**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

Allan R Mottram, Mohammed Alhelail

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Approved by ALS taskforce on webinar 09/21/09

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**Clinical question.**

“In adults with severe cardiovascular or life-threatening toxicity (prehospital or in-hospital) due to opioids (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival, neurologically-intact survival)?”

Clinical question revised as per workgroup conference call.

Standard care (C), as per the treatment algorithm, is defined as the following: Assisted ventilation, naloxone (IV, IO, IM, SQ, ET), tracheal intubation, nalmefene. 19

**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:** New

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**Conflict of interest specific to this question**

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

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**Search strategy (including electronic databases searched).**

PubMed, yield 620 hits: Search for combinations of MeSH terms (“heart arrest” or “arrhythmias, cardiac” or “signs and symptoms, respiratory” or “emergencies” or “overdose”) and (“analgesics, opioid” or “narcotics” or “opiate alkaloids” or “opioid related disorders”) and (“narcotic antagonists” or “naloxone” or “emergency treatment” or “intratracheal intubation” or “respiration, artificial”). Limits: English language publications with abstracts, clinical trials, meta-analysis, randomized-controlled trials, comparative studies, multi-center studies, validation studies.

TOXNET/Toxline, yield 111 hits: Search for combinations of terms “(heart arrest OR arrhythmias, cardiac OR signs and symptoms, respiratory or emergencies OR overdose) AND (analgesics, opioid OR narcotics OR opiate alkaloids OR opioid related disorders) AND (narcotic antagonists OR naloxone OR emergency treatment OR intratracheal intubation OR respiration, artificial)”. Limits: English language, PubMed citations excluded.

Central Register of Controlled Trials, yield 1: Search for the terms (“cardiac arrest” or “resuscitation”), and (“opioid” or “heroin” or “methadone” or “naloxone”).

EMBASE, yield 341 hits: Search for combinations of terms (“heart arrest” or “arrhythmias, cardiac” or “signs and symptoms, respiratory” or “emergencies” or “overdose”) and (“analgesics, opioid” or “narcotics” or “opiate alkaloids” or “opioid related disorders”) and (“narcotic antagonists” or “naloxone” or “emergency treatment” or “intratracheal intubation” or “respiration, artificial”). Limits: English language publications with abstracts.

AHA Master Library: Manual search for the terms cardiac arrest, resuscitation, opioids (including specific opioids), opioid antagonists (including specific opioid antagonists), intubation, and non-invasive ventilation

Manual search of references from current guidelines, articles, and textbooks.

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**State inclusion and exclusion criteria**

**Inclusion criteria:** Scientific papers assessing a specific intervention for resuscitation of the adult patient with severe cardiovascular or life-threatening toxicity from opioids. Opioid poisoning is defined as adverse effects from drugs acting on opioid receptors. The use of naloxone and descriptors of patient populations with terms such as altered mental status, coma, hypoventilation, apnea were considered surrogates for “severe cardiovascular or life-threatening toxicity”

**Exclusion criteria:** Single case reports, review papers, commentaries, pediatric studies. Scientific papers addressing non-opioid receptor mediated adverse effects or those occurring from drug-drug interactions such as serotonin syndrome, seizures, and sodium channel blockade.

Please note that while single case reports were excluded from evaluation for the worksheet, the citations are included at the end of the reference section.

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**Evidence Supporting Clinical Question**

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Evidence Neutral to Clinical Question

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Evidence Opposing Clinical Question

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

Key Points Based on Available Literature:

**Assisted ventilation:** Assisted ventilation prior to naloxone administration is documented as protocol in studies assessing other endpoints, primarily the efficacy of naloxone (LOE 1) [Kelly 2005, 24; Rupreht, 1983, 387], (LOE 3) [Wanger, 1998, 293], (LOE 4) [Leach, 1973, 21; Sporer, 1996, 660; Yealy, 1990, 902], and has been noted to decrease sympathetic outflow in opioid poisoned animals treated with naloxone (LOE 5) [Mills, 1990, 238].

**Naloxone:** The safety and efficacy of naloxone in opioid overdosed patients is supported by evidence from human studies (LOE 4) [Buajordet, 2004, 19; Evans, 1973, 452; Kaplan, 1999, 42; Leach, 1973, 21; Osterwalder, 1996, 409; Sporer, 1996, 660; Yealy, 1990, 902]. Additional support for safety and efficacy comes from studies assessing alternate routes of naloxone administration (LOE 1) [Kelly, 2005, 24], (LOE 3) [Wanger, 1998, 293].
Cardiopulmonary Arrest: usefulness in some patients, it cannot be recommended as a standard treatment based on the weight of evidence (LOE 5) [Boeuf, 2003, CD004443].

Shock: Naloxone routes of administration: Those that are supported include intravenous (LOE 4) [Sporer, 1996, 660; Evans, 1973, 452; Leach, 1973, 21], intranasal (LOE 1) [Kelly, 2005, 24], intramuscular (LOE 1) [King, 2005, 24] (LOE 4) [Sporer, 1996, 660; Leach, 1973, 21], intralingual (LOE 5) [Maio, 1984, 1087], and endotracheal (LOE 5) [Greenberg, 1980, 289]. Note that Sporer, 1996, 660 is considered neutral (LOE 2) for the specific question comparing intranasal to intramuscular routes, and supporting (LOE 4) for naloxone efficacy using either route. Note that Robertson, 2009, 512 B,E is considered neutral (LOE 3) for the specific question comparing intravenous to intramuscular routes, and supporting (LOE 4) for naloxone efficacy using either route.

Shock: One Cochrane review of naloxone for non-opioid related shock concluded that while naloxone did increase blood pressure, and may be useful in some patients, it cannot be recommended as a standard treatment based on the weight of evidence (LOE 5) [Boeuf, 2003, CD004443].

Cardiopulmonary Arrest: There are no human or animal studies addressing specific interventions outside of the standard of care for opioid induced cardiopulmonary arrest. Animal models of opioid and non-opioid related cardiac arrest are equivocal as to benefit from naloxone (LOE 5) [Boyd, 2006, 1271; Gervais, 1997, 255; Rothstein, 1085, 198].

Acknowledgements: None

Reviewer Conclusion: The study indicates that despite a (poorly described) significant side effect profile, naloxone is safe and efficacious for pre-hospital use. Supporting; LOE 4; Quality Poor


Reviewer Summary: Randomized, controlled, unblinded study of the effect of naloxone, in comparison to saline, on resuscitation rate in a rat asphyxia model of cardiac arrest. The high dose naloxone group (1mg/kg) demonstrated increased resuscitation rates compared to saline control. **Reviewer Conclusion:** The study demonstrates that high dose naloxone improves survival in a rat asphyxia model of cardiac arrest, however the applicability of this study to human opioid overdoses is severely limited. Neutral; LOE 5; Quality Fair


Reviewer Summary: Randomized, controlled, unblinded study of the effect of naloxone (1mg/kg), in comparison to saline or epinephrine (0.4 mg/kg), on resuscitation rate in a rat asphyxia model of cardiac arrest. The naloxone and epinephrine groups demonstrated increased resuscitation rates compared to saline control. The rate of return of spontaneous circulation was faster in the epinephrine group. **Reviewer Conclusion:** The study demonstrates that high dose naloxone improves survival in a rat asphyxia model of cardiac arrest, but is not as effective as epinephrine. The applicability of this study to human opioid overdoses is severely limited. Neutral; LOE 5; Quality Fair


Reviewer Summary: A retrospective chart review of EMS records comparing the number of non-fatal presumed heroin overdoses who were admitted to hospital to those who were not admitted as a function of whether or not they received bystander CPR. There was a small but statistically significant decrease in hospitalization for those that received CPR, meaning that they recovered from their event and did not require admission. The authors conclude that provision of bystander CPR is associated with an improvement in clinical outcomes such that a proportion of patients do not require hospital admission. This paper has serious flaws in that bystander CPR is poorly defined, quality of bystander CPR is not controlled, and this intervention is not observed. Most significantly, if serious opioid overdose occurs such that CPR is indicated one would expect the hospital admission rate to increase (ie: survival to hospital admission), not decrease. Lastly, there was inadequate patient follow-up. **Summary:** The paper indicates that there may be a positive effect of bystander involvement. Supporting, LOE 4, Quality Poor


Reviewer Summary: A case series of the safety and efficacy of naloxone for self-reported opioid overdose in comparison to non-opioid overdoses. Controls were self-reported overdoses of non-narcotic sedatives. Confounding factors were self-report and administration of nalorphine in a subset of patients prior to naloxone. The study was not blinded and had significant potential confounding factors. **Reviewer Conclusion:** This study indicated that naloxone was safe and effective, while lacking significant adverse effects in a small convenience sample of overdose patients. Supporting; LOE 4; Quality Fair


Reviewer Summary: An experimental study using pentobarbital anesthetized rabbits to assess the efficacy of endotracheal administration of naloxone to counter morphine induced bradypnea. Questionable statistics and an inadequate sample size hinder applicability of the positive results. **Reviewer Conclusion:** The study indicates that endotracheal naloxone may be effective in the absence of alternative routes of administration. Supporting; LOE 5; Quality Poor


Reviewer Summary: Randomized, controlled, blinded study of the effect of high dose naloxone (10 mg/kg) + epinephrine on cerebral and myocardial blood flow in a swine cardiac arrest model. Naloxone + epinephrine groups failed to demonstrate improved cerebral or myocardial blood flow versus saline + epinephrine control. However, they did have increased mean arterial pressure. **Reviewer Conclusion:** The study demonstrates that high dose naloxone augments blood pressure in a swine model of cardiac arrest, but fails to improve cerebral or myocardial blood flow. The applicability of this study to human opioid overdoses is severely limited. Supporting; LOE 5; Quality Good


Reviewer Summary: Uncontrolled, non-randomized, open label study of
the effectiveness and safety of IV nalmefene for suspected narcotic overdose. The represented data indicates that nalmefene may be safe and effective however the study has several significant flaws. Beyond study design problems, significant confounders were not controlled for. For example, not all patients had opioid exposure confirmed, and an unspecified “many patients were intubated”, which calls in to question the value of the stated outcome measures. **Reviewer Conclusion:** The study indicates that nalmefene may be a safe and effective opioid antagonist. Supporting; LOE 4; Quality Poor

12. Kaplan JL, Marx JA, Calabro JJ, Gin-Shaw SL, Spiller JD, Spivey WL, Gaddis GM, Zhao N, Harchelroad FP. Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. *Annals of Emergency Medicine.* 1999;34:42-50. **Reviewer Summary:** Randomized, controlled, double blinded trial to evaluate the efficacy, safety, and withdrawal symptoms in patients treated with nalmefene, in comparison to naloxone, for suspected opioid overdose. The major limitation of this study was difficulty in enrolling patients that were purely, or primarily, opioid overdosed for randomization to a treatment group. The majority of patients that were opioid positive on toxicology screening were identified as having central nervous system depressant drug co-ingestion. Furthermore, it is likely that not all opioid exposed patients were identified by toxicological screening due to inherent limitations of the assay that was utilized (and not specified). **Reviewer Conclusion:** The study indicates that in this study group of opioid exposed patients, nalmefene performed as well as, but not better than, naloxone. Supporting; LOE 1; Quality Fair

13. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust.* 2005;182:24-27. **Reviewer Summary:** Randomized, controlled, unblinded trial of intranasal versus intramuscular naloxone for suspected out of hospital opioid overdose. Limitations include being a non-blinded trial, lack of confirmation of opioid overdose, and potential for co-ingestion. Patients receiving intranasal naloxone, in comparison to intramuscular naloxone, had a slower time to respiration rate greater than 10, and were less likely to have spontaneous respirations at 8 minutes. **Reviewer Conclusion:** The study indicates that while intranasal naloxone is effective, it is less effective than intramuscular naloxone. Intranasal naloxone may be an option in unique circumstances. Supporting; LOE 1; Quality Poor

14. Leach MW. Naloxone: A New Therapeutic and Diagnostic Agent for Emergency Use. *JACEP.* 1973;2:21-23. **Reviewer Summary:** Case series of 8 patients receiving naloxone for suspected opioid overdose with apparent good result. Confounding factors are acknowledged but not controlled for, and follow-up duration is not clear. **Reviewer Conclusion:** The case series reports early positive experience with naloxone in suspected opioid overdose in the emergency department. Supporting; LOE 4; Quality Poor

15. Maio RF, Grier JC, Clark MR, Gifford G, Wiesenstien JG. Intralingual naloxone reversal of morphine-induced respiratory depression in dogs. *Annals of Emergency Medicine.* 1984;13:1087-1091. **Reviewer Summary:** An observational study of 4 dogs given intralingual naloxone for induced opioid toxicity with expected increase in minute ventilation. **Reviewer Conclusion:** This small observational study demonstrates that intralingual administration of naloxone may be effective in dogs. Supporting; LOE 5; Quality Poor

16. Mills CA, Flacke JW, Miller J, Davis LJ, Bloor BC, Flacke WE. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. *Anesth Analg.* 1988;67:730-736. **Reviewer Summary:** Non-randomized controlled experiment of the cardiovascular effects of fentanyl reversal by naloxone in dogs at varying arterial carbon dioxide tension. Hypercapnic conditions resulted a more rapid and magnified elevation of catecholamine levels during fentanyl reversal as compared to normocapnic and hypocapnic conditions. **Reviewer Conclusion:** The study suggests that acute reversal of opioid intoxication during conditions of normocapnea or mild hypocapnea may reduce sympathetic outflow as compared to reversal in the the hypercapnic state. Supporting; LOE 5; Quality Fair

17. Mills CA, Flacke JW, Flacke WE, Bloor BC, Liu MD. Narcotic reversal in hypercapnic dogs: comparison of naloxone and nalbuphine. *Canadian journal of anaesthesia = Journal canadien d’anesthésie.* 1990;37:238-244. **Reviewer Summary:** Non-randomized controlled experiment of the cardiovascular effects of fentanyl reversal in hypercapnic dogs by naloxone in comparison to nalbuphine. Under hypercapnic conditions the mixed agonist/antagonist nalbuphine induced less hypertension compared to naloxone, and did not show a significant increase in plasma catecholamine levels compared to baseline levels. **Reviewer Conclusion:** The study suggests that the mixed agonist/antagonist nalbuphine causes less sympathetic outflow as compared to naloxone during fentanyl reversal in hypercapnic dogs. Supporting; LOE 5; Quality Fair

use for suspected acute heroin or heroin mixture intoxications. 453 patients received naloxone. Six of 453 (1.3%) patients had severe adverse effects within five minutes after naloxone administration. These patients were critically ill pre-naloxone, most had significant co-morbidities, and there were significant differences in the types of adverse reactions. **Reviewer Conclusion:** The study indicates that the adverse effects in this small group of patients may have been related to naloxone administration, although other factors are also likely. Naloxone was administered safely in the majority of patients. Supporting; LOE 4; Quality Fair

19. Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors.* 2009;13:512-515. **Reviewer Summary:** Retrospective analysis of naloxone use for suspected opioid poisoned patients before and after a change in pre-hospital protocol. The protocol changed from intravenous naloxone to intranasal naloxone as the first line route of naloxone administration. 154 patients enrolled, 104 received intravenous naloxone, 50 received intranasal. Time from initial patient contact to response similar between groups, time from drug administration to clinical effect faster in the intravenous group. The discrepancy seems related to time to establish intravenous access. **Reviewer Conclusion:** The paper supports the use of naloxone and the use of both the intravenous and intranasal routes. It is equivocal regarding superiority of either intravenous or intranasal routes. For the use of naloxone the paper is Supporting, LOE 4, Quality Fair. For comparison of intravenous versus intranasal the paper is Neutral, LOE 3, Quality Fair.

20. Rothstein RJ, Niemann JT, Rennie CJ, Suddath WO, Rosborough JP. Use of naloxone during cardiac arrest and CPR: potential adjunct for postcountershock electrical-mechanical dissociation. *Ann Emerg Med.* 1985;14:198-203. **Reviewer Summary:** Randomized, controlled, non-blinded dog study of the effect of naloxone (5 mg/kg) during closed chest cardiopulmonary resuscitation, in comparison to epinephrine (1mg). Ventricular fibrillation was electrically triggered in all animals, then either naloxone or epinephrine was administered following 15 minutes of chest compressions. No animal in the naloxone group was successfully defibrillated until they later received epinephrine. The epinephrine group was defibrillated into electromechanical dissociation, and converted to a perfusing rhythm following a later dose of naloxone. Naloxone did not improve hemodynamics during ventricular fibrillation, whereas epinephrine did. **Summary:** In this dog model of electrically induced cardiac arrest, naloxone failed to improve hemodynamics during chest compressions and did not facilitate defibrillation. Naloxone facilitated conversion from electromechanical dissociation to a perfusing rhythm when administered to the group that had received epinephrine. Neutral; LOE 5; Quality Fair.

21. Rupreht J, Dworacek B, Oosthoek H, Dzoljic MR, Valkenburg M. Physostigmine versus naloxone in heroin-overdose. *J Toxicol Clin Toxicol.* 1983;21:387-397. **Reviewer Summary:** Prospective randomized trial comparing the efficacy and side effect profile of physostigmine versus naloxone for heroin overdose. The physostigmine group was less likely to experience withdrawal symptoms, however was more likely to require subsequent naloxone, and had persistent, though improved, respiratory acidosis. Significant adverse effects of physostigmine were not demonstrated in the study, however the sample size is not adequate to detect such effects, which are likely in an undifferentiated overdose population. **Reviewer Conclusion:** This study demonstrated that physostigmine was inferior to naloxone in reversing the sedative and respiratory effects of heroin. Considering these results in conjunction with physostigmine’s narrow therapeutic index, the results do not justify it’s use on the grounds of less withdrawal symptoms. Opposing; LOE 1; Fair

22. Sporer K, Firestone J, Isaacs SM. Out-of-hospital treatment of opioid overdoses in an urban setting. *Acad Emerg Med.* 1996;3:660-667. **Reviewer Summary:** Retrospective review of 726 presumed opioid overdose emergency medical services patient records to determine the out of hospital therapy and outcome. Response rates to intramuscular versus intravenous naloxone were also assessed. The standard paramedic protocol was high flow oxygen via bag-valve-mask, 2mg of IM or IV naloxone with a repeat dose in 1-2 minutes as necessary, blood glucose, and intubation followed by standard ACLS interventions as needed. 609 (84%) patients had an initial pulse and blood pressure, of which 94% responded within 5 minutes to naloxone therapy. The most common dose was 2mg, with 35% receiving more than 2 mg. Response rates for IV vs IM naloxone were similar (90% vs 94% p=NS) The most common documented side effect was the requirement for restraints in 7%. Of the 16 (2.7%) patients in cardiopulmonary arrest none survived to hospital discharge. A subset of 444 (74%) patients had additional hospital records available. Of this subset 97% were released after ED evaluation and observation and 12 (2.7%) were admitted for a variety of reasons (4 with NCPE). **Reviewer Conclusion:** This study demonstrated the safety and efficacy of assisted ventilation and naloxone (IM and IV) for out of hospital opioid overdose in patients presenting with initial heart rates and
blood pressures. It also demonstrated equivalence for IM vs IV naloxone. For naloxone use overall it is Supporting; LOE 4; Quality Fair. For IM vs IV naloxone it is Neutral; LOE 2; Quality Fair.

23. Wang Y, Gao L, Meng L. Small-dose naloxone combined with epinephrine improves the resuscitation of cardiopulmonary arrest. *The American Journal of Emergency Medicine*. 2008;26:898-901. **Reviewer Summary:** Randomized, non-blinded, controlled study of the effects of saline (1 mL) versus epinephrine (5μg/100gm) versus naloxone (1mg/kg) + epinephrine (5μg/100gm) in a rat asphyxia model of cardiac arrest. Return of spontaneous circulation was significantly higher, and time to return of spontaneous circulation shorter, in the epinephrine + naloxone and epinephrine group (combination better than epinephrine only). **Reviewer Conclusion:** The study demonstrates that in a rat model of asphyxiial cardiac arrest high dose naloxone improves rate of return of spontaneous circulation and decreases time to return of spontaneous circulation. Neutral; LOE 5; Quality Fair

24. Wang Y, Gao L, Meng L. Naloxone combined with epinephrine decreases cerebral injury in cardiopulmonary resuscitation. *The Journal of emergency medicine*. March 4, 2009. Epub ahead of print. **Reviewer Summary:** This study appears to be a second publication from the data in Wang 2008, above. Additional data provided are neurodeficit scores at 3 days post-resuscitation on surviving animals. While there is a trend toward improved neurodeficit scores in the group receiving naloxone, it does not appear to be statistically significant (p values not reported for this variable). **Reviewer Conclusion:** The study in a rat model of asphyxiial cardiac arrest again reports the data from Wang 2008, and fails to demonstrate a statistically significant improvement in neurodeficit scores for the group receiving naloxone, though there does appear to be a positive trend. Neutral; LOE 5; Quality Fair

25. Wanger K, Brough L, Macmillan I, Goulding J, MacPhail I, Christenson JM. Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med*. 1998;5:293-299. **Reviewer Summary:** Prospective sequential cohort study (historical controls that were prospectively collected) assessing the time interval from arrival at patient side to respiratory rate greater than 10, and duration of bag-valve-mask ventilation, for those treated with 0.8mg SC naloxone vs 0.4mg IV naloxone in the field. Major limitations of this study include that two different doses were used, and significant loss to follow-up (>50%). More significantly, 16 out of 18 of those who failed the initial SC naloxone dose received IV naloxone but were still included in the SC group for analysis, having the effect of reducing the reported duration to onset of effect reported for SC naloxone. As a result of this methodological flaw the authors inappropriately failed to reject their null hypothesis, a type II error. **Reviewer Conclusion:** Contrary to the authors conclusion the paper does not provide evidence that SC naloxone is equivalent to IV naloxone, even when the time to establish an IV is considered. SC naloxone may be a viable alternative in the setting of no IV access, however conclusions regarding this question requires knowledge of SC naloxone efficacy in comparison to other alternative routes of administration. Neutral; LOE 3; Quality Fair

26. Yealy DM, Paris PM, Kaplan R, Heller MB, Marini SE. The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med*. 1990;19:902-905. **Reviewer Summary:** Retrospective chart review of EMS records over a one year period where naloxone was administered to assess the safety of naloxone use by paramedics as measured by the prevalence of vomiting, seizures, significant hypertension, hypotension, and cardiac arrest following naloxone administration. Patients were administered naloxone if they had acutely altered level of consciousness with a normal blood sugar (or significant circumstantial evidence of opioid use prior to glucose determination), or lack of response to dextrose infusion. Of the 813 charts reviewed, only 7.4% of patients developed improvement in their level of consciousness within 5 minutes. One patient out of 813 developed a seizure, two vomited, 8 developed hypertension, one developed hypotension. As only 7.4% of patients overall, and only 1/12 patients in the group developing adverse effects, demonstrated an expected response to naloxone it is clear that this group was poorly selected for antidotal therapy. **Reviewer Conclusion:** The study demonstrated that naloxone use in patients with altered mental status is fairly safe, but the generalizability to opioid poisoned patients is limited. Supporting; LOE 4; Quality Fair

Single Case Reports Excluded from Evaluation for the Worksheet, Included Here for Reference Purposes.


