Overdose Prevention Literature Review

Recently published research on overdose prevention, naloxone and related topics.

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WA State Project to Prevent Prescription Drug/Opioid Overdose (WA-PDO)

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I. INTERVENTIONS IN THE EMEREGNCY DEPARTMENT

Yes, not now, or never: an analysis of reasons for refusing or accepting emergency department-based take-home naloxone. Kestler A, Giesler A, Buxton J, Meckling G, Lee M, Hunte G, Wilkins J, Marks D, Scheuermeyer F. CJEM. 2018 May 23:1-9. doi: 10.1017/cem.2018.368. [Epub ahead of print]

CLINICIAN'S CAPSULE: What is known about the topic? Not all patients at risk of opioid overdose accept emergency department (ED)-based take-home naloxone (THN). What did this study ask? Why do at-risk ED patients refuse or accept THN? What did this study find? **Those refusing THN felt: 1) not at risk of overdose; or 2) their ED visit was not the right time or place for THN. Those accepting THN wanted to save the lives of others.** Why does this study matter to clinicians? Those refusing ED THN may accept THN elsewhere if referred to appropriate community services for overdose risk education and THN distribution.

> *Comment: It's important to understand the reasons why people do not accept naloxone in the ED. Some people are at low risk, so that needs to be acknowledged when prioritizing interventions. Others are at risk, such as those using prescribed opioids, but both providers and patients may underestimate that risk. For these individuals, it's important to avoid language such as "just in case" and even the word "overdose" which is seen as stigmatizing. Referrals to community based naloxone are always appropriate but significantly less likely to result in a person obtaining naloxone compared to directly dispensing it to a person in the ED. That said, it is important that we do what we can to make naloxone acceptable and accessible.*

Naloxone Use Among Emergency Department Patients with Opioid Overdose. Marco CA, Trautman W, Cook A, Mann D, Rasp J, Perkins O, Ballester M. J Emerg Med. 2018 May 16. pii: S0736-4679(18)30360-3. doi: 10.1016/j.jemermed.2018.04.022. [Epub ahead of print]

BACKGROUND: Emergency department (ED) visits for unintentional opioid overdoses have increased dramatically. Naloxone hydrochloride (Narcan®) is an opioid antagonist commonly used to treat these overdoses.

OBJECTIVE: This study was undertaken **to identify experiences regarding naloxone use among ED patients with opioid overdose.**

METHODS: This prospective survey study was conducted at an urban level I trauma center. A survey was administered to eligible ED patients after unintentional opioid overdose. This study identified current and previous use of naloxone among ED patients with opioid overdose.

RESULTS: Eight-nine ED patients with accidental overdose of opioids participated (90% participation rate). Most participants reported a history of opioid overdose (n = 62 [70%]). A significant minority stated they have had access to a naloxone kit (n = 28 [31%]). **Most participants with a naloxone kit stated that their frequency and dosage**

of opiate use did not change after access to naloxone (n = 17 [63%]), and a few used opiates more often (n = 1 [4%]) or less often (n = 9 [33%]). There was a significant negative correlation between total dose and age (Spearman ρ -0.27; p = 0.01). There was no association between dose and sex.

CONCLUSIONS: Many patients presenting with opioid overdose have had a history of opioid overdose. Patients with opioid overdose required a highly variable dose of naloxone. Higher doses of naloxone were associated with lower age. **Despite widespread availability of naloxone to consumers, a minority of patients in this study reported access to naloxone. Participants who had access to a naloxone kit stated that their frequency and dosage of opioid use did not change.**

> *Comment: Despite widespread efforts to distribute naloxone nationally, actual naloxone possession rates among those at highest risk for overdose still vary widely (as reported below by Gjersing et al. in their Norwegian study). This study supports other research indicating that naloxone access in and of itself does not increase opioid use, countering the often stated claim that people with naloxone will "push the envelope" and use more opioids.*

Adoption and Utilization of an Emergency Department Naloxone Distribution and Peer Recovery Coach Consultation Program. Samuels EA, Baird J, Yang ES, Mello M. Acad Emerg Med. 2018 Aug 3. doi: 10.1111/acem.13545. [Epub ahead of print]

OBJECTIVE: Rising rates of opioid overdose deaths require innovative programs to prevent and reduce opioid-related morbidity and mortality. **This study evaluates adoption, utilization, and maintenance of an emergency department (ED) take-home naloxone and peer recovery coach consultation program for ED patients at risk of opioid overdose.**

METHODS: Using a Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework, we conducted a retrospective provider survey and electronic medical record (EMR) review to evaluate implementation of a naloxone distribution and peer recovery coach consultation program at two EDs. Provider adoption was measured by self-report using a novel survey instrument. EMRs of discharged ED patients at risk for opioid overdose were reviewed in three time periods: preimplementation, postimplementation, and maintenance. Primary study outcomes were take-home naloxone provision and recovery coach consultation. Secondary study outcome was referral to treatment. Chi-square analysis was used for study period comparisons. Logistic regression was conducted to examine utilization moderators. Poisson regression modeled utilization changes over time.

RESULTS: Most providers reported utilization (72.8%, 83/114): 95.2% (79/83) **provided take-home naloxone** and 85.5% (71/83) **consulted a recovery coach.** There were 555 unique patients treated and discharged during the study periods: 131 preimplementation, 376 postimplementation, and 48 maintenance. Postimplementation **provision of take-home naloxone increased from none to more than one-third** (35.4%, p < 0.001), **one-third received consultation with a recovery coach** (33.1%, 45/136), and **discharge with referral to treatment increased from 9.16% to 20.74%** (p = 0.003). **Take-home naloxone provision and recovery coach consultation did not depreciate over time.**

CONCLUSIONS: **ED naloxone distribution and consultation of a community-based peer recovery coach are feasible and acceptable and can be maintained over time.**

II. OPIOID USE DISORDER TREATMENT AS PREVENTION

Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Ma J, Bao YP, Wang RJ, Su MF, Liu MX, Li JQ, Degenhardt L, Farrell M, Blow FC, Ilgen M, Shi J, Lu L. Mol Psychiatry. 2018 Jun 22. doi: 10.1038/s41380-018-0094-5. [Epub ahead of print]

ABSTRACT: Opioid use disorder (OUD) is associated with a high risk of premature death. Medication-assisted treatment (MAT) is the primary treatment for opioid dependence. We comprehensively **assessed the effects of different MAT-related characteristics on mortality among those with OUD by a systematic review and meta-analysis.** The all-cause and overdose crude mortality rates (CMRs) and relative risks (RRs) by treatment status, different type, period, and dose of medication, and retention time were pooled using random effects, subgroup analysis, and meta-regression. Thirty cohort studies involving 370,611 participants (1,378,815 person-years) were eligible in the meta-analysis. From 21 studies, the pooled all-cause CMRs were 0.92 per 100 person-years (95% CI: 0.79-1.04) while receiving MAT, 1.69 (1.47-1.91) after cessation, and 4.89 (3.54-6.23) for untreated period. Based on 16 studies, the pooled overdose CMRs were 0.24 (0.20-0.28) while receiving MAT, 0.68 (0.55-0.80) after cessation of MAT, and 2.43 (1.72-3.15) for untreated period. **Compared with patients receiving MAT, untreated participants had higher risk of all-cause mortality** (RR 2.56 [95% CI: 1.72-3.80]) **and overdose mortality** (8.10 [4.48-14.66]), and **discharged participants had higher risk of all-cause death** (2.33 [2.02-2.67**]) and overdose death** (3.09 [2.37-4.01]). The all-cause CMRs during and after opioid substitution treatment with methadone or buprenorphine were 0.93 (0.76-1.10) and 1.79 (1.47-2.10), and corresponding estimate for antagonist naltrexone treatment were 0.26 (0-0.59) and 1.97 (0-5.18), respectively**. Retention in MAT of over 1-year was associated with a lower mortality rate than that with retention ≤1 year** (1.62, 1.31-1.93 vs. 5.31, -0.09-10.71). Improved coverage and adherence to MAT and post-treatment follow-up are crucial to reduce the mortality. Long-acting naltrexone showed positive advantage on prevention of premature death among persons with OUD.

> *Comments: This study reinforces two important points: medications for opioid use disorder significantly reduce both overdose and all-cause mortality and longer retention decreases mortality significantly more than retention less than one year.*

Characteristics of Patients With Opioid Use Disorder Associated With Performing Overdose Reversals in the Community: An Opioid Treatment Program Analysis. Katzman JG[1], Greenberg NH, Takeda MY, Moya Balasch M. J Addict Med. 2018 Oct 9. doi: 10.1097/ADM.0000000000000461. [Epub ahead of print]

OBJECTIVE: The primary outcome of this study is to **identify characteristics of study participants in a large opioid treatment program (OTP) for opioid use disorder (OUD) who used take-home naloxone to perform 1 or more opioid overdose (OD) reversal(s) in the community.**

METHODS: This 6-month prospective cohort study provided take-home naloxone and opioid OD education for 287 study participants with OUD. Characteristics associated with use of the take-home naloxone were determined from among 16 variables using multivariable logistic regression.

RESULTS: The **study participants who had greater odds of using the take-home naloxone to perform OD reversals**, compared to those who did not use the take-home naloxone, (a) **received emergency room care themselves for OD** (OR=4.89, 95% CI 1.54-15.52, P=0.007), (b) **previously witnessed someone else OD** (OR=5.67, 95% CI 1.24-25.87, P=0.025), (**c) tested positive for 2 or more illicit substances at their 6-month urine analysis** (OR=5.26, 95% CI 1.58-17.54, P=0.007) **or were missing their 6-month urine analysis** (OR=3.46, 95% CI 1.42-8.43, P=0.006). In addition, they had greater odds of being (d) less than 30 years old (OR=2.80, 95% CI 1.02-7.66, P=0.045), and (e) Hispanic (OR=3.98, 95% CI 1.41-11.21, P=0.009).

CONCLUSIONS: This study prospectively identified several characteristics of patients enrolled in an OTP with increased odds of using take-home naloxone in their social networks. Future **harm reduction efforts may benefit by using targeted characteristics to identify those most likely to use naloxone in their communities**.

The More Things Change: Buprenorphine/naloxone Diversion Continues While Treatment Remains Inaccessible. Carroll JJ, Rich JD, Green TC. J Addict Med. 2018 Aug 7. doi: 10.1097/ADM.0000000000000436. [Epub ahead of print]

OBJECTIVES: Buprenorphine/naloxone, an evidence-based treatment for opioid use disorder, is sometimes diverted for non-medical use. In Rhode Island, the prevalence of opioid use and, more recently, of fentanyl in the illicit drug supply is driving overdose fatalities, which increases the need for treatment and raises questions about the changing role of diverted medication in shaping overdose risk.

METHODS: This study considered data from 2 Rhode Island based studies (conducted in 2009 and 2016, respectively) of people who use illicit or diverted prescription opioids and their patterns of buprenorphine/naloxone diversion. Using targeted sampling, individuals who use opioids completed a brief questionnaire about their drug use. For the 2016 study, logistic regression was used to **identify associations with recent and lifetime use of diverted medication.**

RESULTS: A total of 128 individuals who use opioids non-medically participated in the 2016 study. Of these, 38% (n=13) reported diverted buprenorphine/naloxone use in the past 2 months, similar to the pattern observed in 2009 (41%, n=41). **Common motivations for using diverted medication included the management of withdrawal symptoms (40%, n=35) and self-treatment of opioid use disorder (39%, n=34). Few reported using to "get high" (12%, n=4). Seeking buprenorphine/naloxone treatment in the previous 12 months was positively associated with using diverted medication in the past 2 months** (odds ratio=5.14, 95% confidence interval=1.0-26.5, P=0.05). Participants of both studies reported the same barriers to care in 2009 and 2016.

CONCLUSION: The use of diverted/buprenorphine remains common among people who use opioids non-medically **and indicates a severe shortage in treatment capacity and inaccessibility of existing services.**

> *Comments: These findings mirror motivations for using non-prescribed buprenorphine found in a King County, WA syringe exchange survey and indicate that illicit use is usually motivated by medical needs.*

III. NALOXONE AND OVERDOSE PREVENTION

Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. Langham S, Wright A, Kenworthy J, Grieve R, Dunlop WCN. Value Health. 2018 Apr; 21(4):407-415. doi: 10.1016/j.jval.2017.07.014. Epub 2018 Feb 4.

BACKGROUND: Heroin overdose is a major cause of premature death. Naloxone is an opioid antagonist that is effective for the reversal of heroin overdose in emergency situations and can be used by nonmedical responders.

OBJECTIVE: Our aim was to **assess the cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by nonmedical responders compared with no naloxone distribution** in a European healthcare setting (United Kingdom).

METHODS: A Markov model with an integrated decision tree was developed based on an existing model, using UK data where available. We evaluated an intramuscular naloxone distribution reaching 30% of heroin users. Costs and

effects were evaluated over a lifetime and discounted at 3.5%. The results were assessed using deterministic and probabilistic sensitivity analyses.

RESULTS: The model estimated that distribution of intramuscular naloxone, would decrease overdose deaths by around 6.6%. In a population of 200,000 heroin users this equates to the prevention of 2,500 premature deaths at an incremental cost per quality-adjusted life year (QALY) gained of £899. The sensitivity analyses confirmed the robustness of the results.

CONCLUSIONS: Our evaluation suggests that **the distribution of take-home naloxone decreased overdose deaths by around 6.6% and was cost-effective with an incremental cost per QALY gained well below a £20,000 willingness-to-pay threshold** set by UK decision-makers. The model code has been made available to aid future research. Further study is warranted on the impact of different formulations of naloxone on cost-effectiveness and the impact take-home naloxone has on the wider society.

> *Comments: The estimated mortality prevention effect of take-home naloxone distribution correspond nearly identically to previous estimates by Coffin and Sullivan (https://www.ncbi.nlm.nih.gov/pubmed/23277895) and re-inforce that take-home-naloxone has a modest impact on mortality and is very cost effective, particularly in comparison to many other common preventive medical interventions.*

Awareness and access to naloxone necessary but not sufficient: Examining gaps in the naloxone cascade. Tobin K, Clyde C, Davey-Rothwell M, Latkin C. Int J DrugPolicy. 2018 Jul 31;59:94-97. doi: 0.1016/j.drugpo.2018.07.003. [Epub ahead of print]

BACKGROUND: Despite promising findings of opioid overdose education and naloxone distribution (OEND) programs, overdose continues to be a major cause of mortality. The "cascade of care" is a tool for identifying steps involved in achieving optimal health outcomes. We **applied the cascade concept to identify gaps in naloxone use.**

METHODS: Data came from a cross-sectional survey of 353 individuals aged 18 and older who self-reported lifetime history of heroin use.

RESULTS: The sample was majority male (65%) and reported use of heroin (74%) and injection (57%) in the past 6 months. Ninety percent had ever witnessed an overdose and of these 59% were in the prior year. Awareness of naloxone (90%) was high. Of those aware, over two-thirds reported having ever received (e.g. access) (69%) or been trained to use naloxone (60%). Of those who had ever received naloxone (n=218) over one-third reported possession never (36%) or rarely/sometimes carrying naloxone (38%), while 26% reported always carrying. Nearly half of those who had ever received naloxone reported ever use to reverse an opiate overdose (45%). Among individuals who had ever received naloxone, possession often/always compared to never was associated with being female (RRR=2.88, 95%CI=1.31-6.27) and ever used naloxone during an overdose (RRR=4.68, 95%CI=2.00-11.0).

CONCLUSIONS: 90% were aware of naloxone, of whom 69% had ever received it, of whom 26% always carried it. 45% of those who had ever received naloxone had used it to reverse an overdose. Women and those who had used naloxone before were more likely to carry it on their person. This study identifies that **consistent possession is a gap in the naloxone cascade. Future research is needed to understand reasons for not always carrying naloxone.**

Grievable lives? Death by opioid overdose in Australian newspaper coverage. Fraser S, Farrugia A, Dwyer R. Int J DrugPolicy. 2018 Jun 30;59:28-35. doi: 10.1016/j.drugpo.2018.06.004. [Epub ahead of print]

ABSTRACT: Opioid overdose deaths are increasing in Australia and around the world. Despite this, measures aimed at reducing these deaths such as safe injecting facilities and take-home naloxone continue to face obstacles to uptake. The reasons for this are manifold, but a key contributor is public discourse on opioid consumption and overdose. In this article we explore this public discourse using Judith Butler's work on 'grievable lives'. The article analyses mainstream newspaper coverage of opioid overdose in Australia to map key articulations of overdose and to consider how public understandings of overdose are shaped. It then goes on to consider ways these understandings might be reshaped, looking at what have been called overdose 'anti-memorials' and a new website Livesofsubstance.org. In concluding we argue that **until the lives of opioid consumers come to be considered grievable, the measures known to reduce overdose deaths may struggle to find public support.**

Naloxone distribution and possession following a large-scale naloxone programme. Madah-Amiri D, Gjersing L, Clausen T. Addiction. 2018 Aug 20. doi: 10.1111/add.14425. [Epub ahead of print]

AIMS: To **examine uptake following a large-scale naloxone programme by estimating distribution rates since programme initiation and the proportion among a sample of high-risk individuals who had attended naloxone training, currently possessed or had used naloxone.** We also estimated the likelihood of naloxone possession and use as a function of programme duration, individual descriptive and substance use indicators.

DESIGN: (1) Distribution data (June 2014-August 2017) and date of implementation for each city and (2) a cross-sectional study among a sample of illicit substance users interviewed September 2017.

PARTICIPANTS: A total of 497 recruited users of illegal opioids and/or central stimulants in seven Norwegian cities.

MEASUREMENTS: Primary outcomes: naloxone possession and use. Random-intercepts logistic regression models (covariates: male, age, homelessness/shelter use, overdose, incarceration, opioid maintenance treatment, income sources, substance use indicators, programme duration).

FINDINGS: Overall, 4631 naloxone nasal sprays were distributed in the two pilot cities, with a cumulative rate of 495 per 100,000 population. In the same two cities, among high-risk individuals, 44% and 62% reported current naloxone possession. The possession rates of naloxone corresponded well to the duration of each participating city's distribution programme. Overall, in the six distributing cities, 58% reported naloxone training, 43% current possession and 15% naloxone use. The significant indicators for possession were programme duration [adjusted odds ratios (aOR) = 1.44, 95% confidence interval (CI = 0.82-2.37], female gender (aOR = 1.97, 95% CI = 1.20-3.24) and drug-dealing (aOR = 2.36, 95% CI = 1.42-3.93). The significant indicators for naloxone use were programme duration (aOR = 1.49 95%, CI = 1.15-1.92), homelessness/shelter use (aOR = 2.06, 95% CI = 1.02-4.17), opioid maintenance treatment (OMT) (aOR = 2.07, 95% CI = 1.13-3.78), drug-dealing (aOR = 2.40, 95% CI = 1.27-4.54) and heroin injecting (aOR = 2.13, 95% CI = 1.04-4.38).

CONCLUSIONS: A large-scale naloxone programme in seven Norwegian cities with a cumulative distribution rate of 495 per 100,000 population indicated good saturation in a sample of high-risk individuals, **with programme duration in each city improving naloxone possession and use**. The **time and intensity of programming may lead to a culture of overdose prevention in a given locality.**