response to naloxone. Other infants received naloxone at 15 minutes. Naloxone was noted to cause further reduction in end-tidal CO2 concentration (no real control group that did not receive drug).

**Kattwinkel, 1999 p71**  

*Kattwinkel J-1999 Critique*  
The advisory statement of ILCOR in 1999 provides NO references for recommendations for naloxone.

**Stephan, 1976 p635**


**Level of Evidence:** 5-animal study
Quality: Poor-Non-randomized, non-blinded, very poor use of statistics (using t-test to compare 9 different treatment groups), not powered

Supportive/Neutral/Opposing: Supportive

Industry Funding: None reported

Comments: Participants: 172 1-day old rabbits exposed to anoxia. Intervention/Comparators: Control, pethidine alone, pethidine + nalorphine 4 mg/kg, pethidine + nalorphine 1 mg/kg, pethidine + naloxone 0.1 mg/kg, naloxone alone 1 mg/kg, naloxone alone 0.1 mg/kg, nalorphine alone 4 mg/kg, nalorphine alone 4 mg/kg given i.p. 30 minutes prior to anoxia. Outcomes (E-Other): duration of dyspnea, preterminal apnea and gasping. Findings: Pethidine caused an increase in period of primary apnea and a decrease in the duration and rate of gasping. Naloxone completely abolished the respiratory depression produced by pethidine.

EXCLUDED due to poor quality of study designSrinivasan-1988

Rabbit pups responded to hypoxia (6% O2 in N2) with a biphasic respiratory pattern, an initial increase by 1 min followed by a decrease. Naloxone (0.8 mg/kg) was found to abolish the declining phase of hypoxia, showing a sustained increase of ventilation throughout the hypoxic challenge. Phentolamine (30 micrograms/kg), an alpha-blocker, had no effect on the normal hypoxic response. However, pretreating the pups with phentolamine and then administering naloxone resulted in a biphasic response to hypoxia. We propose that the naloxone effects on ventilation are mediated in conjunction with the adrenergic system. Rabbit pups exposed to hypoxia had sustained increase in ventilation throughout the hypoxic challenge.

Other Publications Not Included that suggest naloxone may block the physiologic effects of normally occurring enkephalins and endorphins and adversely affect the response of the newborn infant to stress.

Colman, 2001 p157

Colman, 2001 p157 Comments
Both mu1 and mu2 receptors contribute to opioid-induced respiratory depression during neonatal and adult life.

de-Castro, 1993 p747

de-Castro, 1993 p747 Comments

Laudenbach, 2001 p457

Laudenbach, 2001 p457 Comments


Mayock-1986 Comments
**Naltrexone had no effect on ventilation in neonatal animals with moderate-severe hypoxia.**


**Padbury-1987 Comments**  
Narcan at birth markedly augments catecholamine surge in term newborn lamb


**Sheldon-1984 Comments**  
Lamb fetuses received morphine and had respiratory efforts similar to neonatal breathing efforts. Naloxone blocked this response. Speculate that endorphine may have a role in the regulation of breathing in the fetal and newborn lamb.

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**Influence of morphine and naloxone on endothelin and its receptors in newborn piglet brain vascular endothelial cells: clinical implications in neonatal care.**

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**Young, RS-1984E**  

**Young-1984 Comments**  
Narcan exacerbated hypoxic-ischemic brain injury in rats.