International Journal of Paramedicine

Published by the National EMS Management Association (USA)

CONCEPTS

AN OVERVIEW OF THE TREATMENT OF NAUSEA AND VOMITING AND AN ARGUMENT FOR THE PREHOSPITAL USE OF DIPHENHYDRAMINE

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Recommended Citation: Adelberg, I. (2025). An overview of the treatment of nausea and vomiting and an argument for the prehospital use of diphenhydramine. *International Journal of Paramedicine*. (13). Pre-Issue Release: 1-7. https://doi.org/10.56068/WNNS4280. Retrieved from https://internationaljournalofparamedicine.com/index.php/ijop/article/view/3418

Keywords: diphenhydramine, antiemetics, nausea, vomiting, emergency medical services, EMS, paramedicine

Disclosures: None.

Funding: External funding was not used to support this work.

Acknowledgements: This paper is an expansion of a proposal submitted to the Connecticut OEMS Protocol Committee in 2024 which affected a protocol change in v.2025.1. Thanks to Dr. Rob Weiner for copyediting.

Received: June 1, 2025
Revised: October 16, 2025
Accepted: October 16, 2025
Pre-Issue: December 2, 2025

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ABSTRACT

Treatment of nausea and vomiting is among the most frequent treatments provided by out-of-hospital providers with the pharmacologic agents in common use displaying varying pharmacologies and potential interactions. The most commonly administered anttiemetic— ondansetron— targets only one of the four main nausea receptors, with the antidopaminergic agents targeting another receptor. This creates an opportunity for the use of diphenhydramine— an antihistamine with anticholinergic properties— as it targets the third and fourth nausea receptors, providing an inexpensive option for the treatment of nausea without requiring the expansion of supply chains or equipment lists. The following concept paper will provide an overview of the relevant pharmacology and an argument that diphenhydramine is logistically suitable for prehospital medicine.

INTRODUCTION

The treatment of nausea and vomiting is among the most common treatments provided prehospitally, with the NEMSIS database finding that ondansetron was administered to 9% of patients and nausea/vomiting being the sixth most common chief complaint afflicting 6% of patients (National EMS Information System, 2024). That an antiemetic is the third most commonly administered medication in the United States implies the large scope of the problem and the importance which prehospital clinicians place on treating nausea/vomiting. However, the literature supporting the efficacy of any of our current antiemetics is slim in the prehospital setting (Verma et al, 2019). The use of guidelines and literature from other domains of medicine is potentially beneficial, but this should be caveated that the development of evidence-based guidelines specifically devalues the use of literature on patients not part of the population being discussed in the guideline (Prasad, 2024).

PHARMACOLOGIC REVIEW

Nausea is typically induced by activation of receptors in the chemoreceptor trigger zone (CTZ) of the medulla oblongata, with several receptors relevant to prehospital emergency care, including the serotonin (5HT3), dopamine (D2), histamine (H1), and both the nicotinic and especially the muscarinic acetylcholine (M1) receptors. The treatment of nausea involves a combination of both treating the underlying causes of nausea and blocking the stimulation of these nausea receptors. Opioids have both agonist and antagonist effects on the CTZ, and the cytokine substance P's effects on the NK-1 receptor is relevant in the treatment of chemotherapy-induced nausea and vomiting (Zhong et al, 2021). The mechanisms by which these receptors may be stimulated are not entirely understood but the literature in post-operative care, oncology, obstetrics, and the limited research which has been performed in the emergency department setting provides guidance on treatment regimens and the efficacy of different solutions (Shaikh et al, 2016, Singh et al, 2015).

Serotonin is one of the most common causes of nausea, being released primarily from the gut and able to stimulate nausea both directly in the CTZ and through the stimulation of abdominal afferent neurons (Terry & Margolis, 2017). The primary antiserotoninergic medication in EMS is ondansetron, which can be administered intravenously, intramuscularly, or orally/oromucosally, and it is the first-line treatment for chemotherapy/radiation induced nausea, opioid-induced nausea/vomiting, and is highly effective in gastroenteritis (Aapro et al, 2021 Athavale et al, 2020). Ondansetron is a second-line medication in the treatment of morning sickness due to a mildly increased risk of oral cleft deformities when given to pregnant patients in their first trimester (Huybrechts et al, 2019).

Dopamine is a neurotransmitter affecting nausea both centrally in the CTZ as well as in the GI tract. Several classes of antidopaminergics are already in use both prehospitally and in the hospital. The butyrophenone class contains haloperidol and droperidol (both of which have an antihistamine effect at higher doses) while the phenothiazine class contains prochlorperazine (with antihistamine and anticholinergic effects at higher doses) (Farkas, 2024). Metoclopramide— a benzamide with an antiserotinergic side-effect profile— is particularly suited to the treatment of gastroparesis and migraines (Rao & Camilleri, 2009, Becker, 2015). While particularly effective in treating nausea of GI origin and potentially effective in nausea of all kinds, the side-effect profile of antidopaminergics limits their potential use. All the antidopaminergic medications have the potential to cause drug-induced parkinsonism with increased occurrence at higher doses and in patients who already have Parkinson's disease (Alvarez & Evidente, 2008). Of note, the immediate treatment of drug-induced parkinsonism may include treatment with anticholinergics including diphenhydramine (Vanegas-Arroyave, 2024).

Histamine and acetylcholine are two different neurotransmitters whose antiemetic benefits are primarily based in vestibular causes (i.e., motion sickness and vertigo) as well as being beneficial in pregnancy as a first-line pharmacologic agent (Paine, 2005, Committee on Practice Bulletins- Obstetrics, 2018). The treatment of motion sickness is of particular importance in EMS and prehospital medicine as vestibularly derived nausea can be caused by many factors inherent to ambulance transport. Motion sickness is likely caused by a mismatch between expected sensory inputs and actually perceived inputs,

such as unexpected changes in acceleration or direction (particularly when there isn't a fixed visual reference point) and may be exacerbated by stress or sitting backwards, all factors present in ambulance transport (Takov & Tadi, 2023). While the two neurotransmitters are distinct, they are grouped together in this article due to first-generation antihistamines having anticholinergic properties (Church & Church, 2013). More to the point, diphenhydramine — the medication focused on in the second section of this paper — is the prototypical first-generation antihistamine. Diphenhydramine is administered intravenously, intramuscularly, orally, or as an elixir — and its most clinically relevant side effects are sedation, dry mucus membranes, and decreased GI/GU motility (Sicari et al, 2025).

Of note, there are potential serious side effects of diphenhydramine, the most immediately dangerous being its potential to cause sedation that may impact the ability to drive safely after discharge (Verster & Volkerts, 2004). This is compounded when administered alongside the sedative antiemetics, especially droperidol and haloperidol, with diphenhydramine being concomitantly administered alongside haloperidol and lorazepam for sedation purposes greatly increasing its duration of sedation and potential side effects, notably hypotension (Jeffers et al, 2022). Patients should be advised against driving following administration of diphenhydramine for any purpose including as an antiemetic, with particular caution and need for monitoring in patients treated with both diphenhydramine and antidopaminergic medications. There is also a cumulative risk of Alzheimer's disease and other forms of dementia from patients taking anticholinergics of any sort, a risk that has largely contributed to diphenhydramine's being increasingly not recommended for regular treatment of allergies in favor of newer generations of antihistamines (Clark et al, 2025).

There are two further agents relevant in the treatment of nausea, with mechanisms not directly linked to the aforementioned receptors: isopropyl alcohol and parenteral fluids. While the mechanism by which inhalation of isopropyl alcohol vapors is unknown— and may be as straightforward as being a way to prompt patients to breathe calmly and distract from external stimuli— that does not change that the inhalation of isopropyl alcohol is clinically effective in the reduction of nausea (Amaya et al, 2023). Parenteral fluids similarly relieve nausea without having a pharmacologic effect on the patient, either through the treatment of dehydration as cause of the nausea or due to a placebo effect (Taylor et al, 2025, Egarton-Warburton et al, 2018).

LOGISTICS AND RESEARCH DISCUSSION

There are three main arguments supporting the use of diphenhydramine prehospitally in the treatment of nausea. The first, that it is especially suited for the treatment of motion sickness- has been discussed above, with the second being its ease of use in EMS systems. Diphenhydramine is already used prehospitally due to its role in the treatment of anaphylaxis and allergic reactions, which has several implications to the ease of its use for a second indication. Diphenhydramine is a medication which medical directors and paramedics are already familiar: they know the dosing of 25-50 mg for adults, the routes, and the side effect profiles. The training burden for familiarizing providers with a "new" medication would therefore be minimal, likely limited to a single continuing education class or video on the mechanism of action and how it is related to nausea.

From an agency perspective, the benefit of diphenhydramine's current widespread availability continues to manifest as the supply lines are already established for advanced life support agencies, with the only necessary change being to order an increased quantity the next time an order is placed. A cursory search of a nationwide EMS supplier found that one vial of diphenhydramine costs $2.42, while by comparison ondansetron costs $3.04, metoclopramide costs $6.68, haloperidol costs $7.40, prochlorperazine costs $7.50, and droperidol— currently only manufactured by a single company— costs $60.40 per dose (as of October 13, 2025), as much as an entire box of diphenhydramine vials (Bound Tree). While agency-specific cost breakdowns are beyond the scope of this article, the cost of stocking additional diphenhydramine can be readily offset by the potential decreased use of more expensive agents. On the other hand, diphenhydramine has occasionally been in short supply in the US, most recently in May 2025, due to one supplier discontinuing their generic supply It's possible that the increased use of diphenhydramine for another indication may exacerbate future shortages (Wheeler).

This is not a recommendation for agency supply departments to stock diphenhydramine as the sole antiemetic, rather it is a recommendation to include it in the list of antiemetics available on hand. Having multiple antiemetics for the paramedic to choose from prevents the situation in which a patient with a known hypersensitivity to one class having a delay in the treatment of their nausea until arrival at the hospital when another medication can be administered. In addition, the current recommendations from the post-operative literature and the obstetric literature for the treatment of nausea are to administer a second antiemetic of a different class should the first prove ineffective (Gan et al, 2020, Committee on Practice Bulletins-Obstetrics 2018). Regrettably, there is currently no consensus guideline available for prehospital or even emergency-department treatment of nausea and vomiting, and evidence is mixed on any interventions' superiority to placebo (Furyk et al, 2015).

Regarding prehospital literature, a recent meta-analysis published in Emergency Medicine Australasia found only seven pieces of original research on administration of antiemetics and found that none were particularly robust either in terms of methodology or sample size; consequently no conclusions as to the efficacy of any antiemetic either against others or against placebo could be drawn (Verma et al, 2018). Of the seven studies identified by Verma et al (2018), only one assessed diphenhydramine. This study, published in Prehospital and Disaster Medicine, found that in a sample size of seven patients who received diphenhydramine (out of a total of 22, with eight receiving metoclopramide and seven receiving placebo), the diphenhydramine group was indistinguishable from the placebo group at fifteen minutes and there were no statistically significant differences between the three at twenty-five minutes (Rubio et al, 2011). The lack of rigorous data from which guidelines can be based indicates a strong need for further research and severely limits the ability to draw conclusions or offer recommendations.

The current standard for developing evidence-based guidelines for EMS is the use of the multi-step GRADE tool, which evaluates literature based on "study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias" (Martin-Gill et al, 2016, Prasad, 2024). Of note is the criteria of precision, which in this context refers to whether a piece of literature evaluates the population for which a recommendation is being developed. Outside of the recommendations from the obstetrics literature which pertain directly to the recommendation for diphenhydramine as a non-teratogenic agent

in pregnant patients, the reliance on literature outside of prehospital care weakens its already-low strength. GRADE's process for evaluating recommendations is a binary strong-weak system, in which weak recommendations are made due to low-certainty evidence, with weak recommendations providing variability in treatment options for patients (Prasad, 2024). In the same spirit, due to the aforementioned lack of evidence in nausea and emesis treatment prehospitally, this article can only weakly recommend diphenhydramine as a prehospital antiemetic until there are robust comparisons from which an evidence-based guideline can be drawn.

CONCLUSIONS

Given the varying mechanisms by which antiemetic medications work, and with the distinct possibility that they may not work or may not work better than placebo, the ability to provide multimodal treatment for nausea and vomiting is of great practical concern. Further research is needed to compare antiemetics administered prehospitally, and to reinforce what medications are most suited to treat which modalities in the prehospital arena. As a stopgap, the availability of medications of each class approaches the standard of care available to treat nausea. With the additional logistic benefits of diphenhydramine as an already-available medication in most ALS formularies, altering system protocols to permit its use may benefit patients due to its safety profile being comparable to that of the other second-line antiemetics and providers' existing comfort with the medication.

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