MDDCSAM is the Maryland state chapter of the American Society of Addiction Medicine whose members are physicians and other health providers who treat people with substance use disorders.

DRAFT HB 572: Public Health - Opioid Overdose Reversal Drugs

Health and Government Operations February 5, 2025

UNFAVORABLE

Thank you, Chair Pena-Melnyk, Vice Chair Cullison, and members of the committee, for the opportunity to present written testimony.

Peer-reviewed publications have noted possible dangerous unintended consequences of reversal agents that may cause more intense and prolonged opioid withdrawal than naloxone.

This can lead to opioid use after overdose reversal (a vulnerable period for fatal overdose), **avoidance of treatment in medical settings** (Lemen 2024) **or possible reluctance to call for help after overdose**, for fear of severe withdrawal. Nalmefene has a 5-fold higher binding affinity at the opioid receptor compared with naloxone; and a prolonged 11- hour half-life (vs. 60 - 90 minutes for naloxone), suggesting that **it may cause more intense, prolonged withdrawal.**

"The proliferation of powerful opioid antagonists could have unintended consequences that are counterproductive to efforts to prevent opioid-related overdose deaths" (Hill 2022)

The current reversal agent naloxone is fully effective for reversing overdoses caused by fentanyl. [Hill]. Usual doses of naloxone (4 mg. total) were sufficient in 97% of presumed fentanyl/potent opioid cases [Lemen 2024], and effective with carfentanil, 100 times more potent (below).

Reluctance to use an opioid antagonist due to the risk of severe opioid withdrawal is already well-documented. In a study by Neale, et. al, nearly all subjects who were familiar with naloxone described it negatively and indicated it should be avoided, and many expressed mistrust of health professionals' judgment regarding when to administer it. (Neal 2015)

Among people who use opioids, fear of inducing or experiencing prolonged opioid withdrawal was a common reason not to carry naloxone. (Hill 2022)

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Summary of last years' testimony by the Maryland Department of Health, the National Council on Alcoholism and Drug Dependence MD Chapter, and others:

- The effectiveness of MDH's Overdose Education and Naloxone Distribution strategy (OEND) already reflects best practice standards based on the use of naloxone, backed by a large body of evidence in the scientific literature.
- The bill would require MDH to purchase all formulations and brands of an ever-increasing array of overdose reversal drugs which it would need to distribute throughout the state, including to hundreds of Opioid Response Programs (ORPs), expending its limited funds.
- Nalmefene lacks evidence of efficacy in community settings.
- Clinicians have expressed concern about the possible increased likelihood of inducing more severe opioid withdrawal with nalmefene, and have urged further study.
- Nalmefene, and possibly future approved opioid antagonists, are not competitively priced.
- The bill will not be helpful to the state's efforts to reduce overdose mortality and may be harmful.
- The bill would create a logistical burden for ORPs to keep multiple brands on hand and/or refer people elsewhere for a requested formulation or brand.

Additional concerns about nalmefene are summarized below from the position statement presented in 2023 by **the Am College of Medical Toxicology (ACMT) & the American Academy of Clinical Toxicology** (AACT): 'ACMT & AACT Joint Position Statement on Nalmefene Should Not Replace Naloxone as the Primary Opioid Antidote at This Time'
https://www.acmt.net/news/acmt-aact-joint-position-statement-on-nalmefene-should-not-replace-naloxone-as-the-primary-opioid-antidote-at-this-time/

- Efficacy and safety data for the intranasal formulation of nalmefene are not available. (This formulation was FDA-approved through an "Abbreviated New Drug Application Pathway" based on approval of an earlier parenteral (intra-venous, etc.) formulation tested primarily in post-op hospital settings. The newer intranasal formulation only had to demonstrate bioequivalence to intranasal naloxone, not evidence of efficacy or safety).
- The only direct comparison between naloxone and nalmefene (Kaplan, et. al.) was presented to the FDA by the manufacturer, but it was conducted in the 1990s, used only IV formulations of both drugs, and was underpowered to detect difference in the risk of severe opioid withdrawal. The authors wrote in the article, **"Clinicians concerned about possible prolonged withdrawal or adverse reactions to nalmefene may want to try naloxone first."**
- The five-fold increase in nalmafene's binding affinity for the opioid receptor compared to that of naloxone, and its prolonged duration of action, raise concerns that acute opioid withdrawal (which is the primary adverse effect of opioid blockers, and can be dangerous), may be more severe than with naloxone.
- Prolonged opioid withdrawal symptoms could complicate overdose treatment in emergency departments, and may require hours of observation until withdrawal symptoms abate (vs. 90 minutes after intravenous naloxone), increasing costs and possibly risks.
- The current standard opioid antidote, naloxone, has a sufficiently high opioid receptor affinity to reverse novel synthetic opioids. In a study of volunteers given the high-affinity synthetic opioid carfentanil (which is 100 times more potent than fentanyl) administration of 2 mg of IV naloxone blocked 80.6% of receptors at 5 minutes.

NEXT . . .

REFERENCES:

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Respectfully,

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