*Original Article*

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# A Systematic Review of the Management of Chemotherapy-Induced Nausea and Vomiting

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**Abstract**

***Background:*** Chemotherapy induced nausea and vomiting is a debilitating effect of the chemotherapy drugs administered to patients with malignancy and deteriorates the quality of life of the patients. The antiemetic drugs that are commonly prescribed for controlling CINV are 5-HT3 RA, NK1RA, Dexamethasone, Olanzapine and Metoclopramide. These drugs are used either in combinations or alone for treating CINV.

***Objective:*** The purpose of this review is to analyze the various treatment modalities for CINV and to identify the suitable antiemetic agents for nausea and emesis caused by various chemotherapy agents.

***Methods:*** We systematically reviewed randomized controlled trials (RCTs) in adult patients undergoing chemotherapy treatment and are at risk of CINV, extracting and synthesizing data from eligible articles on study design, randomization, withdrawal, blinding, type of analysis, duration, and names and doses of drugs. The primary outcome measure was complete response (no emesis and no administration of rescue medication) in preventing CINV in acute and delayed phases and secondary outcome was incidence of TRAEs.

***Findings:*** This review included seventeen RCTs among which eleven were blinded and six were open label studies. Four studies evaluated the effectiveness of olanzapine in preventing CINV in which one of the study compared efficacy of olanzapine and metoclopramide for the treatment of breakthrough emesis. One of the study compared the efficacy of granisetron as transdermal delivery system with ondansetron in preventing CINV and concluded that granisetron transdermal system was non inferior to ondansetron in controlling CINV. Three studies investigated the change in the prevention of CINV on single day administration of dexamethasone with multiple day administration of dexamethasone. All the three studies reported that single day administration of dexamethasone was similar in efficacy to multiple day dosing. Two studies investigated the efficacy of rolapitant in which one of the study concluded that addition of rolapitant to antiemetic treatment regimen consisting of granisetron and dexamethasone significantly improved CINV compared with treatment regimen without rolapitant. Three studies evaluated the efficacy of NEPA which is a combination of Netupitant (NK1 RA) and Palonosetron (5HT3 RA)among which one study concluded that NEPA was superior to Palonosetron and in another NEPA was compared with palonosetron and aprepitant and concluded that NEPA was similar to them in controlling CINV. One study evaluated the efficacy of fosaprepitant, a prodrug of aprepitant compared to aprepitant and concluded that single dose fosaprepitant was non inferior to multiple day administration of aprepitant. Two studies evaluated fosnetupitant in which one study compared the efficacy of fosnetupitant at the dose of 81 mg and 235 mg and concluded that dose of 235 mg was superior to 81 mg of fosnetupitant. The other study compared the safety profile of fosnetupitant to fosaprepitant and concluded that both were similar.

***Conclusion:*** Antiemetic triplet treatment regimen for CINV consisting of 5HT3 RA, NK1 RA and dexamethasone was found to be effective in this review but the quality of some of the evidence of the studies included in this review contains high risk of bias and is not completely reliable. Hence we recommend that future trials be conducted with minimum risk of bias to ensure high quality of evidence.

**Keywords:** Olanzapine, Rolapitant, Granisetron, Palonosetron, Fosaprepitant, Aprepitant, Metoclo -pramide.

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## INTRODUCTION

Chemotherapy induced nausea and vomiting is an adverse effect that is caused by a large number of chemotherapy drugs that leads to significant decline in the treatment compliance and quality of life of cancer patients undergoing chemotherapy treatment. Thus antiemetic treatment for controlling CINV is necessary for ensuring the compliance to the chemotherapy treatment for cancer. The antiemetic drugs that are widely used for CINV include 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RAs), Neurokinin-1 receptor antagonist (NK-1 RA) and Dexamethasone.[1] Several guidelines have recommended antiemetic drug combinations for chemotherapy induced nausea and vomiting and the choice of antiemetic medication depends on emetogenic nature of the chemotherapy agent. However the adherence to these guidelines for the antiemetic therapy is inadequate for the control of CINV. In a study where the guideline consistent CINV prophylaxis cohort following MASSCC/ European Society of Medical Oncology (ESMO) 2016 antiemetic guidelines and guideline inconsistent CINV prophylaxis cohort were compared it was observed that the guideline consistent CINV prophylaxis cohort had significantly better complete response (CR: no emesis, no rescue medication use)compared to the guideline inconsistent cohort.[2] The age is an important risk factor that influences the likelihood of developing cancer and 50% to 60% of cancers are prevalent among the patients aged 65 years and above. The treatments of cancersin older patients are more challenging due to the comorbid conditions that they possess compared to the younger patients. Age related cognitive impairments such as memory loss can also cause hindrance to compliance to the drug regimen that is mostly complex in nature. NEPA is an oral fixed dose combination containing netupitant (highly selective NK1 RA) and palonosetron (second generation 5HT3 RA) that results in greater inhibition of substance P response than with neputitant or palonosetron given alone. In some studies NEPA has been proven to be well tolerated among volunteers aged ≥ 65 and adjustment of doses is not required in elderly. Neputitant and palonosetron have prolonged half life of 90 hrs and 40 hrs respectively.[3,4] Granisetron is a 5HT3 RA that has also been formulated asgranisetron transdermal system (GTS) that gradually releases the drug to attain the required plasma concentration for sustained effect. Granisetron transdermal system has shown to be effective and comparable to conventional route of administration of granisetron in the control of CINV. The GTS was approved by the U.S. Food and Drug Administration in 2008.[5] Aprepitant was the first launched NK1 RA into clinical care (2003). The NK1 RA and corticosteroids enhance the management of acute (onset less than 24 hrs after administration of chemotherapy) and delayed emesis (onset 24 hrs after administration of chemotherapy) whereas the conventional 5HT3 RA are effective to a great degree in the prevention of acute emesis. The NK1 RAs are well known for preventing delayed phase of emesis in CINV.[6] An antipsychotic drug olanzapine also acts as an antiemetic drug for controlling nausea and vomiting associated with chemotherapy and exhibits its action by blocking several neurotransmitters in the central nervous system. The dopamine receptor antagonists were used conventionally used for prevention of CINV before the development of the serotonin receptor antagonist. The adverse effects that are common to olanzapine includes sedation, weight gain and onset of diabetes mellitus.[7-10] The chemotherapy drugs that induce nausea and vomiting are classified as high (>90% risk of inducing vomiting), moderate (>30-90% risk), and low (10-30% risk), and minimal (<10% risk). Rolapitant is a drug belonging to the class of NK1 RA. It is highly selective NK1 RA that has a high affinity (K1 0.66 nmol/L) towards the human NK1 receptor and sustains greater than 90% receptor binding lasting upto 5 days post dose of 180 mg. The halflife of rolapitant is longer and is neither an inducer nor inhibitor of CYP3A4 enzyme.[11] Fosaprepitantis a phosphorylated and water soluble prodrug of aprepitant an NK1 RA which is converted to aprepitant following administration through intravenous route. Fosaprepitant is available as an intravenous dosage form whereas aprepitant as oral dosage form.[12] Palonosetron is a second generation 5HT3 RA and compared to other 5HT3 RA and exhibits allosteric receptor binding with positive cooperativity and stimulates internalization of cell surface serotonin receptor sites. Palonosetron has superiority over first generation 5HT3 RA such as Ondansetron in its pharmacological and pharmacokinetic action owing to its half life and receptor binding affinity.[13] The chemotherapy induced nausea and vomiting is an unpleasant side effect related to chemotherapy that can interfere with the compliance to the treatment regimen. There are limited studies available on the best antiemetic drugs for the treatment of chemotherapy induced nausea and vomiting, which paves the way for this systematic review on the best antiemetic treatment for CINV inpatients undergoing chemotherapy treatment.

Although many antiemetic medications options are available for CINV still studies on optimized antiemetic treatment for individual patient requirements are lacking which forms the basis for this systematic review.

## MATERIALS AND METHODS

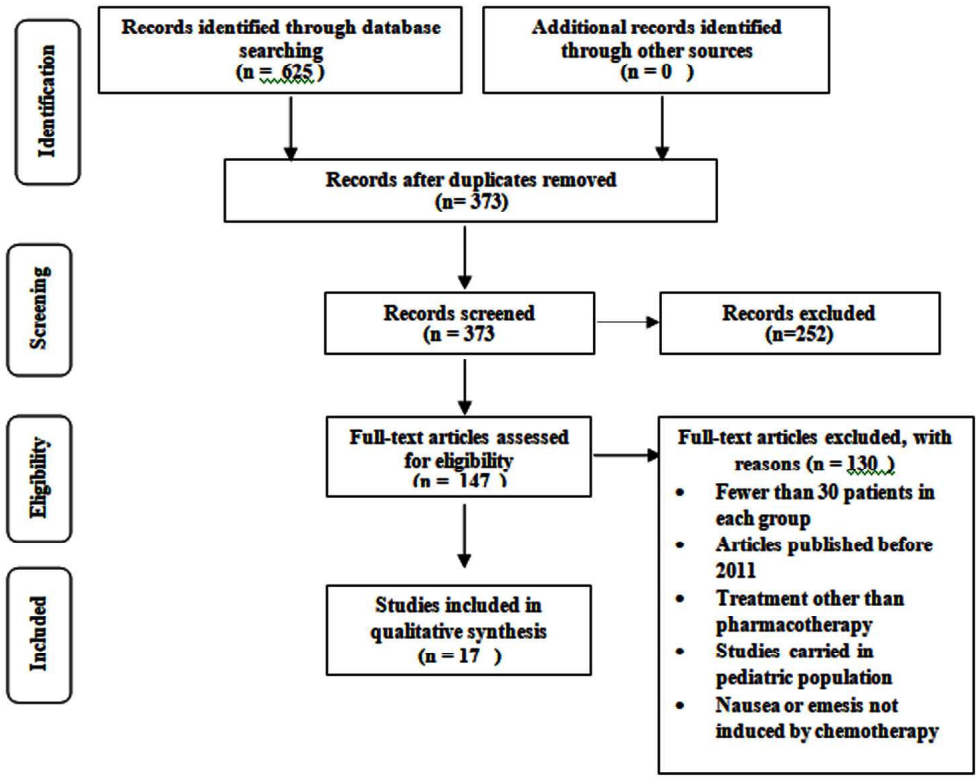


**Fig. 2:** PRISMA (Preferred Reporting Items for systematic Review and Meta-Analysis) flowchart for systematic review. 5-HT3 receptor antagonist, Corticosteroids, Olanzapine, Metoclopramide.

## STUDY PROTOCOL

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) was adopted in this systematic review) statement.

### *Information sources and search strategies*

From commencement of the study from 2022, a comprehensive literature search was performed in the electronic databases PubMed, Science Direct, Springer Link, Google Scholar, Uptodate, The first search term was "Treatment for chemotherapy induced nausea and vomiting" and the second term was " Efficacy and safety of various antiemetics in chemotherapy induced nausea and vomiting". The third search term was an individual drug category such as 5HT3 RA, NK1 RA, corticosteroids and individual drugs such as metoclopramide and olanzapine.

### *Selection criteria*

We included articles of RCTs study design and the study participants included in these study were of age group ≥ 18 yrs. The study participants were clinically diagnosed with malignancy and were on chemotherapy treatment.The articles reporting the outcomes of antiemetic prophylaxis treatment on chemotherapy induced nausea and vomiting were also included. We excluded articles published prior to 2011, studies in pediatric population, reviews, editorials, letters, case reports, inclusion of studies with statistically insignificant results and pilot studies with less than 30 patients. The articles were reviewed by three reviewers independently.

## DATA EXTRACTION AND QUALITY ASSESSMENT

The data for the study such as study characteristics, including author names, number of patients, type of cancer, drug name, dose, adverse effects of the drug, study design, study center, study duration, randomization, blinding, outcome measured,

and type of analysis, were checked and recorded according to preset criteria. The quality of the RCTs were assessed by using revised Cochrane risk of bias tool (ROB 2)

## RESULTS

### *Trial flow*

The protocol for the systematic review is given in Fig. 2. The initial search of the electronic databases resulted in 625 articles. From the above mentioned articles 373 were screened and 147 were identified as potential articles for the study.

### *Study selection:*

All the articles were screened for the inclusion criteria, only seventeen RCTs fulfilled the selection criteria. The exclusion of other articles from the study are due to the following reasons : (1) Sample of fewer than 30 patients, (2) Articles published before 2011 (3) Studies done on pediatric population, (4) Treatments other than pharmacotherapy (5) Nausea or emesis not caused by chemotherapy.

### *Characteristics of included studies*

The characteristics of the various studies included in this trial are described in table 1. The total number of individuals included in the study was9.816 and were evaluated for the appropriate treatment for chemotherapy induced nausea and vomiting based on the chemotherapeutic agent given. All the patients included in the study had malignancy and were receiving or scheduled to receive chemotherapy treatment.

### *Quality assessment of the studies*

In this study we included seventeen RCTs among which eleven were blinded and six were open label studies and parallel group design was adopted in these studies. The RCTs were assessed for risk of bias using revised Cochrane risk of bias tool for randomized trials (ROB 2). Out of the seventeen RCTs; twelve RCTs were found to havehigh risk of bias. Four of the studies were found tohave some concerns of risk of bias in the study. One of the studies had low risk of bias according to revised Cochrane risk of bias tool for randomized trials (ROB 2).

## METHODOLOGICAL QUALITY OF INCLUDED STUDIES JADAD SCALE

| Study | Risk of bias |
|---|---|
| 1. Henk M.W. Verheul et al.(2020) [17] | High |
| 2. Bernardo Rapoport et al.(2015) [11] | Some concerns |
| 3. M. Aapro et al. (2014) [20] | High |
| 4. Jin HYoung Kang et al. (2022) [5] | High |
| 5. R.M. Navari et al. (2013) [7] | High |
| 6. Lee S Schwartzberg et al.(2015) [22] | Some concerns |
| 7. Liu J et al. (2014) [9] | High |
| 8. Luigicelio et al. (2021) [21] | High |
| 9. R.M.Navari et al. (2016) [10] | Some concerns |
| 10. R.J.Gralla et al. (2014) [16] | High |
| 11. Toshiaki Saeki et al. (2022) [18] | High |
| 12. Shunichi Sugawara et al. (2019) [19] | Low |
| 13. Steven Grunberg et al. (2011) [12] | High |
| 14. Yoshito komatsu et al. (2015) [24] | High |
| 15. R.M. Navari et al. (2011) [8] | High |
| 16. Thomas Schmitt et al.(2014) [6] | Some concerns |
| 17. K. Suzuki et al (2016) [23] | High |

## STUDY OUTCOMES:

The study outcomes and analysis are given in table 3. Most of the trials (17) have taken overall complete response rate as the primary efficacy parameter and individual complete response in the acute and delayed phasesas the secondary efficacy parameter. Apart from the primary and secondary other outcomes included in the study were adverse events, quality of life, total control, nausea prevention, use of rescue medication. In three of the studies included in this systematic review supports that NEPA treatment regimenwas effective in preventing chemotherapy induced nausea and[20,21,16] Four of the articles supports that olanzapine treatment regimen was effective in preventing CINV in which one of the article concluded that olanzapine was superior to metoclopramide in the treatment of breakthrough emesis due to highly emetogenic chemotherapy.[8,7,21,10] Three of the studies analyzing the effectiveness of fosnetupitant, a prodrug of aprepitant treatment regimenconcluded that fosnetupitant was effective in controlling CINV and was well tolerated at the dose of 235 mg with results similar to aprepitant respectively.[19,18,12] Two of the study on determining the appropriate dose of rolapitant treatment regimen for controlling CINV concluded that at the dose 180 mg rolapitant was effective and well tolerated.[11,22] One study

compared the effectiveness of palonosetron with granisetronand concluded that palonosetron was similar to granisetron.[1,23] One of the study on graisetronas granisetron transdermal system and ondansetron concluded that granisetron was similar to ondansetron.[5] Two of the studies supports that single dose of dexamethasone was similar in efficacy compared with multiple dose administration of dexamethasone with NEPA and palonosetron respectively.[21,24]

| Authors (Country) | Outcome measures | | | Study outcome | |
|---|---|---|---|---|---|
| | Primary | Secondary | Others | Comparator | Effect |
| 1.K. Suzuki et al. (2016) (Japan)[23] | Overall complete response (CR) rate | 1. CR rates in acute (0-24h) and delayed (24-120h) periods 2. Complete control rates in which nausea is measured by 4 point Likert scale | | Palonosetron 0.75 mg IV on day 1 + aprepitant 125 mg on day 1 and 80 mg on day 2 +dexamethasone 9.9 mg on day 1 and 6.6 mg on days 2-4 vsgranisetron 1 mg on day 1+ aprepitant 125 mg on day 1 and 80 mg on day 2 +dexamethasone 9.9 mg on day 1 and 6.6 mg on days 2-4 | Palonosetron+ aprepitant+ dexamethasone group had significant effect in controlling CINV compared to gravisetron+ aprepitant+ dexamethasone |
| 2.Rudolph M. Navari et al. (2016) (USA)[10] | Nausea prevention | Complete response | | Palonosetron 0.25mg IV or granisetron 1 mg IV or ondansetron 8 mg P.O on day 1+Dexamethasone 12 mg on day 1 and 8 mg on days 2-4 P.O + aprepitant125 mg on day 1 and 80 mg on days 2,3 P.O or fosaprepitant150 mg on day 1 + Olanzapine10 mg on days 1-4vsPalonosetron 0.25mg IV or granisetron 1 mg IV or ondansetron 8 mg P.O on day 1+Dexamethasone 12 mg on day 1 and 8 mg on days 2-4 P.O + aprepitant125 mg on day 1 and 80 mg on days 2,3 P.O or fosaprepitant150 mg on day 1 +Placebo | Olanzapine significantly enhanced nausea prevention and as well as complete response rate |
| 3.Rudolph M. Navari et al. (2013) (USA) [7] | No. of patients with no emetic episodes in the 72 hr observation period | No. of patients with no nausea in 72 hr observation period | The frequency of severe toxicities and adverse events | Palonosetron0.25 mg+ fosaprepitant150 mg IV+ Dexamethasone 12 mg IV on day 1 and dexamethasone 8mg on days 2-4+ Olanzapine 10 mg P.O vsPalonosetron0.25 mg+ fosaprepitant150 mg IV+ Dexamethasone 12 mg IV on day 1 and dexamethasone 8mg on days 2-4+ metoclopramide 30 mg P.O | Olanzapine was more effective than metoclopramide in controlling breakthrough emesis and nausea |
| 4.Jin Hyoung Kang et al. (2021) (Korea)[5] | Percentage of patients achieving complete response of CINV upto 24 hrs | Percentages of patients achieving complete response during per study day (Day1-5) or overall study period | | Granisetron transdermal system 3.1 mg+ aprepitant125 mg P.O on day 1 and 80 mg on days 2,3 + dexamethasone 12 mg IV on day 1 and 16 mg P.O on days 2-4vsOndansetron 24 or 32 mg IV on day 1 and 16 mg on days 2-5 + aprepitant125 mg P.O on day 1 and 80 mg on days 2,3 + dexamethasone 12 mg IV on day 1 and 16 mg P.O on days 2-4 | Granisetron transdermal system was non inferior to ondansetron |

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| 5.Henk M.W. Verheul et al. (2020) (Netherlands) [17] | Total control in the delayed phase | Impact of CINV on qualiy of life and antiemetics associated side effects | Severity of nausea evaluated using 7 point likert scale, Analysis of covariance with Bonferroni correction | Ondansetron 8mg + dexamethasone 8mg on day 1 and dexamethasone 8 mg P.O on days 2-3 vs Ondansetron 8 mg IV+ dexamethasone 8mg IV on day 1 and metoclopramide 30 mg P.O on days 2-3 vspalonosetron 0.25mg IV+ dexamethasone 8mg IV on day 1 | Dex sparing regimens were non inferior to multiple day dex in controlling delayed phase total control rate |
| 7.Steven Grunberg et al. (2011) (USA) [12] | Complete response in the overall phase | Proportions of patients in the delayed phase and no vomiting during overall phase | | Fosaprepitant 150mg IV + ondansetron 32mg IV + dexamethasone 12mg P.O on day 1, dexamethasone 8mg orally on days 2 -4vsAprepitant 125 mg P.O + ondansetron 32mg IV + dexamethasone 12mg P.O on day 1 andaprepitant 80 mg P.O + dexamethasone 8mg on days 2,3 and dexamethasone 8 mg alone on day 4 | Single dose fosaprepitant was non inferior to 3 day oral aprepitant in controlling overall phase and delayed phase in CINV |
| 9.Thomas Schmitt et al. (2014) (Germany) [6] | Complete response within 120 h of melphalan administration | Complete response in the acute (0 to 24h) and delayed phase (25 to 120h) | Adverse events, impact on QOL assessed by FLIE score | Aprepitant 125mg P.O on ady 1 and 80 mg on days 2 to 4 +granisetron 2mg P.O on days 1 to 4 + dexamethasone 8mg on day 1 and 4mg on days 2 and 3 vsPlacebo + granisetron 2mg P.O on days 1 to 4 + dexamethasone 8mg on day 1 and 4mg on days 2 and 3 | The aprepitant significantly reduced CINV |
| 10.Rudolph M. Navari et al. (2011) (USA) [8] | Complete response in acute period, delayed period and overall period | | Adverse events | Olanzapine 10mg P.O+ palonosetron 0.25 mg IV + Dexamethasone 20 mg on day 1 and 10 mg or olanzapine alone on days 2-4 vsAprepitant 125mg , Palonosetron 0.25 mg IV + Dexamethasone 12mg on day 1 and Aprepitant 80mg on days 2-4 and 4mg of dexamethasone BID | Olanzapine regimen was significantly effective in delayed and overall periods in controlling CINV |
| 11.Lee S Schwartzberg [22] | Proportions of patients achieving a complete response in the delayed phase | Proportions of patients achieving complete response in the acute (0-24 h) and overall phases (0-120 h) | Time to first emesis and use of rescue medication, FLIE questionnaire | Rolapitant 180mg + granisetron 2mg P.O + dexamethasone 20 mg P.O on day 1 and granisetron 2mg P.O on days 2-3 vs Placebo + granisetron 2 mg P.O + dexamethasone 20 mg P.O on day 1 and granisetron 2 mg P.O on days 2-3 | Rolapitant group is superior to placebo group in preventing CINV |
| 13.Yoshito komatsu et al. (2015) [24] | Overall complete response rate | Complete response rate in acute and delayed phases, complete control | Frequency / severity of adverse events | Dexamethasone 9.9 mg on day 1 and 8 mg P.O on days 2,3 + Palonosetron 0.75mg IV on day 1 vs Dexamethasone 9.9 mg IV + Palonosetron 0.75mg IV on day 1 | Single day dosing of dexamethasone and palonosetron were non inferior to multiple day dosing of Palonosetron and dexamethasone |

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| 15.Bernado Rapoport et al. (2015) [11] | Complete response in the overall phase | Complete response in the acute (0-24h) and delayed phases (24-120h) | | Rolapitant 9 mg vs 22.5 mg vs 90 mg vs 180 mg + ondansetron 32 mg IV + Dexamethasone 20 mg on day 1 and 16 mg on days 2-4 vs Placebo + ondansetron 32 mg IV + Dexamethasone 20 mg on day 1 and 16 mg on days 2-4 | All rolapitant doses were well tolerated and complete response rates were higher at the dose of 180 mg |
| 16.Liu J et al. (2014) [9] | Complete response and Quality of Life | | Adverse events | azasetron 10 mg IV + dexamethasone 10 mg IV on day 1 + Olanzapine 10 mg P.O on days 1-5 vs azasetron 10 mg IV on day 1 + dexamethasone 10 mg IV on days 1-5 | Olanzapine was superior to Azasetron |
| 17.Luigi Celio et al. (2021) [21] | Complete response | Complete protection (CR and none to mild nausea) | | NEPA (Neputitant 300 mg + palonosetron 0.50 mg) + dexamethasone 12mg on day 1 vs NEPA (Neputitant 300 mg + palonosetron 0.50 mg) + dexamethasone 12 mg and 16 mg on day 2-3 vs NEPA (Neputitant 300 mg + palonosetron 0.50 mg) + dexamethasone 12mg and 4mg b.i.d on day 2-4 | Single dose dexamethasone dosage regimen has similar effect compared to the 4 day dexamethasone dosage regimen |
| 19.M. Aapro et al. (2014) [20] | Complete response during the delayed phase (25-120h) | Complete response during the acute (0-24 h) and overall phases (0-120 h) | Functional Living Index-Emesis (FLIE) questionnaire | NEPA (Netupitant 300 mg + Palonosetron 0.50 mg) + Dexamethasone 12 mg vs Palonosetron 0.50 mg + Dexamethasone 20 mg | NEPA was superior to Palonosetron during the acute, delayed and overall phases |
| 20.R.J. Gralla et al. (2014) [16] | Safety assessment by treatment emergent adverse events | Efficacy of NEPA | | NEPA (NETU 300mg + PALO 0.50 mg)+ Dexamethasone on day 1 vs Aprepitant 125 mg P.O on day 1 and 80 mg days 2-3)+ palonosetron 0.50 mg day 1 + Dexamethasone 12 mg on day 1 and 8 mg on days 2-4 | NEPA was similar to the aprepitant and palonosetron group |
| 21.Toshiaki Saeki et al. (2022) [18] | Incidence of TRAEs | Complete response rate | | Fosnetupitant 235 mg IV + Palonosetron 0.75 mg IV + dexamethasone 9.9 mg IV on day 1 vs Fosaprepitant 150 mg IV + Palonosetron 0.75 mg IV + dexamethasone 9.9mg IV on day 1 | Incidence of TRAE in fosneputitant group was similar to fosaprepitant group |
| 22. Shunichi Sugawara et al. (2019) [19] | Percentage of patients with complete response during overall phase | Percentage of patients with complete response during the acute (0-24 h) and delayed phase (24-120 h) | Complete protection | Fosnetupitant 81 mg + Palonosetron 0.75 mg on day 1 and dexamethasone 9.9 mg on day 2 to 4 vs Fosnetupitant 235 mg + Palonosetron 0.75 mg on day 1 and dexamethasone 9.9 mg on day 2 to 4 vs Placebo + Palonosetron 0.75 mg on day 1 and dexamethasone 13.2 mg on day 2 to 4 | Fosnetupitant 235mg was superior to 81 mg and placebo |

**Demography**

| Authors (Country) | Partic-ipants (M/F) | Median Age in yrs | Type of cancer | Inclusion c riteria | Exclusion c riteria | Sample (interv ention/ control) | Treat-ment period (per cycle) | Adverse events |
|---|---|---|---|---|---|---|---|---|
| 3. Luigi celio et al. (2021) (Italy) [21] | 252 (169/ 83) | Median 61.5 | Non-small cell lung cancer | Age ≥18 yrs with confirmed diagnosis of non-small cell lung cancer and chemo naïve and scheduled to receive cisplatin (≥70mg/m2) alone or in combination with low and minimal emetogenicity, ECOG PS of 0 or 1, and adequate hematologic, hepaic and renal functions) | Patients to receive concurrent radiation therapy or radiotherapy to abdomen or pelvis within 1 week prior chemotherapy, symptomatic brain metastasis, contraind-ications for cortico-steroids, routine use of corticosteroid or any agent with emetogenic potential before 24 hrs of chemo therapy | 252 (84/ 85/ 83) | 4 days | Fatigue, Gastritis, consti pation, Diarrhoea |
| 4. K. Suzuki et al. (2016) (Japan) [23] | 827 (616 /211) | Median 63 | Non- small cell lung<br>Small- cell lung<br>Esophageal<br>Gastric<br>Head and neck<br>Other | Patients with cisplatin-naïve solid tumor to receive cisplatin (≥50mg/m2), aged ≥ 20 yrs, ECOG PS 0-2, adequate organ function (aspartate transaminase <100 IU/l, alanine transaminase <100 IU/l, total bilirubin <2.0 mg/dl, creatinine clearance ≥60 ml/min) | Inability to stay at the study hospital, currently using antiemetic drugs, gastrointestinal obstruction, ascites or pleural effusion, symptomatic brain metastasis, current radiotherapy directed towards, patients with uncontrolled complications and pregnant women | 827 (414, 413) | 4 days | |
| 5.Liu J et al. (2015) (China) [9] | 229 (137/92) | Median 50.5 | Lung<br>Breast<br>Colorectal<br>Lymphoma<br>Ovarian<br>Stomach<br>Oesophageal<br>Teratoma<br>Oropharyngeal cancer Thymus cancer Cervical cancer<br>Gingival cancer<br>Malignant melanoma<br>Laryngeal cancer<br>glioblastoma | Diagnosis of malignant cancer or previously treated by chemotherapy (MEC or HEC), adequate bone marrow, liver, normal cardiac function, electrocardiogram performance status ≥ 2, | Nausea in 24 hrs preceding olanzapine or chemotherapy, severe cognitive compromise, CNS disease, antipsychotic medications, concurrent abdominal radiotherapy, hypersensitivity to olanzapine, uncontrolled diabetes mellitus, concurrent medical disease. | 229 (121 / 108) | 5 days | |
| 6.M. Aapro et al. (2014) (Switzer land) [20] | 1449 | Median (54) | Breast<br>Other | Aged ≥ 18 yrs chemotherapy naïve patients scheduled to receive 1st course of AC MEC regimen for solid malignant tumor, ECOG PS 0,1 or 2 | HEC from day 1-5 or additional MEC from day 2 to 5 following chemotherapy, radiation therapy to the abdomen or pelvis | 1449 (724/ 725) | 1 day | |
| 6.M. Aapro et al. (2014) (Switze rland) [20] | 1449 | Median (54) | Breast<br>Other | Aged ≥ 18 yrs chemotherapy naïve patients scheduled to receive 1st course of AC MEC regimen for solid malignant tumor, ECOG PS 0,1 or 2 | HEC from day 1-5 or additional MEC from day 2 to 5 following chemotherapy, radiation therapy to the abdomen or pelvis | 1449 (724/ 725) | 1 day | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7. Bernardo Rapoport et. al. (2015) (South Africa) [11] | 454 (244/ 210) | Median (55) | | Aged ≥18 yrs with karnofsky Performance Status (KPS) ≥60, had predicted life expectancy of ≥ 3 months, had adequate bone marrow, kidney, and liver function and were scheduled to receive HEC | Received cisplatin, or 5 HT3 RA, NK1 RA or other drugs that interfere with the study, if they are scheduled to receive any radiation therapy to the abdomen or pelvis, received systemic corticosteroids | 454 ( 91/91/ 91/ 90/91) | 4 days | Consti-pation, headache, fatigue, dizziness |
| 8. Henk M. W. Verheul et al. (2020) (Nethe rlands) [17] | 189 (101/ 88) | Median (65) | Colorectal Ovarian Lung Gastric Pancreatic Other | Aged ≥ 18 years, naïve to chemotherapy, confirmed solid tumor malignancy, scheduled to receive first course of MEC, ECOG PS of 0-1 and acceptable hematologic, hepatic, and renal functions | Patients scheduled to receive radiotherapy, antiemetic drugs 48 hrs before chemotherapy, vomiting, retching, or mild nausea 48 hrs before chemotherapy, intestinal obstruction, active peptic ulcer, hypercalcemia, uncontrolled diabetes mellitus, pheochromocytoma, brain or leptomeningeal metastases, parkinsonism, epilepsy, or psychiatric disorders, pregnant and nursing women and use of corticosteroids | 189 (60/66/ 63) | 3 days | Inso-mnia, Decr-eased appetite, Depre-ssion, Rash /Acne, Thrush/ oral yeast infection |
| 9. Lee S Schwar tzberg et. (2015) ( USA) [22] | 1332 (265/ 1067) | Median 55 | Breast Colon or rectum Head and neck Lung Ovary Stomach Other tumours | Aged ≥ 18 yrs with karnofsky performance score of 60 or more, predicted life expectancy of 4 months or longer, and had adequate bone marrow, kidney and liver function | Previously received MEC or HEC., uncontrolled disorder other than malignant disease, contraindication | 1332 (666/666) | 3 days | Consti-pation, headache, fatigue, dizz iness |
| 10.Yoshi to komatsu et. (2015) (Japan) [24] | 305 (173/ 132) | Median 54 | Colorectal Lung breast | Aged ≥ 20 yrs, diagnosis of malignant tumor, no history of chemotherapy, planned administration of non AC MEC, and sufficient marrow, renal and kidney function | History of grade 2 or higher nausea prior to enrollment, previous palonosetron use, planned administration of MEC on multiple sequential days, and planned administration of cisplatin regardless of dose | 305 (154/151) 298 (150/148) | 3 days | Consti-pation, hiccups, anorexia, elevated ALT |
| 11.Jin Hyoung Kang et al. (2021) (Korea) [5] | 370 (257/ 113) | Median (60) | Lung Gastrointestinal Head or neck Breast Other | Age ≥ 20 yrs, life expectancy ≥ 3 months, ECOG status ≤ 2. Patients to receive one cycle of chemotherapy (for ≤ 5 days with HEC) | Hypersensitivity to skin patches, contraindications to 5HT3 RA, any other cause that can induce nausea and vomiting, radiation therapy to brain, abdomen, or whole body within 7 days of study entry, abnormality on ECG, drugs that control symptoms of brain metastasis, brain tumour, seizure disorders, SSRI, antidepressants | 370 (184 /186) | 5 days | Consti-pation, decrea-sed appetite, dyspe psia, hiccups and cough, pruritus in patch related AE. |

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| 12. R.M. Navari et al. (2013) (USA) [7] | 108 (50/58) | Median (62) | Bladder Breast Lung (Non small cell) Malignant Lymphoma | Serum creatinine of≤2.0 mg/dl, serum bilirubin of ≤2.0 mg/dl, SGOT or SGPT values of ≤3 times the upper limits of normal, absolute neutrophil count of ≥ 1,500mm3,Patients with nausea in 24 hrs prior chemotherapy, Patients of child bearing potential must use contraception throughout protocol therapy, women of child bearing potential must have a negative urine pregnancy test | History of CNS disease, use of other antipsychotics for 30 days prior to therapy, concurrent use of ethyol, abdominal radiotherapy, concurrent use of quinolone antibiotic, chronic alcoholism, hypersensitivity to olanzapine, cardiac arrhythmia, uncontrolled congestive heart failure, acute myocardial infarction within previous 6 months, diabetes mellitus | 108 (OLN 56/ METO 52) | 4 days | , Fatigue, disturbed sleep, Lack of appetite, sedation, |
| 13. R.M. Navari et al. (2016) (USA) [10] | 380 (105/275) | Median 57 | Breast Lung Other | Aged ≥ 18 yrs with malignant disease, not received chemotherapy previously, ECOG PS 0,1 or 2, serum creatinine level of 2 mg/dL,AST or ALT ≤3 times the upper limit of normal range, absolute neutrophil count of atleast 1500 per mm3 | Nausea and vomiting 24 hrs before enrollment, severe cognitive impairements, CNS disease, another antipsychotic agent. Within 30 days before enrollment, concurrent use of amifostine, concurrent abdominal radiotherapy, concurrent use of quinolone antibiotic therapy, chronic alcoholism, hypersensitivity to olanzapine, cardiac arrhythmia,congestive heart failure, myocardial infarction, diabetes mellitus, negative pregnancy test in women. | 380 (olanz apine 192, Placebo 188) | 4 days | Fatigue, hypergl-ycemia, abdo-minal pain, diarrhoea |
| 14. Shun-ichi Suga-wara et al. (2019) (Japan) [19] | 584 (441/143) | Median 66.7 | Lung Other | Aged ≥ 20 yrs, confirmed malignant solid tumor, scheduled to receive cisplatin at a dose of ≥ 70 mg/m2, received no chemotherapy or prior low or minimally emetogenic chemotherapy regimen, ECOG PS 0 or 1, adequate hematologic, hepatic, and renal function | Gastrointestinal stenosis, any vomiting, retching, or nausea within 24 hours prior to enrollment, severe complication, infection, diabetes mellitus that could be associated with difficulties with the administration of dexamethasone; hypersensitivity to NK1 RAs, 5-HT3 RAs, or dexamethasone. Patients who had received a cytochrome P450 3A4 inhibitor or inducer, had received an opioid analgesic, had undergone surgery, or had undergone radiotherapy within 7 days before registration and pregnant and nursing women also were excluded. | 584 (195/195 /194) | 4 days | Anemia, Febrile neutropenia, Leukopenia, Neutropenia, Hypergly -cemia, Hyponat -remia, Insomnia, constipation, hiccups, reatment-related injection site thrombo phlebitis, Stomatitis |

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| 15. Steven Grunberg et al. (2011) (USA) [12] | 2322 (1470/ 852) | Median 56 | Lung GI cancer Reproductive or genitourinary Renal and urinary tract Breast | Aged ≥18 yrs with histologically confirmed malignancies, Karnofsky scores ≥ 60, predicted life expectancy ≥3 months, scheduled to first course of cisplatin (≥70 mg/m2), Absolute neutrophil count ≥ 1,500 cells/μL,platelet count ≥100,000 cells/ μL, AST and ALT ≤2.5 × upper limit of normal (ULN), bilirubin ≤ 1.5×ULN, and creatinine≤ 1.5× ULN | pregnant and breastfeeding women, scheduled to receive radiation therapy to the abdomen or pelvis, scheduled to receive stem-cell rescue therapy, vomiting in 24hrs before treatment, active infection or uncontrolled disease other than malignancy, Patients taking systemic corticosteroids | 2322 (1,143/ 1,175) | 4 days | Throm bophl- ebitis, Erythema, Priritus, Phlebitis, swelling, injection site pain, infusion related reaction, vessel puncture site pain |
| 18. Thomas Schmitt et al. (2014) (Germany) [6] | 362 (230/132) | Median 58.1 | Multiple myeloma | Aged ≥18 yrs with multiple myeloma undergoing autologus transplantation after high dose melphalan conditioning | Nausea or vomiting12 hrs before planned high dose emotherapy,antiemetic treatment 24 hrs prior high dose chemotherapy, corticosteroid intake, hypersensitivity to investigational product | 362 (181/181) | 4 days | Leuko- penia, hypoc- alcemia, fatigue, edema, const' ipation |
| 20. Rudolph M. Navari et al. (2011) (USA) [8] | 241 (77/164) | Median 62 | Bladder Brreast Lung (non-small cell) Malignant Lymphoma | Aged ≥18 yrs with malignant disease who were chemotherapy naïve and scheduled to receive HEC, serum creatinine ≥ 2.0 mg/dL, serum bilirubin ≥2.0 mg/ dL, serum glutamic-oxaloacetictransa,inase (SGOT) or SGPT ≤ 3 or more times the upper limits of normal, absolute neutrophil count ≥1.500 mm3 | Nausea in 24hrs prior to chemotherapy, severe cognitive compromise. History of CNS disease, use of other antipsychotic medications 30 days prior to protocol therapy, concurrent use of amifostine, abdominal adiotherapy, quinolone antibiotic use, chronic alcoholism, cardiac arrhythmia, uncontrolled congestive heart failure, acute myocardial infarction within previous 6 months,uncontrolled diabetes mellitus | 241 (121/120) | 4 days | |
| 21. Toshiaki Saeki et al. (2022) (Japan) [18] | 102 (0/102) | Median 56 | | Patients scheduled to receive AC/EC, | | 102 (52/50) | 1 day | headache, diarrhea, urticaria, malaise, and decreased appetite, neutrophil count decreased and white blood cell count decreased |

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| 22.R.J. Gralla et al. (2014) (USA) [16] | 412 (50 %/50%) | Median 58 | Lung<br>Ovarian<br>Colon<br>Head and neck<br>Colorectal<br>Rectal<br>Gastric<br>Bladder<br>Other | Aged ≥ 18 yrs, diagnosed with malignant tumor, naïve to chemotherapy, Single IV dose of one or more HEC (cisplatin, mechlorathamine, streptozocin, cyclophosphamide, carmustine, dacarbazine) MEC ( oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamise, azacitidine, alemtuzumab, bendamustine or clofarabine, on day 1, ECOG PS 0-2 | Patients with breast cancer scheduled to receive anthracycline-cyclophosphamide (AC) chemotherapy, scheduled to receive MEC or HEC from day 2-5, bone marrow transplant or stem cell rescue therapy, Previously received NK1 RA, hypersensitivity or contraindication to 5HT3 RA or dexammethasone | 412 (308/ 104) | 3 days |

## ADVERSE EFFECTS

NEPA (Netupitant + Palonosetron) was well tolerated in the patients without major adverse events leading to withdrawal of the patients from the study.[20] Metoclopramide induced dyskinesis was observed in six patients enrolled in a study involving patients with histologically or cytologically confirmed tumor malignancies.[17] In a study with Rolapitant it was found to be well tolerated and common adverse events observed were constipation, fatigue dizziness and headache. In another study evaluating the safety of rolapitant in various doses also it was found to be well tolerated.[22,11] In a study comparing Granisetron (TDS) with ondansetron both groups had common adverse events such as constipation, decreased appetite, dyspepsia, hiccups, cough.[5] In a study two patients in granisetron group had grade 4 adverse events of gastric perforation and acute kidney dysfunction.[23] Acute psychosis was observed in a study with NEPA as the intervention and reported that it might be associated with dexamethasone.[16] In a study conducted among patients receiving doxorubicin-cyclophosphamide and epirubicin cyclophosphamide the treatment related adverse event reported in fosnetupitant group were headache, urticaria, malaise, decreased appetite, neutropenia, leucopenia and constipation.[18] The frequently observed adverse events in the patients receiving aprepitant and placebo were leucopenia, hypocalcemia, fatigue, edema, constipation.[6] A study comparing the efficacy of single dose fosaprepitant regimen with ondansetron and dexamethasone regimen reported that adverse event profiles between both the treatment regimen were similar and were well tolerated.[12]Olanzapine was reported to be well tolerated in a study consisting of patients receiving cisplatin or cyclophosphamide and doxorubicin with no grade 3 to 4 toxicities.[10]

## DISCUSSION

Rudolph M. Navari et al. (2011) compared the efficacy of olanzapine andaprepitant for the prevention of chemotherapy induced nausea and vomiting in combination with palonosetron and dexamethasone in both the groups. This study was conducted in patients receiving cisplatin or cyclophosphamide and doxorubicin. The authors reported that the control of CINV in acute and delayed phases were similar in olanzapine andaprepitant groups respectively.[8] Shunichi sugawara et al. (2019) evaluated the efficacy and safety of fosnetupitant in combination with palonosetron and dexamethasone for the prevention of CINV in patients scheduled to receive cisplatin based chemotherapy for malignant solid tumor. The authors concluded that fosnetupitant at the dose of 235 mg was effective in preventing CINV with reasonable safety profile.[19]

Thomas Schmitt et al. (2014) evaluated the efficacy of aprepitant, granisetron and dexamethasone in preventing chemotherapy induced nausea and vomiting in patients with multiple myeloma and received melphalan as conditioning regimen prior to autologus stem cell transplantation. The authors concluded that addition of aprepitant in the treatment regimen along with granisetron and dexamethasone significantly reduced CINV and enhanced the quality of life of the patients.[6]

Bernado Rapoport et al. investigated the drug rolapitant for its safety and efficacy in the prevention of CINV at various doses of 9 mg, 22.5 mg, 90 mg, 180 mg. This study was conducted in

patients receiving cisplatin based chemotherapy and rolapitant was given in combination of ondansetron and dexamethasone. The authors concluded that all the doses of rolapitant were well tolerated and dose of 180 mg had significant efficacy in preventing CINV.[11]

Rudolph M. Navari et al. compared the effectiveness of olanzapine with metoclopromide for the treatment of breakthrough chemotherapy induced nausea and vomiting caused by highly emetogenic chemotherapy. The patients developing break through emesis or vomiting even though receiving prophylactic treatment were included in this study and randomized to receive olanzapine or metoclopramide. The authors concluded that olanzapine was more effective than metoclopramide in controlling breakthrough emesis and nausea caused by highly emetogenic chemotherapy.[7] Yoshitokomatsu et al. evaluated the non inferiority of single administration of dexamethasone along with palonosetron over multiple day administration of dexamethasone with palonosetron inthe prevention of CINV in patients receiving moderately emetogenic chemotherapy. The authors concluded that single administration of dexamethasone was similar in efficacy in comparison to multiple day administration of dexamethasone and hence multiple doses can be omitted to prevent dexamethasone associated ADRs.[24] M. Aapro et al. (2014) analyzed the safety and efficacy of NEPA, a fixed dose combination of Netupitant and Palonosetron with dexamethasone in the prevention of CINV in patients receiving moderately emetogenic chemotherapy. The authors concluded that NEPA with dexamethasone exhibited superiority in preventing CINV in the delayed and overall phases compared to palonosetron with dexamethasone. Moreover the safety profile of NEPA was similar to palonosetron and was well tolerated.[20] Toshiaki Saeki et al. (2021) investigated the safety of fosnetupitant when administered as an antiemetic agent for CINV in patients receiving doxorubicin and cyclophosphamide or epirubicin and cyclophosphamide as treatment for cancer. The authors concluded that fosnetupitant was well tolerated with minimal treatment related adverse events in the patients.[18] Henk M.W. Verheul et al. (2020) compared three antiemetic treatment regimen for prevention of CINV in which two were dexamethasone sparing treatment regimen. The other treatment regimen consisted of multiple day administration of dexamethasone with ondansetron. The two dexamethasone sparing antiemetic treatment regimen consisted of ondansetron, metoclopramide and palonosetron respectively and received single day administration of dexamethasone. The authors concluded that the two dexamethasone sparing regimens were non-inferior to multiple day administration of dexamethasone in controlling delayed phase nausea and vomiting.[17]

Luigi celio et al. compared the efficacy of three treatment regimens with NEPA and varied dexamethasone frequency of administration to reduce the overall exposure to dexamethasone and thereby reducing the dexamethasone associated adverse drug reactions. The authors concluded that single dose of dexamethasone with NEPA provided comparable CINV prevention with other frequencies of administration of dexamethasone in patients receiving cisplatin based highly emetogenic chemotherapy.[21] K. Suzuki et al. compared the efficacy of Palonosetronand granisetron in patients diagnosed with malignant tumor and receiving highly emetogenic chemotherapy. All the patients included in this study received aprepitant and dexamethasone along with their respective treatment regimen. The authors concluded that palonosetron was similar in efficacy compared to granisetron and was not found to be significantly superior.[23]

Liu J et al. evaluated the efficacy of olanzapine and 5HT3 RA respectively in preventing CINV in patients with cancer receiving chemotherapy and improving their quality of life. The authors concluded that olanzapine was superior to 5HT3 RA in controlling delayed phase CINV and improved global health status, emotional functioning and insomnia.[9] Lee S Schwartzberg et al. evaluated the safety and efficacy of rolapitant with granisetron and dexamethasone in preventing CINV. The authors concluded that rolapitant was significantly effective in the prevention of CINV in the delayed phase and was well tolerated in the patients.[22]

Rudolph M. Navari (2016) et al. evaluated the efficacy of olanzapine with dexamethasone, aprepitant or fosaprepitant and a 5HT3 RA in preventing chemotherapy induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. The authors concluded that olanzapine was significantly effective in the prevention of nausea and vomiting in the delayed and acute phases.[10] RJ Gralla et al. evaluated the safety and efficacy of NEPA containing netupitant and palonosetron with dexamethasone for prevention of CINV in patients with malignant tumor and receiving highly or moderately emetogenic chemotherapy. The authors concluded that NEPA was well tolerated and was more

effective in preventing CINV compared to treatment regimen containing aprepitant withpalonosetron and dexamethasone>[16]

Jin Hyoung Kang et al. compared the efficacy of granisetron transdermal system with ondansetron in controlling CINV in patients receiving highly emetogenic chemotherapy. The authors concluded that granisetron was non-inferior to ondansetron in controlling CINV in patients receiving multiple day highly emetogenic chemotherapy and therby improving QoLand was well tolerated.[5] Steven grunberg et al. compared single dose administration of fosaprepitant with multiday administration of aprepitant for the prevention of CINV in patients receiving cisplatin based chemotherapy. The authors concluded that fosprepitant was non inferior and similar in efficacy to aprepitant with well tolerated safety profile.[12]

## CONCLUSION

Our systematic review provides evidence for the effectiveness of triple antiemetic regimen for CINV consisting of 5HT3 RA, NK1 RA and dexamethasone. Most of the studies used multiple day dosing of dexamethasone although some studies suggest that reduction of dexamethasone exposure in order to avoid adverse effects related to dexamethasone is possible. Few studies have also evaluated olanzapine as an antiemetic drug and have found to have significant efficacy in controlling CINV. In addition olanzapine was also found to be superior to metoclopramide when used as rescue medication for breakthrough emesis. The present RCTs included in this review have high to some concern in risk of bias and cannot be considered reliable source of evidence and only one study had low risk of bias. Hence we recommend that future trials be conducted with minimum risk of bias to ensure high quality of evidence.

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