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Inside this Issue:

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Replacement of Promethazine With Ondansetron for Treatment of Opioid- and Trauma-Related Nausea and Vomiting in Tactical Combat Casualty Care

TCCC Guidelines: Proposed Change 14-03

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ABSTRACT

The current Tactical Combat Casualty Care (TCCC) Guidelines recommend parenteral promethazine as the single agent for the treatment of opioid-induced nausea and/or vomiting and give a secondary indication of "synergistic analgesic effect." Promethazine, however, has a well-documented history of undesired side effects relating to impairment and dysregulation of the central and autonomic nervous systems, such as sedation, extrapyramidal symptoms, dystonia, impairment of psychomotor function, neuroleptic malignant syndrome, and hypotension. These may be particularly worrisome in the combat casualty. Additionally, since 16 September 2009, there has been a US Food and Drug Administration (FDA) black box warning for the injectable form of promethazine, due to "the risk of serious tissue injury when this drug is administered incorrectly." Conversely, ondansetron, which is now available in generic form, has a well-established favorable safety profile and demonstrated efficacy in undifferentiated nausea and vomiting in the emergency department and prehospital settings. It has none of the central and autonomic nervous system side effects noted with promethazine and carries no FDA black box warning. Ondansetron is available in parenteral form and an orally disintegrating tablet, providing multiple safe and effective routes of administration. Despite the fact that it is an off-label use, ondansetron is being increasingly given for acute, undifferentiated nausea and vomiting and is presently being used in the field on combat casualties by some US and Allied Forces. Considering the risks involved with promethazine use, and the efficacy and safety of ondansetron and ondansetron's availability in a generic form, we recommend removing promethazine from the TCCC Guidelines and replacing it with ondansetron.

Proximate Cause for the Proposed Change

The current Tactical Combat Casualty Care (TCCC) Guidelines recommend parenteral promethazine as the single agent for the treatment of opioid-induced nausea and vomiting, and note a secondary "synergistic analgesic effect." These are current and historically frequent uses of promethazine; however, there is now a significant amount of evidence and experience to indicate that it should not be the preferred agent for either indication, particularly in the combat trauma patient.[1]

The original selection of promethazine over ondansetron for the TCCC Guidelines was made at a time when ondansetron was still being sold under patent. Generic forms of the drug were not available and Zofran (ondansetron; GlaxoSmithKline plc; www.gsk.com) was prohibitively expensive for use as a battlefield antiemetic.

Ondansetron is an antiemetic that is increasingly being used as the agent of choice in the treatment of nausea and vomiting in the emergency department (ED)[2] and the prehospital environment,[3] as well as the inpatient, obstetrical, and surgical settings. Although FDA approved for use in nausea associated with chemotherapy and ionizing radiation for cancer treatment and for postoperative nausea, there is an extensive body of literature describing the safe and effective use of ondansetron in many other scenarios, including undifferentiated nausea in the ED.[4] It has a well-established record of both efficacy and safety and a mild side effect profile that make it a much better choice than promethazine for use on the battlefield and in the tactical care environment.

Considering the safety and effectiveness of ondansetron and the risks of promethazine, we propose to remove

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promethazine from the TCCC Guidelines and replace it with ondansetron.

Background

Nausea and vomiting are common side effects of opioid use. The incidence of nausea and vomiting in trauma is also common but perhaps less well appreciated. Easton et al.[5] showed a larger-than-expected number of trauma patients with nausea (38%), a smaller-than-expected number who were properly treated (40%), and a significant difference in nausea between the treated and untreated groups (4 of 79 [5%] versus 71 of 117 [61%]; $p < .0001$).

Promethazine hydrochloride is a phenothiazine derivative that is structurally different from the neuroleptic phenothiazines, resulting in a relative lack of dopamine antagonist properties. Promethazine is a competitive H1 receptor antagonist that possesses antihistaminic, sedative, anti–motion-sickness, antiemetic, and anticholinergic effects.[6,7] Clinical effects are generally apparent within 5 minutes of an intravenous (IV) injection and within 20 minutes of an intramuscular (IM) injection. Duration of action is reliably 6 hours, although effects may persist up to 24 hours. Promethazine was introduced in the 1940s and is still used in contemporary medicine.[8]

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist that does not have dopaminergic properties. Its exact mechanism of action has not been precisely defined. Serotonin receptors of the 5-HT_3 type are present on vagus nerve terminals and in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or both.[9]

Ondansetron is increasingly becoming the antiemetic of choice in the prehospital and ED settings, including the combat operational environment. Between 1995 and 2009, ondansetron administration in US EDs increased from 38,000 to 12.6 million doses annually.[10] In a review of 13,863 patients given an antiemetic in the United States between 2006 and 2009, ondansetron was the most prescribed agent, given 54.8% of the time. Promethazine was the second most frequent agent used, at 50.3%.[2] Data from the Joint Theater Trauma System (JTTS) show an even greater propensity for ondansetron use (E. Burrell, personal communication, 17 June 2014).

Two other commonly used agents were briefly considered: metoclopramide and droperidol. Each of these has been issued FDA black box warnings—metoclopramide for tardive dyskinesia,[11] and droperidol for prolonged QT intervals and torsades de pointes at doses at or below recommended doses.[12] Metoclopramide has a side effect profile similar to promethazine, including extrapyramidal symptoms, neuroleptic malignant syndrome, akathisia, and hypotension, although these symptoms are less common.[11] More concerning in the combat casualty, metoclopramide is a prokinetic agent, stimulating upper gastrointestinal tract motility, and, therefore, would be contraindicated in a casualty with abdominal trauma. Droperidol use has been associated with fatal dysrhythmias in patients with no preexisting history or risk factors who received single therapeutic doses.[12] Due to these concerns, neither drug will be given consideration as a replacement for promethazine.

Methods

A PubMed search was performed for the keywords "promethazine" and "ondansetron," each using the following filters: English language journal articles published after 1 January 1984; human subjects; and adults at least 19 years old. This produced 344 articles for promethazine and 1,165 articles for ondansetron. An additional filter to remove articles from cancer literature produced 750 articles for ondansetron.

Searches were screened for titles that appeared relevant to this topic. Specific exclusion criteria included the following: combinations of promethazine or ondansetron with any other drug; comparison of either agent against a corticosteroid; ondansetron use in cancer treatment–related nausea and vomiting (unless specifically reporting adverse reactions or, for a subgroup analysis, comparing the effectiveness of oral versus IV ondansetron); special topics in unique surgical populations (e.g., middle-ear surgery); and non–clinically oriented research (e.g., "influence of ondansetron on gastric sensorimotor responses to short duodenal acid infusion"). Considering surgery from the perspective of a planned, controlled, traumatic injury, gynecologic, orthopedic, and general surgical titles were also screened for inclusion. Abstracts were examined for pertinent content and those articles were reviewed.

Data from a retrospective review and preliminary analysis were obtained from an ongoing, nonpublished study on antiemetic use in Afghanistan being conducted by the JTTS. This information is included to present recent experience with antiemetic use in the TCCC environment (E. Burrell, personal communication, 17 June 2014).

Additionally, information was obtained from the FDA website and some general drug information was obtained from open-source pharmacology websites.

Discussion Points

The Case Against Promethazine

Promethazine is an H1-receptor–blocking agent that also has sedative and antiemetic effects along with its

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antihistaminic properties. Its effectiveness as both an antiemetic and a sedative are well established.[13–16] Even at low doses of 6.25mg, parenteral promethazine is as effective of an antiemetic as parenteral ondansetron, 4mg.[16] It is frequently used primarily for its antiemetic effects and is often considered as an adjunct to analgesia or anesthesia because of the sedation it causes. It has even been shown effective solely for use as a hypnotic sleep-induction agent.[17] This sedative effect is concerning when used in the acute trauma patient and particularly in patients with head injury and altered mental status.

There are other significant side effects with promethazine that may be particularly worrisome in the combat casualty. Promethazine has a well-documented history of undesired side effects relating to impairment and dysregulation of the central and autonomic nervous systems. Of particular importance, promethazine may cause sedation and respiratory depression when used independently and in conjunction with opioids.[4,18–20] Behrbalk et al.[18] demonstrated that morphine with promethazine, when compared with morphine alone, increased drowsiness by more than 70% and increased ED stay times by 78 minutes in patients with acute low back pain, with no discernible difference in analgesia. In a review of a hospital adverse drug event (ADE) database, Sheth et al.[19] found an increase in ADE rates for promethazine when compared with all other antiemetics combined, and they also found that concurrent use of opioids or other sedating drugs contributed to ADEs with promethazine in 78.6% of patients.

Additionally, promethazine has risks for extrapyramidal symptoms, dystonia and other movement abnormalities, impairment of psychomotor function, neuroleptic malignant syndrome, and hypotension.[1,21–27] Cowings et al.[22] demonstrated that therapeutic doses of promethazine cause significant impairment of operational task performance in astronauts. Ridout and Hindmarch observed similar results when promethazine was compared to fexofenadine or placebo in healthy volunteers.[27]

Although promethazine is effective as an antiemetic,[14] there are multiple agents that are equally or more effective for the primary indication of nausea.[13] Compared with prochlorperazine, for example, promethazine had slower onset, increased incidence of side effects, and less benefit.[28] There are multiple studies showing that ondansetron is at least equivalent to promethazine as an antiemetic. These will be discussed in detail in the following section.

The well-designed and executed study by Vella et al.[29] compared promethazine, metoclopramide, and placebo when given with pethidine (meperidine) in laboring mothers. They demonstrated that promethazine and metoclopramide were equally effective and better than placebo in reducing nausea, but patients receiving metoclopramide or placebo had significantly better reductions in pain and significantly less sedation than patients receiving promethazine.[29]

Since 16 September 2009, there has been an FDA black box warning for the injectable form of promethazine, due to "the risk of serious tissue injury when this drug is administered incorrectly."[20] Foret et al.[30] reported two cases of accidental intra-arterial promethazine injection that led to necrosis, gangrene, and eventual upper extremity amputation. Keene et al.[31] reported a case of accidental intra-arterial injection in the dorsum of the hand that ultimately resulted in complete amputation of the thumb and distal index, ring, and little finger. Finally, Paula et al.[32] reported two cases of necrosis, one leading to gangrene and amputation, and one case of chronic pain and hypersensitivity, with a permanent decrease in range of motion, from promethazine IV injection.

Although the published literature reports no incidents of adverse events, such as those noted in the previous paragraph, in combat casualties in Afghanistan and Iraq, the potential exists for these events to occur. Combined with the more advantageous current pricing of generic ondansetron, its potential benefits versus the risks of promethazine make this a good time to reevaluate the preferred medication for nausea and vomiting in combat casualties.

The Case for Ondansetron

Ondansetron is used as an antiemetic with the FDA indications for treatment of nausea from cancer-related chemotherapy and radiation therapy and for postoperative nausea and vomiting (PONV). It is very commonly used off-label for various other causes of nausea and vomiting, including opioid use, migraine headache, and prepartum and intrapartum pregnancy-related nausea and vomiting, as well as undifferentiated acute nausea.[4,13,33] It does not cause sedation or hypotension and has a favorable safety profile.[34] In comparison with other agents, ondansetron has performed at least as well as droperidol, metoclopromide, prochloperazine, promethazine, and other 5-HT_3 receptor antagonists and is at least as safe.[1,4,33–39] This has been demonstrated in the prehospital, outpatient and inpatient settings, and in gravid and laboring women.

In 2008, Braude and Crandall[4] demonstrated that ondansetron was noninferior to promethazine as an antiemetic when treating undifferentiated nausea in the ED. Ondansetron had antiemetic and anxiolytic effects that were not significantly different than promethazine but caused significantly less sedation. Additionally, there were no reports of akathisia in the ondansetron group

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but a 3.3% rate in the promethazine group.[4] A small, early comparison of ondansetron and promethazine in the treatment of hyperemesis gravidarum showed equivalence in the relief of nausea, weight gain, days of hospitalization, and total number of doses of medication.[38]

Two separate systematic reviews published in 1999 compared ondansetron with metoclopromide or droperidol in the treatment of PONV.[34,35] Cox[35] demonstrated that compared to metoclopramide, 10mg, ondansetron, 4mg, had higher patient satisfaction and better treatment of nausea. The findings of Domino et al.[34] were confirmatory, showing that ondansetron (1mg, 4mg, and 8mg) demonstrated essentially equivalent therapeutic effects to droperidol (0.625mg, 1mg, and 1.25mg) with no increase in the incidence of adverse effects.[34] A 2014 head-to-head comparison of ondansetron, metoclopramide, and placebo for acute, undifferentiated nausea in the ED showed equivalence in patient satisfaction, effects, and side effects in all three arms.[36] Of note, this study compared ondansetron, 4mg, to metoclopramide, 20mg, which is double the normal recommended dose of metoclopramide.

Compared to other 5-HT_3 antagonists (i.e., granisetron, tropisetron, and dolasetron), ondansetron was as effective for prophylaxis of PONV, but granisetron, when studied by Tang and Malone,[40] was more effective than ondansetron in the treatment of postoperative nausea. Metaxari et al.[41] found ondansetron equal to granisetron in control of PONV in thyroid surgery, but only for 6 hours compared to granisetron's 12 hours. Ondansetron, however, is far more commonly used, especially in the ED setting, than granisetron,[2] and there are much more data and experience for its safe and effective use in that environment.

Ondansetron has been shown to be effective in prophylaxis of PONV. Chen et al.[42] studied patients who received ondansetron IV 30 minutes before the end of shoulder arthroscopy and found it reduced the incidence of PONV. Additionally, the patients using ondansetron had "lower pain intensity and lower analgesic injection needs than the control group."[42] In a series of 100 patients undergoing mandibular osteotomy, Talesh et al.[39] compared the effectiveness of ondansetron and metoclopramide for the prevention of PONV and found ondansetron provided a significant improvement in effect: an 11% incidence of vomiting with ondansetron compared with 28% in the metoclopramide group. In a randomized, double-blind, placebo-controlled study of 65 women undergoing total abdominal hysterectomy, Tzeng et al.[43] compared ondansetron versus saline placebo for the prophylactic treatment of PONV. All patients received epidural morphine, 3mg, for postoperative pain relief. Before morphine injection, the treatment group received ondansetron, 4mg IV, and the placebo group received IV saline. In the ondansetron group, the frequency of PONV was significantly decreased from 52% to 22%.[43]

Unlike promethazine, for which there is good evidence to demonstrate antagonism to opioid analgesia, as described,[29] ondansetron appears to have a neutral or synergistic effect. Jellish et al.[44] compared patient-controlled analgesia administration of morphine, morphine plus ondansetron, and placebo for pain control in patients immediately recovering from skull surgery and found the morphine-plus-ondansetron combination had the lowest pain scores, shortest postanesthesia discharge time, lowest rescue dose, and highest patient satisfaction, although, paradoxically, they reported equivalent incidence and severity of nausea and vomiting.

Like promethazine, ondansetron is available in oral form, as well; however, ondansetron is available as an orally disintegrating tablet (ODT) that is absorbed through the buccal and sublingual mucosa and does not require swallowing or gastrointestinal absorption.[7] Ondansetron ODT has been shown to be just as effective as IV ondansetron in the management of chemotherapy-related nausea[45] and PONV[46,47] and better than IV saline in the management of undifferentiated nausea in the prehospital setting.[48] Although oral ondansetron reaches peak serum levels at 2.3 hours, compared to 5 minutes after IV administration,[49] it has essentially the same bioavailability,[49] and there do not appear to be any clinically significant differences in time of onset and time to therapeutic effect.[3,46,48]

A prospective study of 2,071 patients (2,005 adults, 66 children) who received either ondansetron, 4mg (in adults) given either IV, IM, or ODT, in a nonrandomized, uncontrolled, observational protocol, found effective control of nausea in all three groups.[3] ODT and IM ondansetron were statistically equivalent and IV was better than both IM (–0.8 on a 10-point visual analog scale [VAS]; $p = .03$) and ODT (–1.1; $p < .001$); however, all three showed a statistically significant change in VAS for nausea.[3]

In a randomized, double-blind, placebo-controlled comparison of IV and ODT ondansetron, Grover et al.[46] found no difference between ondansetron, 4mg IV, and ondansetron, 8mg ODT. An argument can be made that this was not an equivalent treatment, since the bioavailability of ODT ondansetron appears to be 90%,[50] but both 4mg and 8mg doses of ondansetron have been shown to be effective in oral and parenteral forms.

Additionally, ondansetron ODT does not appear to have the same arrhythmogenic side effects as the IV form,

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perhaps due to the rate of administration, and may also be used along with IV ondansetron.[10]

It is important to note that all of the studies we cite describing the use of oral ondansetron were specifically evaluating the ODT formulation.[45–49] There is a nondissolving oral tablet form of ondansetron that, unlike the ODT, relies on the gut for absorption and is, therefore, not as useful in the combat trauma casualty. Also, the oral formulation has a much lower bioavailability than the ODT formulation—56% versus 90%.[14,49,50]

Ondansetron has an excellent side effect profile and has been demonstrated to be safe in multiple patient populations. It has been used safely and effectively by paramedics in the prehospital environment.[3] There have been concerns raised regarding the possibility of it lowering seizure thresholds, and there have been at least three reports of seizure activity in otherwise healthy patients after ondansetron administration.[51] This is a controversial concern, since data have demonstrated both proepileptogenic and antiepileptogenic potential in animal models,[51] and its use in neurosurgical trauma patients has not been associated with either extrapyramidal symptoms or increased seizure activity.[52]

Most concerning of ondansetron's known adverse effects is a prolonged QT interval that could develop into torsades de pointes. This has been of particular concern in patients with a preexisting long QT syndrome or with existing or acutely developing cardiovascular disease (i.e., heart failure or acute coronary syndromes).[53] The FDA revised the Drug Safety Communication for ondansetron in September 2011 to reflect the dose-response effect of IV ondansetron administration.[54] GlaxoSmithKline plc similarly announced that it removed the 32mg single-dose option from the drug labeling.[54] This high dose was specifically associated with episodes of prolonged QT intervals, with an average increase of 20 milliseconds; however, at single IV doses of 16mg or less, QT prolongation is minimal (approximately 6 milliseconds).[53]

Another retrospective review of the 5-HT_3 receptor agonists ondansetron and dolasetron looked at a total of 1,429 patients given a study drug and 1,022 control subjects. The researchers found that 17% of patients given 5-HT_3 receptor antagonists (n = 242) and 22% of controls (n = 220) had postoperative QTc exceeding 500 milliseconds, but that the average QTc prolongation was only 6%.[55] They did not record torsades de pointes events or any other life-threatening dysrhythmias. Although the antiemetic dose was not reported in the study, it is reasonable to expect that ondansetron dosing was consistent with standard perioperative dosing of 4mg to 8mg, and certainly not more than 16mg per individual dose

Most recently, Freedman et al.[10] performed an extensive systematic analysis of the published literature, the manufacturer's database, the FDA Adverse Events Reporting System, and the World Health Organization Individual Safety Case Reports Database (VigiBase), looking for all cases of documented or perceived arrhythmia within 24 hours of ondansetron administration. They found no reports of arrhythmia occurring with a single dose of oral ondansetron (the primary end point). Their secondary end point, arrhythmia after parenteral administration, identified 49 cases of arrhythmia, 48 of which occurred with IV administration. All of the cases involved patients being treated for PONV, having preexisting cardiac disease, concomitant administration of proarrhythmic agents, or a combination of these. There were four cases of torsades de pointes: three involving significant contributing history and one involving prolonged scheduled use of oral ondansetron. There were no reports of torsades in patients who approach our target patient population—the relatively young, previously healthy, acutely injured trauma patient.[10]

Torsades de pointes, specifically, is very rare and has not been reported in trauma patients who have been given IV ondansetron (PubMed search, June 2014). Unlike droperidol, which has an FDA black box warning regarding QT prolongation at or below recommended doses, ondansetron has no such warning and this side effect is most likely of no concern in the acute trauma setting. Interestingly, promethazine has also been found to prolong QTc intervals but is not believed to be significantly torsadogenic.[8]

Information gathered from the JTTS on medication administration to combat casualties in Afghanistan from 4 January 2013 to 8 May 2014 looked at 576 patients, 247 of whom received a total of 395 doses of a study drug (at least one dose of fentanyl, ketamine, morphine, ondansetron, and/or promethazine). Twenty-seven percent of patients received multiple doses of the analgesics studied. Of these, 31 received one of the antiemetics; 23 of those 31 patients (75%) received ondansetron. No patient received both antiemetic drugs, although one patient received two doses of ondansetron and 39% received an antiemetic simultaneously or within 1 minute of analgesic administration. Although the registry does not have data on the effectiveness of treatment or the incidence of adverse events (E. Burrell, personal communication, 17 June 2014), the simple demonstration of the predominant use of ondansetron and the general lack of repeated dosing or the need for rescue with promethazine or another antiemetic indicate ondansetron's wide acceptance by operational medical personnel and a likely favorable experience with its use. This preference for ondansetron is not limited to US medical personnel.

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The current UK Clinical Guidelines for Operations recommend use of ondansetron and do not mention promethazine (R. Russell, personal communication, 18 June 2014).

Conclusion

Although promethazine is an effective antiemetic,[13–16] the side effects and adverse events associated with it make it a suboptimal choice for the treatment of nausea and vomiting in the trauma patient.[4,18–20] Specifically, sedation, respiratory depression, extrapyramidal symptoms, dystonia, impairment of psychomotor and cognitive function, neuroleptic malignant syndrome, and hypotension[1,21–27] are at least confounding and potentially life-threatening side effects in the combat casualty. Taking into consideration these side effects, along with the FDA black box warning for injection site necrosis,[20] administration of promethazine, particularly by the parenteral route, should be discouraged.

Conversely, ondansetron is a safe and effective alternative with demonstrated benefit and much lower risk.[3,4,10,13,33–40,48] It has a well-established record of use in multiple settings, including the prehospital environment and the ED.[2–4,13,36,37] Its major adverse reaction, prolonged QT interval, is not of significant consideration in this patient population or at the doses we recommend.[10,53,55] Additionally, the availability of ondansetron in both parenteral (IV and IM) and an ODT form makes it more useful and easier to administer.

Promethazine should be removed from the TCCC Guidelines and replaced with ondansetron for prophylaxis and treatment of opioid- and trauma-related nausea and vomiting.

PROPOSED CHANGE TO THE TCCC GUIDELINES

Current Wording

Basic Management Plan for Tactical Field Care

13k. Provide analgesia as necessary.
- Promethazine, 25 mg IV/IM/IO every 6 hours as needed for nausea or for synergistic analgesic effect

Basic Management Plan for Tactical Evacuation Care

13k. Provide analgesia as necessary.
- Promethazine, 25 mg IV/IM/IO every 6 hours as needed for nausea or for synergistic analgesic effect

Proposed Wording

Basic Management Plan for Tactical Field Care

13k. Provide analgesia as necessary.
- **Ondansetron, 4mg ODT/IV/IO/IM, every 8 hours as needed for nausea or vomiting. Each 8 hour dose can be repeated once at 15 minutes if nausea and vomiting are not improved. Do not give more than 8mg in any 8 hour interval. Oral ondansetron is NOT an acceptable alternative to the ODT formulation.**

Basic Management Plan for Tactical Evacuation Care

13k. Provide analgesia as necessary.
- **Ondansetron, 4mg ODT/IV/IO/IM, every 8 hours as needed for nausea or vomiting. Each 8 hour dose can be repeated once at 15 minutes if nausea and vomiting are not improved. Do not give more than 8mg in any 8 hour interval. Oral ondansetron is NOT an acceptable alternative to the ODT formulation.**

Level of Evidence (AHA): A (AHA/ACC)

The levels of evidence used by the American College of Cardiology and the American Heart Association were described by Tricoci in 2009:

- Level A: Evidence from multiple randomized trials or meta-analyses.
- Level B: Evidence from a single randomized trial or nonrandomized studies.
- Level C: Expert opinion, case studies, or standards of care.

Using this taxonomy, the level of evidence for the use of ondansetron in the acute trauma setting is Level A.

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Disclaimer

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Release

This document was reviewed by the Director of the Joint Trauma System and by the Public Affairs Office and the

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Operational Security Office at the US Army Institute of Surgical Research. It is approved for unlimited public release.

Disclosures

The authors have no disclosures to report.

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