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| Question | |
| **Should Bystander naloxone administration (intramuscular or intranasal), in addition to standard CPR vs. Standard CPR only be used for Adults with suspected opioid-associated cardio / respiratory arrest ?** | |
| **Population:** | Adults with suspected opioid-associated cardio / respiratory arrest |
| **Intervention:** | Bystander naloxone administration (intramuscular or intranasal), in addition to standard CPR |
| **Comparison:** | Standard CPR only |
| **Main outcomes:** | Survival outcomes |
| **Setting:** | Pre-hospital setting |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | Castren, Perkins & Olasveengen (none) |

# Assessment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Deaths from drug overdose are an increasing public health burden in many countries. In the United States alone > 70 000 deaths were attributed to drug overdose in 2017, and the US Centers of Disease Control and Prevention considers the opioid overdose epidemic is the public health crisis of our time. (www.cdc.gov/opioids) |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | There is no direct evidence comparing outcomes for patients with opioid induced respiratory or cardiac arrest treated with naloxone in addition to standard CPR compared to those treated with CPR alone. In a meta-analysis of crude unadjusted data from four studies including 66 patients, 39/39 patients who received naloxone after a opioid overdose recovered compared to 24/27 who did not receive naloxone.(Giglio 2015) At the population level, there is evidence to demonstrate improved outcomes in communities after implementation of various naloxone distribution schemes. A recent systematic review identified 22 observational studies evaluating the effect of overdose education and naloxone distribution using Bradford Hill criteria, and found causation between implementation of these programs and decreased mortality rates to be likely. (McDonald 2016) | Respiratory or cardiac arrest diagnosis is not always straight forward, and lay rescuers would be expected to have a high suspicion of drug overdose. Naloxone administration is likely to have preventive effects if given after a drug overdose which has not yet manifest into respiratory or cardiac arrest. This strengthens the anticipated desirable effects. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | There is no direct evidence comparing outcomes for patients with opioid induced respiratory or cardiac arrest treated with naloxone in addition to standard CPR compared to those treated with CPR alone. In a meta-analysis of crude unadjusted data from four studies including 66 patients, 39/39 patients who received naloxone after a opioid overdose recovered compared to 24/27 who did not receive naloxone.(Giglio 2015) At the population level, there is evidence to demonstrate improved outcomes in communities after implementation of various naloxone distribution schemes. A recent systematic review identified 22 observational studies evaluating the effect of overdose educationn and naloxone distrubution using Bradford Hill criteria, and found causation between implementation of these programs and decreased mortality rates to be likely. (McDonald 2016) | Very few side-effects from Naloxone reported.(Wermeling 2015 20) While it is possible that bystanders might spend valuable time finding and administering Naloxone instead of starting CPR during respiratory or cardiac arrest, lack of reports of harm from large scale implementation of Naloxone distribution schemes indicate this is probably likely to be a big problem. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No studies directly assessing the clinical treatment question was identified. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  | There is no important uncertainty in how much people value saving more lives from opioid overdose. |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know | As there is no formal evaluation of naloxone + CPR vs. CPR alone in opioid overdose, it is not possible to formally balance desirable and undesirable effects of naloxone administration. by lay persons. As a response to the growing epidemic, naloxone has been widely distributed by health care authorities to lay people in various opioid overdose prevention schemes. Overall these programs report beneficial outcomes at the population level. We consider it very likely that the desirable effects outweigh undesirable effects. |  |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know | Available research suggest that cost associated with naloxone distribution and overdose prevention education is much less than costs associated with untreated drug overdose. A study from North Carolina found a 2742 USD benefit for every dollar spent on their naloxone kit distribution program. (Neumann 2019 107536) |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ● Moderate ○ High ○ No included studies | There is a growing body of literature evaluating the cost effectiveness of naloxone distribution programs witch report costs related to various education and naloxone distribution strategies. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies | Available research suggest that cost associated with naloxone distribution and overdose prevention education is much less than costs associated with untreated drug overdose. A study from North Carolina found a 2742 USD benefit for every dollor spent on their naloxone kit distribution program. (Neumann 2019 107536) |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know |  | Although opioid dependency afflicts broadly, vulnerable groups are over-represented on overdose statistics, and interventions to treat or present overdose deaths will positively impact health equity. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Overdose education and Naloxone distribution programs are widely implemented and are acceptable to key stakeholders. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Overdose education and Naloxone distribution programs are widely implemented and are acceptable to key stakeholders. |

# Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | Moderate | Large |  | Varies | **Don't know** |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **Don't know** |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | **Large savings** | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | No included studies |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | **Increased** | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Type of recommendation

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| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
| ○ | ○ | ○ | **●** | ○ |

# Conclusions

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| Recommendation |
| We suggest naloxone be used by lay rescuers in attempting resuscitation in suspected opioid related respiratory or circulatory arrest. (Weak recommendation, based on expert consensus) |
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| Justification |
| Health care authorities in many parts of the world acknowledge opioid dependency and overdose as a major public health problem, and overdose education and naloxone distribution programs are being widely implemented. As opioid dependency and overdose afflicts many young people, significantly impacting on their life-expectancy and ability to contribute to society - the public health issue is particularly costly left untreated.    While the role of naloxone in cardiac arrest is unclear, the exact diagnosis is difficult in the opioid overdose setting. A victim may gradually progress from unconsciousness to respiratory to circulatory arrest without a rescuer being able to confidently distinguish between these stages. Naloxone reverses the effects of opioids, and administered early will prevent progression to cardiac arrest. While it is important Naloxone administration does not delay recognition of cardiac arrest and initiation of CPR, it is a drug with few reported side effects that has undisputable benefit in the setting of reduced consciousness and breathing after opioid overdose, It is therefore our expert opinion that naloxone should be administered during attempting resuscitation in suspected opioid related respiratory or circulatory arrest whenever readily available. |

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| Subgroup considerations |
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| Implementation considerations |
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| Monitoring and evaluation |
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| Research priorities |
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