Drug Class Review

Newer Antiemetics

Expanded Scan Report

February 2017

Last Report: Update #1, January 2009

Last Preliminary Update Scan: Scan #6, July 2016

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OBJECTIVE

The purpose of this expanded version of a preliminary updated literature scan is to provide an overview of the volume and nature of new research that has emerged subsequent to the previous full review, with some additional features to allow more insight into the potential impact of the new evidence (e.g. quality assessment and key findings).

In consultation with DERP participating organization representatives, methods and scope for this expanded scan were developed. This scan on antiemetic drugs focuses on evidence for new drugs (approved after the last full report; Table 2 below). Emphasis is placed on head-to-head evidence and health outcomes, with placebo-controlled trials included where there are few or no head-to-head studies (e.g. granisetron transdermal patch, which was approved very near the end of the review period for the last report). Comprehensive review and synthesis of the new research presented in this report, along with previous evidence, would be included in a full update of the report.

Dates of Previous Reports

Update #1: January 2009 (searches through October 2008)

Dates of Previous Preliminary Update Scans

Scan #6: July 2016 (searches through May 2016)
Scan #5: July 2015 (searches through June 2015)
Scan #4: May 2014 (searches through May 2014)
Scan #3: April 2013 (searches through April 2013)

Scope and Key Questions *(last update report)*

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

3. Are there subgroups of patients based on demographics (e.g. age, race, and gender), pregnancy, other medications, or comorbidities for which a newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria (last update report)

Populations

Adults or children at risk for or with nausea and/or vomiting (including retching) related to receiving chemotherapy of varying emetogenicity, radiation therapy, a surgical procedure, or are experiencing nausea and/or vomiting during pregnancy.

Interventions

Table 1. Antiemetic drugs included in prior DERP report (2009)

Drug	Trade name	Formulations
Aprepitant/Fosaprepitant	Emend®	Injectable, oral
Doxylamine Succinate/Pyridoxine Hydrochloride	Diclegis	Delayed release tablet (FDCP)
Dolasetron	Anzemet®	Injectable, oral
Granisetron	Kytril, Sancuso®	Injectable, oral, transdermal patch
Ondansetron	Zofran®, Zuplenz®	Injectable, oral, orally disintegrating tablet
Palonosetron	Aloxi®	Oral, Injectable

FDCP = Fixed-dose Combination Product

Outcomes

In the full report the primary effectiveness outcomes included varying definitions of success, which involved absence of vomiting and/or retching, nausea, and use of rescue medications. These were reported in the acute/early and delayed/late period following chemotherapy, radiation or surgery (timing varied by specific population). Other outcomes included patient satisfaction and quality of life, and, for pregnant women, fetal outcomes. These were measured as either prevention or treatment for patients receiving chemotherapy, radiation, or surgery. Adverse events outcomes were overall adverse events, specific adverse events (e.g. headache, constipation, dizziness, and sedation), withdrawals due to adverse events, and serious adverse events.

Methods For Expanded Scan

To identify new drugs, we searched the FDA website and CenterWatch (Table 2). To identify relevant studies, we searched Ovid MEDLINE® from June 2016 through January 2017 for randomized controlled trials (RCTs) of the new antiemetic drugs listed in Table 2. Any trials of new drugs identified in prior scans were also included. We searched for relevant comparative effectiveness reviews using DERP standards.[1] We included primary publications of head-to-head RCTs, but for drugs without head-to-head evidence we included placebo-controlled trials. Secondary publications (e.g. subgroup analyses) were screened to identify any that resulted in strongly differing results compared to the overall trial. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. A single reviewer, using DERP methodology, assessed quality of included studies. A second reviewer reviewed any study rated poor quality, and any differences in judgment resolved through consensus. For fair or good quality trials, we abstracted key information, including:

- Success (e.g. absence of vomiting/retching, absence of any emetic event – including nausea), early and/or late (timing of measurement varies by population)
- Use of rescue medications
- Overall adverse events and withdrawals due to adverse events
- The author's conclusion statement.

RESULTS

New Drugs or Formulations

Identified Since the Last Update Report

Table 2. Newly approved antiemetic drugs and formulations since last report

Drug	Trade name	FDA Approval	Mechanism	Formulations
Ondansetron	Zuplenz®	7/2010	5-HT3 antagonist	Oral film
Granisetron	Sancuso®	9/2011	5-HT3 antagonist	Transdermal patch
Doxylamine Succinate 10mg / Pyridoxine HCL 10mg (FDCP)	Diclegis®	4/2013	Other	Delayed release tablet
Netupitant/Palonosetron (FDCP)	Akynzeo®	10/2014	NK1/5-HT3 antagonist	Capsule
Rolapitant hydrochloride	Varubi™	9/2015	NK1 antagonist	Tablet
Granisetron	Sustol®	9/2016	5-HT3 antagonist	Subcutaneous injection, extended release*
Doxylamine Succinate 20 mg/ Pyridoxine HCL 20 mg(FDCP)	Bonjesta®	11/2016	Other	Delayed release tablet*

Abbreviations: FDCP = fixed-dose combination product
*New since last Preliminary Update Scan report; Scan #6, July 2016

New Serious Harms (Boxed Warnings)

Identified Since the Last Update Report

No new serious harms (boxed warnings) were found for the newer antiemetic drugs that were included in this expanded scan.

New Comparative Effectiveness Reviews

Identified Since the Last Update Report

No comparative effectiveness reviews included the drugs listed in Table 2, above.

New Evidence: Randomized Controlled Trials

We identified 13 RCTs (in 16 publications) of newer antiemetic drugs that met our criteria[2-5,6-16]; doxylamine 10 mg/pyridoxine 10 mg; granisetron extended release injection and transdermal patch; rolapitant; and netupitant/palonosetron. There were no studies of ondansetron oral film (Zuplenz®) or the newer, higher dose combination product of doxylamine succinate 20 mg/pyridoxine HCL 20 mg (Bonjesta®). The majority of studies were in patients receiving emetogenic chemotherapy (10 trials), with 1 trial in surgical patients experiencing post-operative nausea/vomiting and 2 trials in pregnant women experiencing post-operative nausea/vomiting. Seven studies directly compared 2 regimens (head-to-head), 4 evaluated add-on treatments with an NK1 antagonist, and 1 was placebo-controlled. No study compered NK1 antagonists with each other. The number of participants ranged from 36 to 1,998; mean age was 57 years in the chemotherapy studies, 46 years in studies of surgical patients, and 26 years in studies of pregnant women. The trials were mostly fair quality, with 4 studies being good quality[2,9,10,11] and 2 studies

being poor quality.[4,12] Assessments of study quality are available in Appendix A (a separate document).

Granisetron Transdermal System

Three RCTs compared the granisetron transdermal system to other drugs or formulations of granisetron (Table 3). One RCT compared the transdermal formulation to an all-oral regimen of granisetron in patients receiving moderately and highly emetogenic chemotherapy,[2] and another trial compared the transdermal formulation to an IV/oral granisetron regimen in patients receiving moderately emetogenic chemotherapy.[3] These were designed as non-inferiority trials and found the transdermal formulation to be non-inferior using a margin of less than a 15% difference (at the lower bound of the 95% confidence interval) for either complete control (no vomiting and/or retching, mild or no nausea, and no use of rescue medication) or complete response (no vomiting and/or retching and no use of rescue medication) in the acute phase (0-24 hours). Rates of response or control were in the range of 60% to 75%, with lower rates in the study that included highly emetogenic regimens. Both studies found the occurrence of adverse events to be comparable for the granisetron transdermal versus oral or IV/oral, and one study reported no difference in withdrawals due to adverse events.

The third RCT was a poor-quality study comparing transdermal granisetron with IV palonosetron (see Appendix A).[4]

Table 3. Granisetron transdermal versus oral and IV granisetron in patients receiving emetogenic chemotherapy

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Boccia, 2011 (good) N = 641 54.5 years Moderate and highly emetogenic chemotherapy in adults x 1 cycle	Granisetron transdermal patch x 7 days vs. Oral granisetron 2 mg/d x 3-5 days	Granisetron oral vs. transdermal Complete response[a] acute phase, 62% (176/284) vs. 68% (203/298); difference: -6.6%; 95% CI, -14.4 to 1.3 Rescue medication: NR	Oral granisetron vs. Granisetron transdermal Any AEs, % (n/N): 40.5% (128/316) vs. 39.3% (126/321) Withdrawal due to AE, % (n/N): 2.2% (7/316) vs. 2.2% (7/321)	"The granisetron transdermal delivery system provides effective, well-tolerated control of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron."
Kim, 2015 (fair) N = 276 56.5 years Moderately emetogenic chemotherapy in adults x 1 cycle	Granisetron transdermal patch vs. IV 3mg x 1 dose/oral 1mg/day granisetron X 4 days	Granisetron transdermal vs. IV/oral Complete response[a]: acute phase: 75.0% (84/112) vs. 74.6% (91/122); difference: 0.4 %; 95% CI, -10.7 to 11.6 Rescue medication: NR	Granisetron transdermal patch vs. Intravenous/oral granisetron Any AEs, % (n/N): 45.0% (59/131) vs. 34.1% (45/132) Withdrawal due to AE: NR	"The granisetron transdermal system showed non-inferior efficacy to intravenous and oral granisetron. The safety, tolerability, and Functional Living Index-Emesis scores of the granisetron transdermal system were comparable to those of control group."

NR = not reported; AE = adverse event

[a]Complete response = no vomiting and/or retching and no rescue medication use.

Granisetron Extended-Release Subcutaneous Injection

One fair-quality crossover trial (in 3 publications) assessed 2 doses (250 or 500 mg) of extended-release subcutaneous injection of granisetron compared with IV palonosetron in patients receiving moderately and highly emetogenic chemotherapy (Table 4).[5 6,7] Both doses of the extended release injection granisetron were non-inferior to IV palonosetron for the primary outcome of complete response in the acute period, using the same criteria and definitions described above for trials of transdermal granisetron. Delayed nausea and vomiting were found similar between drugs only in patients receiving moderately emetogenic chemotherapy, but palonosetron was better with highly emetogenic chemotherapy IV. Differences in adverse events or withdrawals due to adverse events were not found. Reclassification of chemotherapy emetogenicity using a different system increased the proportion of patients having complete response in the moderately emetogenic group and decreased it in the highly emetogenic group, but did not alter the findings in the acute phase. [6]Subgroup analysis of only patients with breast cancer did not meaningfully alter these results.[7]

Table 4. Granisetron extended release (ER) subcutaneous injection versus intravenous palonosetron n patients receiving emetogenic chemotherapy

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Raftopoulos, 2015 (fair) N = 1428 56.5 years Moderate and highly emetogenic chemotherapy in adults x up to 4 cycles (re-randomization after each cycle if patient agreed to continue)	Granisetron ER SC injection 250mg or 500 mg vs. Palonosetron IV 0.25 mg given prior to chemotherapy	Granisetron 250 mg vs. Granisetron 500 mg vs. Palonosetron 0.25 mg Complete response[a] *Moderately emetogenic:* Acute: 74.8% (160/214); p=1.0 vs. 76.9% (163/212); p=0.73 vs. 75.0% (208) Delayed: 51.4% (110/214); p=0.24 vs. 58.5% (124/212); p=0.84 vs. 57.2% (119/208) *Highly emetogenic:* Acute: 77.7% (178/229); p=0.49 vs. 81.3% (195/240); p=0.91 vs. 80.7% (192/238) Delayed: 62.4% (143/229) p=0.70 vs. 67.1% (240); p=0.56 vs. 64.3% (153/238) Rescue medication: NR	Granisetron 250 mg vs. Granisetron 500 mg vs. Palonosetron 0.25 mg There were no significant between treatment groups in percentages of patients who had AEs or percentages of patients who discontinued because of a treatment related AEs	"A single subcutaneous APF350 (granisetron) injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC"

CINV, chemotherapy-related nausea and vomiting; HEC = highly emetogenic chemotherapy; IV = intravenous; MEC = moderately emetogenic chemotherapy; NR = not reported; SC = subcutaneous

[a]Complete Response = no emesis or use of rescue medication

Rolapitant

Five trials (in 4 publications) were found that evaluated rolapitant; 4 in adults receiving moderately or highly emetogenic chemotherapy where rolapitant was added to a 5-HT3 antagonist compared to the 5HT-3 antagonist alone[8-10]; and 1 in women receiving abdominal surgery, where rolapitant was compared directly with a 5HT-3 antagonist to prevent post-operative nausea and vomiting (PONV) (Table 5).

In adult's receiving highly emetogenic chemotherapy, adding rolapitant 180 mg to an intravenous 5HT-3 antagonist resulted in significantly more patients having complete response in both the acute (0-24 hours) and delayed phases (24-120 hours) compared with the 5HT-3 antagonist alone in 3 RCTs (2 reported combined in 1 publication).[8, 9] In a dose-ranging study, only the 180 mg dose was superior to ondansetron. This study also reported that the 180 mg dose resulted in lower use of rescue medications (14% vs. 25%) and time to first emesis than with ondansetron. Adverse events and withdrawals due to adverse events were similar across groups in both studies of highly emetogenic chemotherapy regimens.

In patients receiving moderately emetogenic chemotherapy, adding rolapitant to oral granisetron resulted in more patients having complete response in both the acute and delayed periods compared with oral granisetron alone, and adverse event rates were very similar.

In a meta-analysis of all of these trials, the durability of these effects over multiple cycles of chemotherapy was examined. Significantly more patients on rolapitant had complete response in cycles 2-6 than with a 5HT-3 antagonist alone ($p<0.001$).[16]

One head-to-head RCT directly compared rolapitant to ondansetron in women with PONV in a dose-ranging study. [11] Complete response was similar between the rolapitant 70 mg, rolapitant 200 mg, and ondansetron 4 mg groups at all time points, and time to first rescue medication use was similar between the 200 mg rolapitant and ondansetron groups (10.4 vs. 11.9 hours).When limiting the analysis to patients with no emesis, but retaining patients who used rescue medication, significantly more women met this criteria with rolapitant 200 mg than with ondansetron at all time points, and with 70 mg of rolapitant in the acute phase (0-24 hours) and the overall time (0-120 hours). Adverse events were not clearly different between groups.

Table 5. Trials of rolapitant

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Chemotherapy Studies: Add-on to 5HT3 antagonists				
Rapoport, 2015b HEC-1 & 2 (good) N = 1087 59 y Highly emetogenic chemotherapy in adults x 5 cycles	Rolapitant 180 mg + granisetron 10 mcg/kg vs. Granisetron 10 mcg/kg X 2-4 days	Rolapitant + granisetron vs. Granisetron Pooled HEC 1&2 studies Complete response[a] Acute (120 hours): 84% (447/535) vs. 77% (410/535); OR 1.6; 95% CI, 1.2 to 2.1; p=0.0045 Delayed: 71% (382/535) vs. 60% (322/535); OR 1.6; 95% CI, 1.3 to 2.1; p<0.0001 Rescue medication: NR	Rolapitant + granisetron vs. Granisetron Pooled HEC 1&2 Any AEs: 61% (329/535) vs. 62% (332/537) Withdrawal due to AE: 4% (20/535) vs. 5% (29/537)	"Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well-tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the at-risk period (120 h) after administration of highly emetogenic cisplatin-based chemotherapy."

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Rapoport, 2015a (fair) N = 454 55 y Highly emetogenic chemotherapy in adults x 5 cycles	Rolapitant 9mg, 22.5mg, 90mg, 180mg (all arms + ondansetron 32 mg) vs. Ondansetron 32 mg (IV) x 6 days	Rolapitant 9 mg vs. Rolapitant 22.5mg vs. Rolapitant 90 mg vs. Rolapitant 180 mg vs. Ondansetron Complete response[a] Acute (120 hours): 66.7% (61/91) vs. 70.8% (64/91) vs. 74.7 (68/91) vs. 87.6% (79/90), P≤0.001 vs. 66.7% (61/91) Delayed: 50.5% (46/91) vs. 54.5% (50/91) vs. 58.2% (53/91) vs. 63.6% (57/90), p<0.05 vs. 48.9% (44/91) Rescue medication: 14% vs. 25% time to first emesis significantly longer for rolapitant (p=0.011)	Rolapitant 9 mg vs. Rolapitant 22.5mg vs. Rolapitant 90 mg vs. Rolapitant 180 mg ondansetron Any AEs, % (n/N): 13% (12/91) vs. 13% (12/91) vs. 23% (21/91) vs. 10% (9/90) vs. 9% (8/91) Withdrawal due to AE: 2% (2/91) vs. 5% (5/91) vs. 2% (2/91) vs. 6% (5/90) vs. 3% (3/91)	"All doses of rolapitant were well tolerated and showed greater complete response rates than active control. Rolapitant 180 mg demonstrated significant clinical efficacy for preventing chemotherapy-induced nausea and vomiting in the overall, delayed, and acute phases for patients receiving highly emetogenic chemotherapy."
Schwartzberg, 2015 (good) N = 1369 57 y Moderately emetogenic chemotherapy in adults x5 cycles	Rolapitant 180 mg[a] + granisetron 2 mg vs. Granisetron 2 mg X 5 d	Rolapitant + granisetron vs. Granisetron Complete response[a] Acute (120 hours): 83% (556/666) vs. 80% (535/666); OR 1.2; 95% CI, 0.9 to 1.6; p=0.1425 Delayed: 71% (475/666) vs. 62% (410/666); OR 1.6; 95 CI, 1.2 to 2.0; p=0.0002 Rescue medication: NR	Rolapitant + granisetron vs. granisetron Any AE: 64% (431/670) vs. 66% (447/674) Withdrawal due to AEs: 0.9% (6/684) vs. 1.0% (7/685)	"Rolapitant in combination with a 5-HT3 receptor antagonist and dexamethasone is well tolerated and shows superiority over active control for the prevention of chemotherapy-induced nausea and vomiting during the 5-day (0–120 h) at-risk period after administration of moderately emetogenic chemotherapy or regimens containing an anthracycline and cyclophosphamide."
Post-Operative Nausea & Vomiting Study: Head-to-head Comparison				
Gan, 2011 (good) N = 619 46.1 y Women with postoperative nausea and vomiting	Rolapitant 5mg, 20mg, 70mg, 200mg vs. Ondansetron 4 mg X 1 day 30-60 days follow-up	Rolapitant 5mg vs. Rolapitant 20mg vs. Rolapitant 70mg vs. Rolapitant 200mg vs. Ondansetron 4 mg Complete response[a] Acute (0-24 hr): 34/103 (33%) vs 33/102 (32%) vs 38/103 (37%) vs 40/104 (39%) vs 38/104 (37%) Overall (0-120 hr): 24% (24/103) vs. 24% (24/102) vs. 33% (34/103) vs. 31% (32/104) vs. 26% (27/104) Time to first rescue medication use, mean hours: 8.4 vs. 9.8 vs. 6.1 vs. 10.4 vs. 11.9	Rolapitant 5mg vs. Rolapitant 20mg vs. Rolapitant 70mg vs. Rolapitant 200mg vs. Ondansetron 4 mg Any AEs: only postoperative ileus >2% (range 0 to 4% across all groups) Withdrawals due to AEs: 3 (groups NR)	"Rolapitant reduced the incidence of postoperative vomiting in a dose-dependent manner and was superior to placebo at all doses studied, while exhibiting no difference in side effect profile to placebo. Furthermore, there was no statistically significant difference between Rolapitant (at any of the studied doses) and ondansetron in terms of primary outcome variables."

AE = adverse event; CI, confidence interval; NR = not reported
[a]Complete Response = no emesis or use of rescue medication

Netupitant/Palonosetron

Two RCTs evaluated the addition of netupitant to palonosetron in preventing nausea and vomiting in patients receiving chemotherapy.[12,13] One was a head-to-head trial evaluating the fixed-dose combination product (FDCP) of netupitant 300 mg/palonosetron 0.5 mg compared with aprepitant (125 mg/80mg) plus palonosetron (0.5 mg) (N=413). In general, the two regimens had similar effects on success in the acute phase and cumulative adverse events over multiple cycles of chemotherapy. There were some small differences between groups in delayed nausea and vomiting, with differences of 2% to 6% greater success in the netupitant/palonosetron group. However, this trial was rated poor quality due to problems with the randomization – there were differences at baseline in cancer types and prognostic factors, which the authors posited to have influenced their results (see Appendix A).[12]

The other RCT evaluated adding netupitant to palonosetron (separately, not as a FDCP) versus palonosetron alone in patients receiving highly emetogenic chemotherapy (Table 6). [13] This was a dose-finding trial, with 3 doses of netupitant (100, 200, and 300 mg). The combination of netupitant 300 mg plus palonosetron 0.5 mg provided statistically significantly higher rates of complete response (no emesis and no rescue medication) at all 3 doses compared with palonosetron alone during both the acute and delayed phases. The numbers of people reporting adverse events were very similar between these 2 groups. The lower doses of netupitant also resulted in significantly greater complete response in the delayed period, but were similar in the acute period, and the 100 mg dose group had the lowest proportion of people reporting adverse events.

Table 6. Netupitant plus palonosetron versus palonosetron alone in patients receiving highly emetogenic chemotherapy

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Hesketh, 2014 (fair) N = 694 54.5 y Highly emetogenic chemotherapy in adults (# cycles NR)	Netupitant 100mg, 200mg, 300mg (all arms + palonosetron 0.50mg) vs. palonosetron 0.50mg X 6 days (120 h)	Netupitant 100mg vs. Netupitant 200mg vs. Netupitant 300mg vs. Palonosetron 0.50mg Complete response[a] Acute: 93.3% (126/135) vs. 92.7% (127/137) vs. 98.5% (133/135) vs. 89.7% Delayed: 90.4% (122/135); p ≤ 0.05 vs. 91.2% (125/137); p ≤ 0.05 vs.90.4% (122/135); p ≤ 0.05 vs. 80.1% (109/136)	Netupitant 100mg vs. Netupitant 200mg vs. Netupitant 300mg vs. Palonosetron 0.50mg Any AEs: 40.7% (55/135) vs. 51.4% (71/138) vs. 50.0% (68/136) vs. 49.3% (67/136) Withdrawal due to AE, % (n/N): 0 vs. 0.7% (1/135) vs. 0.7% (1/142) vs. 0 vs. 0	"Each Netupitant plus palonosetron dose provided superior prevention of chemotherapy-induced nausea and vomiting compared with palonosetron following highly emetogenic chemotherapy; however, Netupitant plus palonosetron 300 was the best dose studied, with an advantage over lower doses for all efficacy endpoints."

AE = adverse event; NR = not reported
[a]Complete Response = no emesis or use of rescue medication

Doxylamine succinate/pyridoxine hydrochloride

We found only 1 placebo-controlled trial of the delayed release doxylamine 10 mg/pyridoxine 10 mg FDCP (Table 7).[14,17] The study enrolled pregnant women with persistent nausea and vomiting associated with pregnancy (not pre-existing) whose symptoms were not responding to conservative management or treatment with other drugs. Women had to have at least moderately severe symptoms, a score of >6 on the Pregnancy-unique quantification of emesis and global assessment of well-being (PUQE) scale, which ranges from 3 to 15. Dosing ranged from 2 tablets at bedtime (10 mg of each drug) to 4 tablets daily, divided. After 2 weeks of treatment, the combination drug resulted in a 1.1-point (9%) greater improvement on the PUQE symptoms scale, and a similar difference on the well-being scale, which ranges from 0 to 10). These differences were statistically significant. Additionally, 36% of women taking placebo used additional therapies for nausea and vomiting, compared with 23.7% taking the combination drug. Adverse events were not different between the groups.

A second small trial (N = 36) compared individual doxylamine 12.5 mg and pyridoxine 25 mg (three times daily) compared with ondansetron 4 mg daily for 5 days in pregnant women (at least 16 weeks gestation) seeking treatment for nausea and vomiting (Table 7).[15] Ondansetron was statistically superior to doxylamine plus pyridoxine in reducing both nausea and emesis, including when limited to those who had clinically significant reductions (defined as at least 25% reduction). Sensitivity analyses due to 17% missing data resulted in similar findings.

Table 7. Trials of doxylamine and pyridoxine for nausea and vomiting during pregnancy

Study Characteristics	Intervention Characteristics	Benefit Outcomes	Harms Outcomes	Author's Conclusion's
Koren, 2010 Koren 2015 (fair) N = 256 25.6 years pregnant woman with N/V	Doxylamine succinate 10 mg/pyridoxine hydrochloride 10 mg Delayed-release FDCP vs. Placebo 2-4 doses/day X 15 days	Doxylamine/pyridoxine vs. placebo Change in PUQE score: -4.8 vs -3.9; P =0 .006 (12 point scale) Change in global assessment of well-being score: 2.8 vs. 1.8; P=0 .005 (10 point scale)	Doxylamine/pyridoxine vs. placebo Any AEs, % (n/N): 56.5% (74/131) vs. 51.2% (65/127); p=0.393 Withdrawal due to AE, % (n/N): 4.6% (6/131) vs. 3.1% (4/127) ; p=0.749	"Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy."
Oliveira 2014 (fair) N = 36 pregnant women with N/V	Pyridoxine 25 mg + doxylamine 12.5 mg 3 times daily vs. Ondansetron 4 mg daily X 5 days	Pyridoxine + doxylamine vs. Ondansetron Change in emesis[a]: median: 41 mm vs. 17 mm; p=0.049 At least 25mm reduction: 6/17 (35%) vs. 10/13 (77%); p=0.033 Change in nausea[a]: median 51 mm vs 20 mm; P=0 .019 At least 25mm reduction: 12/13 (92%) vs 7/17 (41%); P=0.007	Pyridoxine + doxylamine vs. Ondansetron Any AEs: "there were no unexpected adverse events" Withdrawal due to AE: NR	"Our investigation showed ondansetron to be superior to the combination of pyridoxine and doxylamine in the treatment of nausea and emesis in pregnancy."

AE = adverse event; NR = not reported; N/V, nausea or vomiting; PUQE, Pregnancy-Unique Quantification of Emesis.
[a]Change measured using visual analog scale (0 to 100)

REPORT SUMMARY

Evidence for the newest antiemetics, based on 13 fair- and good-quality RCTs, found:

- Granisetron transdermal patch and extended release subcutaneous injection were non-inferior to other 5HT-3antagnosists (oral and intravenous) in patients receiving moderately to highly emetogenic chemotherapy. (3 trials)

- Rolapitant added to a 5HT-3 antagonist was superior to a 5HT-3 antagonist alone in patients receiving moderately to highly emetogenic chemotherapy. (4 trials)

- Rolapitant alone was similar to a 5HT-3 antagonist alone in preventing PONV in women. (1 trial)

- Netupitant/palonosetron FDCP was better than palonosetron alone in patients receiving highly emetogenic chemotherapy. (1 trial)

- The delayed-release FDCP doxylamine/pyridoxine was superior to placebo in reducing nausea and vomiting in pregnant women over 2 weeks. (1 trial)

- Doxylamine plus pyridoxine (administered separately) was inferior to ondansetron in reducing nausea and vomiting in pregnant women over 5 days. (1 small trial)

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APPENDIX A. QUALITY RATINGS FOR INCLUDED TRIALS

Author, Year Trial Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcomes assessors blinded? Clinician blinded? Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?	Acceptable level of differential attrition (<10%)?	Overall quality
Boccia 2011 NCT00273468	yes	yes	yes	yes	yes	yes	yes	good
Kim 2015	Unclear	Unclear	Yes; except for metastatic disease	No; open label	Yes	Yes	Yes	Fair
Gralla 2014 NCT01376297	unclear	unclear	No; not cancer types and prognostic factors	Yes	Yes	Yes	Yes	Poor
Gan 2011 NCT00539721	yes	yes	yes	yes	yes	yes	yes	good
Hesketh 2014 NR	unclear	unclear	yes	yes	yes	yes	yes	fair
Schwartzberg 2015 NCT01500226	yes	yes	yes	yes	yes	yes	yes	good

Rapoport 2015 NCT00394966	unclear	unclear	yes	unclear	yes	yes	no	fair
Rapoport 2015 NCT01499849, NCT01500213	yes	yes	yes	yes	yes	yes	yes	good
Koren 2010, 2015 NCT00614445	yes	unclear	yes	yes	unclear	yes	yes	fair
Seol NR 2016	Unclear	Unclear	Yes	No; open label	Yes	No; 21% loss	Yes	Poor
Raftopoulos 2015 NCT00343460	unclear	unclear	yes	unclear	yes	yes	yes	fair
Oliveira 2014 NCT01668069	yes	yes	yes	yes	unclear	unclear	yes	fair