A GROUP SEQUENTIAL, RESPONSE ADAPTIVE RANDOMIZED DOUBLE-BLINDED CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF AN ADD-ON COMBINATION OF OLANZAPINE AND PREGABALIN FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN PATIENTS RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPEUTIC REGIMEN IN A DAYCARE SETTING

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1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the factors significantly affecting the patient's quality of life and reduces compliance to chemotherapy medication. When antiemetic prophylaxis is not given, the incidence of CINV is as high as 90% with highly emetogenic regimens (HEC) and 30-90% with Moderately Emetogenic regimens (MEC) (1). With extensive research work in this area, control of vomiting is better than nausea control (2).

Chemotherapy-induced nausea and vomiting are divided into 3 phases: acute phase – on the day of chemotherapy (0-24 hrs), delayed phase (25-120hrs) following chemotherapy, and anticipatory phase. The acute phase is mediated by serotonin through 5-HT3, whereas the delayed phase is due to substance-P through the NK-1 receptor in the brain (3). Anticipatory nausea/vomiting is due to the conditional response to previous chemotherapy cycles mediated by various physiological and pathological mechanisms (4).

The current guidelines approach CINV prophylaxis and management according to their emetogenic potential (1). The chemotherapy regimens are classified into four levels according to their emetogenic potential: Highly emetogenic ->90%, moderately emetogenic - 30 % to 90%, low-10% to 30%, and minimal-<10% (1).

At present, 5-HT3 receptor antagonists, dexamethasone, and NK-1 receptor antagonists are used to prevent CINV. The 5-HT3 receptor antagonists act centrally (in the area postrema) and peripherally (in the intestine) to prevent emesis. Currently approved agents in this category are ondansetron, palonosetron, granisetron, and dolasetron (5). Dexamethasone is used as a prophylactic antiemetic, but its exact mechanism is unknown (6). The neurokinin-1 receptor antagonists currently available are aprepitant, fosaprepitant, and netupitant. They generally prevent the delayed phase of CINV (6).

Even with antiemetic prophylaxis still, patients experience nausea and vomiting, especially nausea during cancer chemotherapy. Studies assessing the patient's quality of life using the Functional Living Index Emesis (FLIE) questionnaire signify that CINV had a negative impact on the quality of life (QOL) of the patient (7). The cost of an NK-1 receptor antagonist is also high and creates a cost burden on a patient with low socio-economic status (8). So, an alternative cheaper agent is needed.

Olanzapine, an atypical antipsychotic, is used as an antiemetic agent through its ability to block the multiple neurotransmitters in the brain, such as dopamine, histamine, serotonin, and acetylcholine (9). Olanzapine 10mg is recently added to guidelines (National comprehensive cancer network) as one of the components of a four-drug combination to manage CINV due to highly emetogenic chemotherapeutic agents (1). Recent studies have suggested low doses (5mg) will have the same efficacy with less sedation (10).

Pregabalin, a gabapentinoid, acts on the alpha-two delta subunit of the presynaptic calcium channel and inhibits the release of many excitatory neurotransmitters, including substance-P, dopamine, serotonin, glutamate, and norepinephrine (11). A meta-analysis showed that pregabalin reduced the incidence of postoperative nausea and vomiting (12). Rossi et al. (13) explored its role in CINV and concluded that there is no role in the management of CINV. Nevertheless, its role combined with olanzapine has not been explored in CINV until now. Gabapentin, another gabapentinoid, has shown some efficacy in reducing CINV (14).

Neutipant plus palonosetron has shown good efficacy in controlling delayed nausea and vomiting. However, their cost burden is a significant concern inhibiting their use in patients with low socio-economic status (8). So, the search for an alternative treatment regimen that is cheaper and has less CYP interaction, unlike NK-1 antagonists, is needed. Despite the newer antiemetic regimens, the control of nausea is not optimal. We hypothesize that there might be a synergism as pregabalin could reduce the release of neurotransmitters, and olanzapine could block the action of the released neurotransmitters. So, the present study is conducted to evaluate the safety and efficacy of the add-on combination of olanzapine plus pregabalin for preventing CINV in patients with low economic status receiving highly emetogenic chemotherapeutic agents.

2 Review of literature

2.1 Search Strategy

2.1.1 Electronic search

An electronic search was carried out using the following databases- PubMed, Google Scholar, and Medline. Web sites of the National Comprehensive Cancer Network (NCCN), Multinational Association of Supportive Care in Cancers (MASCC), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) were also searched. Attempts were made to retrieve the grey literature, like unpublished data and conference proceedings.

2.1.2 Manual search

A manual search was done in the central library and the Departmental library of Pharmacology, All India Institute of Medical Sciences, Bhubaneswar.

2.1.3 Keywords used for literature review.

The following keywords and their combinations were used while searching for relevant literature.

"CINV, chemotherapy-induced nausea and vomiting, Anticancer chemotherapy, Prepatent, Olanzapine, Ondansetron, Pregabalin, FLIE, HEC, highly emetogenic chemotherapy, MEC, Moderately emetogenic chemotherapy, Dopamine receptors, NK-1 receptor antagonists, 5-HT3 receptor antagonists, No nausea".

A review of the literature is detailed in the following subdomains:

2.2 Chemotherapy-induced nausea and vomiting (CINV) and phases
2.3 Complications of CINV
2.4 Risk factors for CINV
2.5 Mechanism of CINV
2.6 The emetogenic potential of cancer chemotherapy agents
2.7 Currently available drugs
2.8 5HT3 receptor antagonists
2.9 Dexamethasone
2.10 Recommendation by international guidelines
2.11 Unmet need and justification for the present study

2.2 Chemotherapy-induced nausea and vomiting (CINV) and phases

Chemotherapy-induced nausea and vomiting (CINV) are one of the common adverse effects that occur after the administration of cancer chemotherapeutic agents. It will significantly affect the patient's quality of life and reduce compliance to further administration of chemotherapeutic agents. Even with the advent of newer antiemetics, complete control of chemotherapy-induced nausea is not achieved and is still a major problem for many patients. CINV can be classified based on the onset of nausea and vomiting into acute, delayed, and late delayed phases(4).

- The acute phase occurs within the first 24 hours after the administration of chemotherapy, often due to the direct effect of chemotherapy on the gastrointestinal tract. It is usually managed with prophylactic antiemetics such as 5-HT3 receptor antagonists (like ondansetron, palonosetron, or granisetron), corticosteroids (dexamethasone), and NK-1 receptor antagonists (like aprepitant, fosaprepitant or neutipitant).
- The delayed phase occurs 25-60 hours after the administration of chemotherapy due to the delayed effects of chemotherapy on the gastrointestinal tract and central nervous system. These phases are often more challenging and may require different antiemetic agents, such as corticosteroids and NK-1 receptor antagonists.
- The late-delayed phase occurs more than 60 hours after the administration of chemotherapy only in some cases.

Apart from the onset of nausea and vomiting, CINV can also be classified as anticipatory or breakthrough (6).

- Anticipatory CINV occurs before chemotherapy administration and is often due to conditioned responses from previous chemotherapy experiences. Breakthrough CINV, on the other hand, occurs despite prophylactic antiemetic treatment and may require rescue antiemetics such as dopamine receptor antagonists, benzodiazepines, and cannabinoids.
- Refractory CINV occurs when nausea and vomiting do not respond to any medications. This phenomenon is often due to patient-related factors such as anxiety and depression and chemotherapy-related factors such as high-dose chemotherapy and emetogenic chemotherapy agents.

2.3 Complications of CINV

CINV can lead to various complications, such as dehydration, electrolyte metabolic imbalance, and oesophageal tears. These complications may also compromise treatment efficacy by increasing the patient's refusal to further chemotherapy administration.

One of the most significant complications of CINV is dehydration. Patients with chemotherapy-induced vomiting will lose body water in terms of vomiting and reduce total fluid intake due to chemotherapy-induced nausea. This will cause electrolyte imbalances, affecting various organ systems, including the heart, kidneys, and nervous system. The metabolic imbalance can be severe, leading to significant health issues (4).

Oesophageal tears are another potential complication of CINV. Patients who vomit repeatedly may experience damage to the oesophageal lining, leading to tears and inflammation. This can cause significant pain and discomfort, and in some cases, it may require surgical intervention (1).

In addition to physical complications, CINV can significantly impact a patient's mental health. Patients who experience persistent nausea and vomiting may become anxious and depressed, affecting their overall performance. This can be incredibly challenging for cancer patients who are already struggling with the emotional toll of their diagnosis and treatment.

Furthermore, CINV can also lead to a decline in a patient's quality of life, negatively affecting their treatment outcomes (15). Patients who experience CINV may be less likely to adhere to their treatment regimen, which can compromise the effectiveness of chemotherapy. In some cases, patients may even refuse treatment altogether, leading to delays in care and potentially compromising their chances of full recovery. It also increases the length of stay in the hospital and increases the financial burden (2).

2.4 Risk factors for CINV

The risk factors for CINV are complex, and the severity of CINV symptoms can vary depending on the individual. Patients with the following characteristics will have a significant risk of CINV such as,

- During chemotherapy, female sex was more likely than men to experience nausea and vomiting.
- Younger age is also a risk factor for CINV. Children and young adults tend to have more severe CINV symptoms than older adults, possibly due to physiological differences.
- Patients who have received prior anticancer agents may also be at a higher risk of developing CINV, as they are more sensitive to the drugs.
- Patients with a history of low alcohol consumption, travel sickness (motion sickness), or morning sickness are likelier to experience CINV.

Healthcare providers must carefully consider each patient's medical history and current health status to develop an appropriate plan for managing CINV during and after cancer treatment.

2.5 Mechanism of CINV

Vomiting is a complex process that involves the activation of multiple neurotransmitter reflex pathways (5). Afferent signals from various sources, including the peripheral gastrointestinal tract (GIT), pharynx, labyrinth, and central neuro cortex, are relayed to the vomiting center in the medulla oblongata, specifically in the area postrema (5). The dorsal vagal complex, which comprises the Nucleus tractus solitarius (NTS), area postrema, and dorsal motor nucleus of the vagus nerve, receives afferent fibres from the GIT, which respond to various chemical transmitters such as serotonin (5-HT), substance-PP, and cholecystokinin (5). This afferent pathway is responsible for most cases of acute nausea.

Endogenous toxins and exogenous chemotherapy drugs can also act directly on the vomiting center through the area postrema, devoid of the blood-brain barrier. The neurochemicals in coordinating nausea and vomiting in the vomiting center include substances-P, serotonin, dopamine, histamine, acetylcholine, and their receptors. Efferent

signals are sent simultaneously in a coordinated manner to the salivation center, respiratory center, esophagus, stomach, and abdominal muscles, resulting in nausea and vomiting (5).

In the case of chemotherapy-induced nausea and vomiting (CINV), a multistep reflex pathway is involved (5). The vomiting center (VC) is in the medulla oblongata, integrating various peripheral and central inputs for the emetic reflex. Stimulation of the pharynx and distension of the gastric or duodenum activate the peripheral pathways, which are transmitted through the vagal afferent fibres of the abdomen. The peripheral pathways contain different types of receptors, including 5HT-3, NK-1, and Cholecystokinin-1, of which 5-HT3 is the primary receptor. The peripheral pathway fibres terminate in the dorsal vagal complex (comprised of the Nucleus tractus solitarius (NTS), area postrema, and dorsal motor nucleus), which relays the input to the VC. The chemoreceptor zone (comprised of NTS and area postrema) also relays its input to the VC (5). Some drugs can directly act on the area postrema's receptors, causing emesis because the area postrema lacks the blood-brain barrier. The central emesis pathway contains chemical mediators such as substance-P and NK-1 receptor, serotonin and 5-HT3 receptors, dopamine, and its receptor (5).

Nausea, the subjective sensation of unpleasantness and more common and disabling than vomiting, is difficult to describe, and its pathophysiology is less widely understood. It is hypothesised that nausea involves multidimensional domains, including cognitive, emotional, and interoceptive domains. The same neurotransmitters involved in vomiting responses, such as serotonin and substance-P, are also responsible for nausea and dopaminergic, histaminic, and muscarinic receptors (4).

Besides cancer chemotherapeutic agents, various factors, such as cancer-related gastric outlet obstruction, impaired gastric emptying, metabolic effects, brain and spinal metastasis, pain, and anxiety, can cause nausea and vomiting. When administered to an individual, cancer chemotherapeutic agents generate free radicals that act on the enterochromaffin cells in the GIT. This process releases serotonin, which acts on the vagal nerve endings through the 5-HT3 receptor. The resulting cascade of events results in nausea and vomiting, mainly in the acute phase of CINV (4).

In addition to the neurotransmitter reflex pathways, other factors, such as individual susceptibility and the timing and dosage of chemotherapy, can also influence the occurrence of CINV. Patients with a history of motion sickness or previous episodes of CINV are more likely to experience these symptoms during chemotherapy. The timing and dosage of

chemotherapy also play a critical role in developing CINV. Chemotherapy drugs that are more emetogenic, meaning they have a higher likelihood of causing vomiting, include cisplatin, cyclophosphamide, and doxorubicin. Patients who receive higher doses of these drugs are more likely to experience CINV than those who receive lower doses or less emetogenic drugs.

2.6 The emetogenic potential of cancer chemotherapy agents

The incidence of CINV depends on the type of chemotherapy agents and their emetogenic potential, the dosage of the agents, and individual patient susceptibility. The cancer chemotherapy regimens are classified into four levels according to their emetogenic potential (percentage of individuals getting cancer chemotherapy experiencing CINV) (6).

Table 1) Classification of cancer chemotherapy regimens according to their emetogenic potential

Cancer chemotherapy regimen category	Emetogenic potential
Highly emetogenic (HEC)	>90%,
Moderately emetogenic (MEC)	30 % to 90%
Low emetogenic	10% to 30%
No/Minimal emetogenic	<10%

Table 2) Highly emetogenic chemotherapy agents

Highly emetogenic drugs
Anthracycline/cyclophosphamide combination
Cyclophosphamide >1,500 mg/m^2
Carmustine
Cisplatin
Dacarbazine
Streptozocin
Mechlorethamine

2.7 Currently available drugs

The currently available drugs to prevent CINV are 5-HT3 receptor antagonists, NK-1 receptor antagonists, and corticosteroids. While these drugs are ineffective when used alone, they are most effective when combined as prophylactic agents before chemotherapy administration (2). Combining these drugs can provide a more comprehensive approach to preventing CINV, as they target different mechanisms involved in developing nausea and vomiting. For example, 5-HT3 receptor antagonists target the serotonin receptors in the gut and brain that trigger nausea and vomiting, while NK-1 receptor antagonists block the action of substance-P, a neurotransmitter that also contributes to nausea and vomiting (16). Corticosteroids, on the other hand, have anti-inflammatory properties that can help reduce inflammation and swelling in the gut, which can also contribute to CINV.

It is recommended that these prophylactic agents be continued for the same duration as the chemotherapy administration to achieve optimal results (16). However, the antiemetic response can vary among patients depending on their individual experiences and risk factors. For example, patients who have previously experienced CINV or receive chemotherapy with a high emetogenic risk may require more aggressive antiemetic therapy (16). Additionally, patient characteristics such as age, sex, and overall health can affect the response to antiemetic therapy (15).

Overall, using a combination of prophylactic agents is currently the most effective approach to prevent CINV in chemotherapy patients. However, individualised therapy may be required based on patient-specific factors to achieve optimal results. Additional research is needed to understand the mechanisms of CINV better and develop more effective treatment options to improve the quality of life for cancer patients undergoing chemotherapy (17).

2.7.1 5-HT3 receptor antagonists

5-HT3 antagonists are commonly used to prevent CINV. 5-HT3 antagonists available for preventing CINV are 1st generation agents such as ondansetron, dolasetron, granisetron, and 2nd generation agent-palonosetron. The first-generation agents can prevent the cute CINV but are not effective in the delayed phase of CINV prevention. Ondansetron is orally and intravenously administered and has been available for many years. It can cause adverse effects such as headaches, constipation, and diarrhoea (18).

Dolasetron is another 5-HT3 receptor antagonist available as an oral or intravenous formulation. Like ondansetron, it is more effective in acute CINV prevention than in delayed CINV prevention. It can cause headaches, constipation, and dizziness.

Granisetron is a 5-HT3 receptor antagonist available as an oral or intravenous formulation. Studies demonstrated that it could prevent both acute and delayed CINV phases. It can also cause adverse effects such as headaches, constipation, and diarrhoea.

Palonosetron – a second-generation 5-HT3 antagonist, differs from first-generation agents in its prolonged half-life of about 40 hours, allowing for sustained suppression of CINV. Additionally, Palonosetron suppresses the crosstalk between the substance-P and the 5-HT3 receptor pathway, which plays a role in delayed CINV. An RCT showed that palonosetron is more effective than palonosetron in preventing acute and delayed CINV (18). A recent meta-analysis of randomised controlled trials (RCTs) also demonstrated that palonosetron prevents acute and delayed CINV. Palonosetron can also be used to prevent CINV in paediatric patient populations. A study done by Aapro et al. (19) showed that palonosetron is more effective than ondansetron in preventing acute and delayed CINV in the paediatric population.

Additionally, in a study of patients receiving multiple cycles of chemotherapy, palonosetron was found to be more effective than granisetron in preventing delayed CINV in the later cycles (1). Palonosetron is generally well-tolerated by patients and has a favourable safety profile. In clinical trials, the most reported adverse events were headache, constipation, and fatigue, which are generally mild to moderate in severity and thus do not require treatment discontinuation. In addition to its use in preventing CINV, palonosetron has also been investigated for its potential use in other conditions, such as postoperative nausea and vomiting.

2.7.2 Dexamethasone

Dexamethasone is a corticosteroid commonly used for its anti-inflammatory and immunosuppressive properties. However, it is also effective as an antiemetic, which can help prevent or alleviate nausea and vomiting. Dexamethasone exerts its antiemetic effects by acting directly on the brainstem’s nucleus tractus solitarius (NTS). The NTS is an important centre for the regulation of vomiting. It receives inputs from various sources, including the chemoreceptor trigger zone (CTZ), the gastrointestinal tract, and the vestibular system. By

modulating the release of neurotransmitters such as serotonin and substance-P in the NTS, dexamethasone can reduce the activity of the vomiting reflex (17, 20).

In addition to its direct effects on the NTS, dexamethasone can enhance the activity of other antiemetic drugs, such as 5-HT3 receptor antagonists and NK-1 receptor antagonists. These drugs work by blocking the activity of specific brain receptors involved in the vomiting reflex. Combined with dexamethasone, they can provide more effective and long-lasting relief from nausea and vomiting (21). The optimal dose of dexamethasone for preventing acute emesis is typically 8-12 mg. However, when combined with an NK-1 receptor antagonist and a CYP3A4 inhibitor (which can increase the levels of dexamethasone in the body), the dose of dexamethasone may need to be reduced to avoid side effects (21).

One potential side effect of dexamethasone is sleeping disturbance, including insomnia. This may be partly due to the drug's effects on the HPA axis, which regulates the body's stress response and circadian rhythm. Corticosteroids like dexamethasone can disrupt the HPA axis and interfere with standard sleep patterns. Prolonged drug use can lead to various adverse effects, including osteoporosis, diabetes, and increased infection susceptibility. It can also cause changes in mood and behavior, including anxiety, depression, and irritability (21).

2.7.3 NK-1 receptor antagonist

NK-1 receptor antagonist will block the action of substance-P and suppress the CINV, especially in the delayed phase of nausea and vomiting. For patients receiving highly emetogenic chemotherapy, the NK-1 receptor antagonist has been included in some oncology centres' standard of care as the prophylactic four-drug regimen. The NK-1 receptor antagonists currently available are aprepitant (oral), fosaprepitant (IV), netupitant (oral), fosnetupitant (IV), and rolapitant (oral). Netupitant is available in combination with palonosetron only. It is also be used in patients receiving the MEC regimens who are at high risk for CINV) (22). Even though the incidence of CINV is decreased with this agent as a standard care regimen, some patients still experience nausea. Moreover, the cost of these agents is also high (14).

One of the significant contributors to CINV is substance-P, a neuropeptide found in the gastrointestinal tract and central nervous system. This activates a vomiting reflex by binding to NK-1 receptors in the brainstem. Thus, avoiding or reducing the incidence of

CINV is possible by blocking the NK-1 receptor. This will inhibit the action of substance-P by binding to an NK-1 receptor. Currently there are NK-1 receptor antagonists in the market such as aparepitant, fosaprepititant, netupitant, fosnetupitant and rolapitant. Aprepitant is an oral agent, while fosaprepitant and fosnetupitant are intravenous formulations. Netupitant and rolapitant are available as oral agents. Netupitant is available in combination with the 5-HT3 receptor antagonist palonosetron. In patients receiving highly emetogenic chemotherapy (HEC) in oncology centres, NK-1 receptor antagonists have been included in the standard of care for preventing CINV(23).

In several studies, adding NK-1 receptor antagonists to standard antiemetic therapy has significantly reduced CINV, particularly at a delayed phase that is usually challenging to manage. In a delayed stage, the use of NK-1 receptor antagonists combined with 5-HT3, and dexamethasone has been shown to lead to better control of CINV than if both were used independently. However, despite using NK-1 receptor antagonists, patients may still experience chemotherapy-induced nausea and vomiting. The exact reasons for this are not fully understood but may be due to individual variability in drug metabolism and receptor expression. Other factors that can contribute to CINV include the type and dose of chemotherapy, patient age, sex, and medical history. Therefore, individualized management of CINV is essential, and clinicians should consider patient-specific factors when choosing antiemetic regimens (23).

Another limitation of NK-1 receptor antagonists as they are costly. The cost of these agents can be a barrier to their use, especially in resource-limited settings. However, some studies have shown that the cost of these agents may be offset by their effectiveness in reducing the need for rescue medication and hospitalizations due to CINV. These agents also be used in patients undergoing MEC, particularly those at high risk of CINV. High-risk factors for CINV include female sex, younger age, history of morning sickness, motion sickness or previous episodes of CINV, and certain chemotherapy drugs. They have a favorable safety profile, and most adverse reactions are minor or moderate in severity. Fatigue, hiccups, constipation, and diarrhea are the most common side effects of these medicines (23).

2.7.4 Olanzapine

Olanzapine is an FDA-approved atypical antipsychotic medication for the treatment of psychosis. It blocks multiple neurotransmitters in the brain, including dopamine, histamine, serotonin, and acetylcholine. This ability to modulate multiple neurotransmissions in the brain could prevent the incidence of delayed phase CINV. Olanzapine effectively prevents delayed emesis due to certain unknown factors, possibly due to its action at multiple receptors, notably at 5-HT2C, 5-HT3, and D2, that produce an antiemetic effect. Guidelines currently recommend it as the three-drug or four-drug regimen combination with the standard of care for preventing CINV. Olanzapine-containing regimens are also cost-effective.

However, olanzapine can cause side effects such as sedation, fatigue, diminished vision, and oedema in short-term doses. Additionally, it can cause glucose intolerance for 3-6 months, so it must be used cautiously in patients with diabetes. Olanzapine usage in older patients with dementia-related psychosis has a black box warning from the FDA since it can result in death in this population.

Olanzapine was first investigated as an antiemetic for CINV in the early 2000s. Based on case reports, Passik et al. (24) conducted a phase I study on cancer patients receiving their first cycle of chemotherapy. They were given olanzapine for eight days, starting two days before chemotherapy administration. Olanzapine effectively prevented delayed emesis (DE), and the maximum tolerated dose was 5 mg for days -2 and -1 and 10 mg for days 0-7. Complete control of DE was achieved in 4 out of 6 patients receiving highly emetogenic chemotherapy and 9 out of 9 patients receiving moderately emetogenic chemotherapy. Following this, Navari et al. (25) conducted phase 2 RCT with olanzapine in 30 patients receiving HEC and MEC. The researchers found that patients who received olanzapine had significantly lower rates of nausea and vomiting with minimal side effects than those who received placebo. The study concluded that olanzapine was a promising option for managing CINV in patients receiving emetogenic chemotherapy regimens.

Another notable study by Tan et al. (26) involved 229 patients receiving moderate-to-highly emetogenic chemotherapy. The study demonstrated that the olanzapine group had notable improvements in complete response rates for delayed nausea and vomiting in highly and moderately emetogenic chemotherapy patients and across the overall period. The researchers concluded that olanzapine was a practical option for managing CINV in this patient population.

In addition to these studies, several meta-analyses have been conducted to synthesize the results of multiple trials. Wang et al. conducted a meta-analysis by searching various databases to find randomized controlled trials on this topic, and six studies involving 726 patients were included in the meta-analysis. The results showed that antiemetic regimens containing olanzapine were more effective at reducing CINV, especially in the delayed phase, than those without olanzapine (18).

The literature search indicates that olanzapine is a safe and effective option to prevent CINV in chemotherapy patients. The medication is particularly effective in preventing delayed CINV, which can be more challenging to manage with traditional antiemetic medications. However, it is worth noting that olanzapine can have side effects, such as significant sedation, and may not be appropriate for all patients. As with any medication, the treating physician should evaluate the patient's circumstances before prescribing olanzapine for CINV (27).

Sedation is more common on day two but reduces over time. Less sedation is noticed at low dosages in the range of 5 mg. Another meta-analysis conducted by Wang D et al. (28) for add-on olanzapine 5mg vs. 10 mg has shown that for patients with HEC and MEC, the efficacy of 5 mg olanzapine is comparable to that of 10 mg olanzapine, while its sedative effect is less pronounced. However, due to the limited number of studies conducted on 5 mg olanzapine, its effectiveness and safety data are inconclusive. Therefore, they suggested that more randomised controlled trials focusing on 5 mg olanzapine are necessary to establish a balance between its effectiveness and safety (17).

Table 3) Table of evidence from previous studies for the usage of Olanzapine alone in the management of nausea and vomiting in cancer chemotherapy.

S.No	Author name and date	Type of chemotherapy regimen	Intervention (add on to the standard of care)	Outcome (% patient with no nausea)		
				Acute period	Delayed period	Overall period
1	Navari et al. 2011 (29)	HEC	Olanzapine 10mg	87	69	69
			Aprepitant	87	38	38
2	Tan et al. 2009 (26)	HEC	Olanzapine 10mg	95	70	69
			Placebo	87	80	28
3	Navari et al. 2016 (30)	HEC	Olanzapine 10mg	74	42	37
			Placebo	45	25	21
4	Tienchaiananda et al. 2019 (31)	HEC	Olanzapine 10mg	50	35	30
			Placebo	10	15	0
5	Clemmons, Orr et al. 2018 (32)	HEC	Olanzapine 10mg	34	20	36
			Placebo	24	8	62
6	Ithimakin S et al 2020(33)	HEC	Aprepitant	47	35.4	33.3
			Olanzapine 5mg	47	40.4	37
			Olanzapine 10 mg	46	31.11	43.2
7	Yeo et al. 2020 (34)	HEC	Olanzapine 10mg	76	76	58
			Placebo	53	63	33
8	Dula et al. 2019 (35)	HEC	Olanzapine	84.3	68.7	68.7
			Haloperidol	81.2	76	71.8
9	Babu et al (36)	HEC	Olanzapine 10mg	88	84	84
			Aprepitant	88	84	84
10	Sukauichai et al (37)	HEC	Olanzapine 5mg	70	45	43.5
			Olanzapine 10mg	68.6	48.6	47.9

2.7.5 Gabapentanoids

Pregabalin belongs to the gabapentinoid group that includes gabapentin, which binds to presynaptic alpha-2-delta subunit of voltage-sensitive calcium channels and reduces their downstream effects. This process inhibits the release of many neurotransmitters, including the substance-P (11). Initially, gabapentinoid were prescribed for partial seizures, and later they were used to manage neuropathic pain, fibromyalgia, and even acute post-surgical pain (38). Gabapentin is an anticonvulsant medication used off-label to manage various conditions, including neuropathic pain, anxiety, and sleep disorders. Some studies have also investigated the use of gabapentin for CINV management.

One proposed mechanism of action for gabapentin in preventing CINV is its ability to reduce the release of substance-P, a neurotransmitter involved in its development. Substance-P is a neuropeptide released in response to chemotherapy and is thought to play a vital role in developing acute and delayed CINV (39).

First, a case report finding by Guttuso T (40) in 2005 suggested the antiemetic efficacy of gabapentin in preventing CINV. Following this, in a pilot study by Cruz FM et al. (39), 80 chemotherapy-naive patients were given ondansetron, dexamethasone, and ranitidine before chemotherapy. They were randomly assigned to receive gabapentin or placebo. Results showed that patients who received gabapentin had a higher complete response rate and delayed complete control without significant adverse events. Several clinical studies have investigated the efficacy of gabapentin in preventing CINV and suggested it can decrease the incidence of delayed CINV. However, not all studies have found a benefit of gabapentin in preventing CINV. Kiani et al. (41) conducted an RCT and found that gabapentin was ineffective in reducing the severity of CINV in patients receiving high-dose chemotherapy.

In terms of safety, gabapentin is generally well-tolerated. Common side effects include dizziness, somnolence, and ataxia, which can be dose dependent. It is worth noting that there are some limitations to the existing literature on gabapentin for CINV prevention. Many studies have been small or have methodological limitations, such as a lack of blinding or inadequate control for confounding variables. There is also a lack of consensus on the optimal dose and duration of gabapentin therapy for CINV prevention (42).

Hence the evidence on the efficacy of gabapentin for CINV prevention is mixed, with some studies showing a benefit and others showing no significant difference compared to placebo. Hence more research is needed to establish the optimal dosing and duration of

gabapentin therapy for CINV prevention, as well as its efficacy in different patient populations and chemotherapy regimens (42).

Pregabalin is a medication used to treat neuropathic pain, epilepsy, and anxiety disorders. It has been proposed as a potential treatment for CINV based on its mechanism of action. Pregabalin binds to the alpha-2-delta subunit of voltage-gated calcium channels, reducing the release of neurotransmitters such as glutamate, substance-P, and noradrenaline. A meta-analysis of pregabalin showed its role in preventing postoperative nausea and vomiting, but there is little evidence regarding its role in CINV (12). Pregabalin acts through the exact mechanism of gabapentin but has not been adequately explored in its role in managing CINV. The common adverse effects of pregabalin include sedation, dizziness, blurring of vision, and edema.

2.8 Recommendation by international guidelines

The management of CINV is an essential part of supportive cancer care. International guidelines have been developed which provide recommendations for preventing and treating CINV. The current guidelines (16), such as the National Comprehensive Cancer Network antiemesis (NCCN) guideline, Antiemetic American Society of Clinical Oncology (ASCO) guideline, Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) antiemetic guideline all approach the management/prevention of CINV according to the emetogenic potential of cancer chemotherapy agents.

The National Comprehensive Cancer Network antiemesis guideline is widely recognized and recommends preventing and treating CINV(2). The guideline recommends that chemotherapy patients be evaluated for their risk of developing CINV. The emetogenic potential of the chemotherapy agents is used to determine the level of risk. The guideline also recommends antiemetic medication use based on the risk level.

The Antiemetic American Society of Clinical Oncology (ASCO) (1, 16) guideline is another set of recommendations for preventing and treating CINV. The ASCO guideline recommends that chemotherapy patients receive prophylactic antiemetic therapy based on the chemotherapy agent’s emetogenic potential. The guideline also recommends using rescue antiemetic medications if prophylactic therapy is ineffective.

The Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASCC/ESMO) antiemetic guideline is a global set of recommendations for preventing and treating CINV. The guideline recommends that chemotherapy patients be evaluated for their risk of developing CINV(1). The emetogenic potential of the chemotherapy agents is used to determine the level of risk. The guideline also recommends antiemetic medication use based on the risk level.

All these guidelines take a similar approach to preventing and treating CINV. The emetogenic potential of the chemotherapy agents is used to determine the level of risk of developing CINV. Antiemetic medications are then used based on the level of risk. The guidelines also recommend using rescue antiemetic medications if prophylactic therapy is ineffective.The use of these guidelines can improve the management of CINV and help to reduce its impact on patients' quality of life. Healthcare providers should familiarise themselves with these guidelines and use them to treat chemotherapy patients.

2.9 Unmet need and justification for the present study

The prevention and management of CINV are crucial for improving the quality of life of cancer patients undergoing chemotherapy. Antiemetic therapy is the mainstay of CINV management and includes a combination of drugs that target different neurotransmitter pathways involved in the emetic reflex. Combining a 5-HT3 receptor antagonist, such as ondansetron or granisetron, an NK-1 receptor antagonist, such as aprepitant or fosaprepitant, corticosteroids, such as dexamethasone, can also be beneficial in reducing the incidence of CINV (17). The search for more effective and cost-efficient treatment options for nausea and vomiting is an ongoing endeavor in the field of medicine. One particular challenge is to address the unwanted sedation caused by olanzapine at a 10mg dose while maintaining its efficacy. A recent study has suggested that reducing the dose to 5mg does not compromise the drug's efficacy. However, this dose reduction has not been extensively studied, and more research is needed to confirm its efficacy and safety.

Another challenge in the treatment of nausea and vomiting is the use of NK-1 receptor antagonists. While these drugs are recommended in standard treatment guidelines, they have many drug-drug interactions. They inhibit CYP-3A4 and CYP2C9 enzymes in a dose-dependent manner, which can lead to potentially harmful interactions with other medications. This inhibitory effect can also increase the risk of adverse effects and toxicities. Moreover, the high cost of these drugs can be a significant concern, particularly for patients with low socio-economic status.

Despite the availability of newer antiemetic regimens, the control of nausea is still not optimal. Therefore, there is a need to explore alternative treatment regimens that are more effective, cost-efficient, and have fewer drug-drug interactions. One potential alternative treatment regimen involves combining two drugs: pregabalin and olanzapine.

Pregabalin is a drug that reduces the release of neurotransmitters by binding to the α2-δ subunit of voltage-gated calcium channels. It is approved for treating neuropathic pain, fibromyalgia, and generalised anxiety disorder. However, its potential use in chemotherapy-induced nausea and vomiting treatment has not been extensively studied.

Olanzapine, on the other hand, is an atypical antipsychotic that blocks the action of dopamine, serotonin, and histamine receptors in the central nervous system. It is approved for treating schizophrenia, bipolar disorder, and depression. However, at a dose of 10mg, it can cause unwanted sedation, significantly limiting its use for treating nausea and vomiting.

Theoretically, the combination of pregabalin and olanzapine can have a synergistic effect on the treatment of nausea and vomiting. Pregabalin can reduce the release of neurotransmitters, while olanzapine can block the action of the released neurotransmitters (figure 1). This combination can potentially result in better control of nausea and vomiting.

A randomised, double-blind, placebo-controlled trial is needed to investigate the potential of this combination therapy. We hypothesise that the combination of pregabalin and olanzapine will result in a higher complete response rate compared to the other two groups. We also hypothesise that this combination therapy will result in less sedation than olanzapine alone.

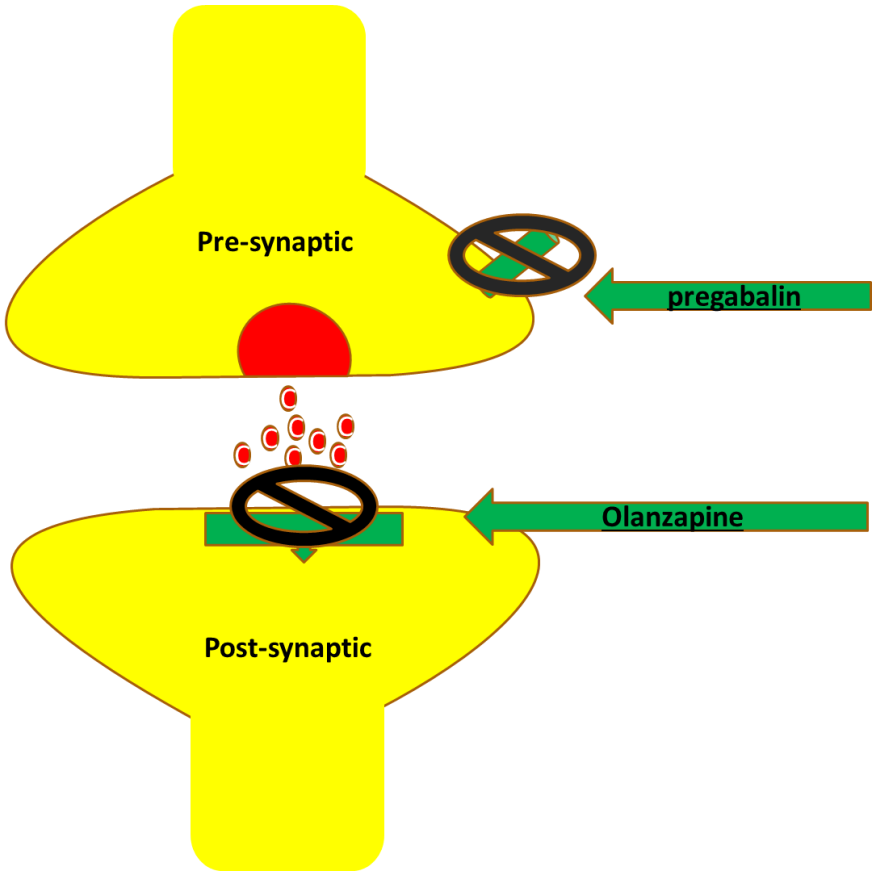

Figure 1) Theoretical synergism for combination of pregabalin plus olanzapine.

3 Aim and objectives

Aim: To evaluate the safety and efficacy of the add-on combination of olanzapine plus pregabalin for preventing CINV in patients receiving highly emetogenic chemotherapeutic agents.

Primary Objective

- To determine the efficacy of the add-on combination of olanzapine and pregabalin as the difference in the percentage of patients with "overall no nausea" (VAS = 0) between the groups over five days from the day of administration of cancer chemotherapy.

Secondary Objectives

1. To determine the difference in the percentage of patients with no nausea in the acute (0 to 24 hours of post-chemotherapy) and delayed periods (26-120 hours of post-chemotherapy).
2. To determine the difference in the percentage of patients with no significant nausea (VAS $\leq$ 25mm) in overall, acute, and delayed periods.
3. To determine the difference in nausea rating in terms of VAS scores for nausea in overall, acute, and delayed periods.
4. To determine the difference in the percentage of patients with no vomiting in overall, acute, and delayed periods.
5. To determine the difference in the usage of rescue medication between both groups.
6. To determine the difference in the percentage of patients with complete response (no vomiting without any rescue medication) in the overall, acute, and delayed periods.
7. To determine the difference in the percentage of patients with complete control (no nausea/vomiting without any rescue medication) in overall, acute, and delayed period.
8. To measure the intervention's effectiveness in improving patient quality of life using the FLIE questionnaire (39).
9. To determine the proportion of patients with FLIE score >108 representing no or minimal impact on their daily life.

10. To monitor the overall treatment-emergent adverse events such as undesired sedation, appetite, and difficulty in vision.
11. To evaluate the effect of the intervention on CINV risk factors by subgroup analysis (the subgroups considered were gender, age<55, chemotherapy agents, adjuvant/ neo-adjuvant regimens, previous history of CINV, history of alcohol consumption/ motion sickness/ morning sickness)

Tertiary objective

- To evaluate the association of baseline substance P level with overall VAS for nausea.

4 Methods

4.1 Study design

The study was a prospective group-sequential, response-adaptive randomised, double-blinded, add-on placebo-controlled clinical trial.

4.2 Study site

This study was conducted at the Department of Pharmacology and Department of Radiation oncology of AIIMS, Bhubaneshwar, Odisha. Interviews, allocation of subjects, and medication administration were done in the daycare of the Department of Radiation oncology.

4.3 Study population

It comprised individuals above 18 years old of either sex diagnosed with any malignancy who were planned to receive the first or repeated cycle (up to 3 cycles) of the drug regimen containing moderately to highly emetogenic chemotherapeutic agents.

4.4 Study groups

a) Add-on placebo group
b) Add-on pregabalin (75 mg/day) and olanzapine (5 mg/day)

4.5 Inclusion criteria

1. Cancer patients whose Eastern Cooperative Oncology Group (ECOG) performance status of between 0-2 (0-indicates no symptoms and 5- dead) (43) who had received a cancer chemotherapy regimen containing highly emetogenic cancer chemotherapeutic agents and the standard care premedication as Inj.Ondansetron 8mg + Inj.Dexamethasone 8mg.
2. Patients who have a primary education qualification and gave written informed consent.
3. Patients who can swallow the capsule.

4.6 Exclusion criteria

Following patients were excluded from the study,

1. Patients with history of (H/O) nausea or vomiting within 24 hours before enrolment.
2. Elevated lab parameters such as serum creatinine level of more than 2.0 mg per decilitre, aspartate, or alanine aminotransferase level greater than three times the normal upper limit, and absolute neutrophil count were less than 1500/mm^3.
3. Patients with either primary or secondary CNS malignancy.
4. Patients with a H/O central nervous system (CNS) disease such as seizure disorder, Parkinson's disease, psychiatric illness, and severe cognitive compromise.
5. Patients on treatment with either pregabalin or another antipsychotic agent within 30 days of enrolment or planned to receive them during the study period.
6. Patient with known H/O hypersensitivity to Olanzapine or pregabalin.
7. Patients who are planned to receive concurrent radiotherapy coincide with the current chemotherapy cycles.
8. Patients with known H/O uncontrolled congestive heart failure, cardiac arrhythmia, or acute myocardial infarction events within the previous six months.
9. Patient with uncontrolled diabetes mellitus.
10. Patients with a condition causing upper gastrointestinal tract obstruction as per radiological findings.
11. Patients with metabolic disorders (such as hypercalcemia, hyperglycemia or hyponatremia, and uremia causing nausea and vomiting.
12. Pregnant and lactating women.

4.7 Study period

After obtaining approval from the institutional Ethics committee and the registration of the clinical trial in CTRI (CTRI/2021/08/035451), the recruitment of the participants for the study started in August 2021, and the follow-up of the last patient recruited ended in December 2022.

4.8 Treatment

All participants received the standard of care regimen (Inj. ondansetron 8mg IV plus Inj. dexamethasone 12mg IV) half an hour before the administration of chemotherapy agents on Day 1. Olanzapine 5 mg and pregabalin 75 mg immediate-release oral formulations or similar-looking placebo were given along with the standard regimen on day 1. Following these, the participants were given the experimental drugs or similar-looking placebo formulations once daily at night for the next four days, along with oral dexamethasone 8 mg (days 2 to 4) in both groups.

4.9 Materials for clinical data recording

a) Case Record Form
b) VAS scale for nausea and sedation
c) FLIE (Functional living index emesis) questionnaire
d) Consent form
e) Participants information sheet
f) Four-point verbal scale for adverse events

4.10 Sample size calculation

A sample size of 42 per group was powered at 80% to detect a difference of 30% in the response rate in terms of no nausea between the two groups assuming that the add-on placebo group response rate was 35%. The alpha error considered for the calculation was 5%.

We have planned for four analyses (3 interim and the final analyses). For the interim analysis to control the type 1 error inflation, the O'Brien-Fleming boundary (figure 2) was defined using “rpact” package (44) in R. The sample size in the figure was used only if the allocation ratio remains one throughout the study. The study will be terminated if the z value of the effect size crosses the boundary on either side during an interim analysis. However, adaptive randomization will be adopted after each interim analysis to minimize the exposure to harmful or ineffective treatment to the trial participants. After each interim analysis, this procedure changed the allocation ratio (discussed in randomization in detail). Because of interim analysis and adaptive randomization, the sample size was changed during the course of the study based on the response of the trial participants after the first interim analysis.

4.11 Randomisation – Adaptive randomisation

This study involved a group-sequential response adaptive randomization procedure in which every participant had an equal chance to be allocated to either of the study arms at the start of the study. The randomization codes were generated using R. We planned four analyses (3 interim analyses and one final analysis) during the study as described in the sample size calculation section.

Depending on each interim analysis result, the allocation ratio was changed, and more patients were allocated to the well-performing arm. The sample size was altered depending on the allocation ratio (If the z value of the effect size is less than one at an interim analysis, the trial would have continued with a 1:1 allocation ratio. If the z value falls between 1 and 1.5, the allocation ratio would have changed to 1.5:1. If the z value is between 1.5 to 2, the allocation ratio would have 2:1. If the z value falls beyond 2, the allocation ratio would have 2.5:1)

$$Group\ with\ the\ favorable\ response = \frac{n(R+1)}{2}$$

$$Group\ with\ the\ unfavorable\ response = \frac{n(R+1)}{2R}$$

n = Expected sample size per group if the allocation is equal.

R = Allocation ratio.

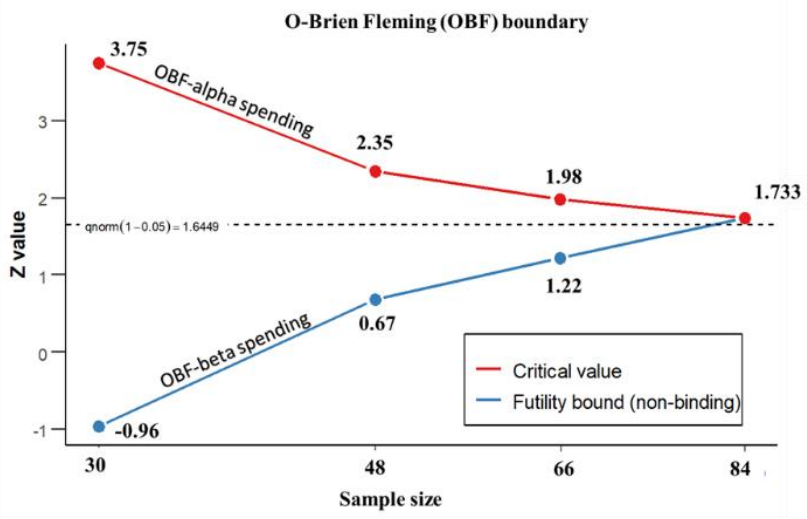

Figure 2) O'Brien Flemming boundary targets and sample size provided the allocation ratio is maintained as 1:1 throughout the study.

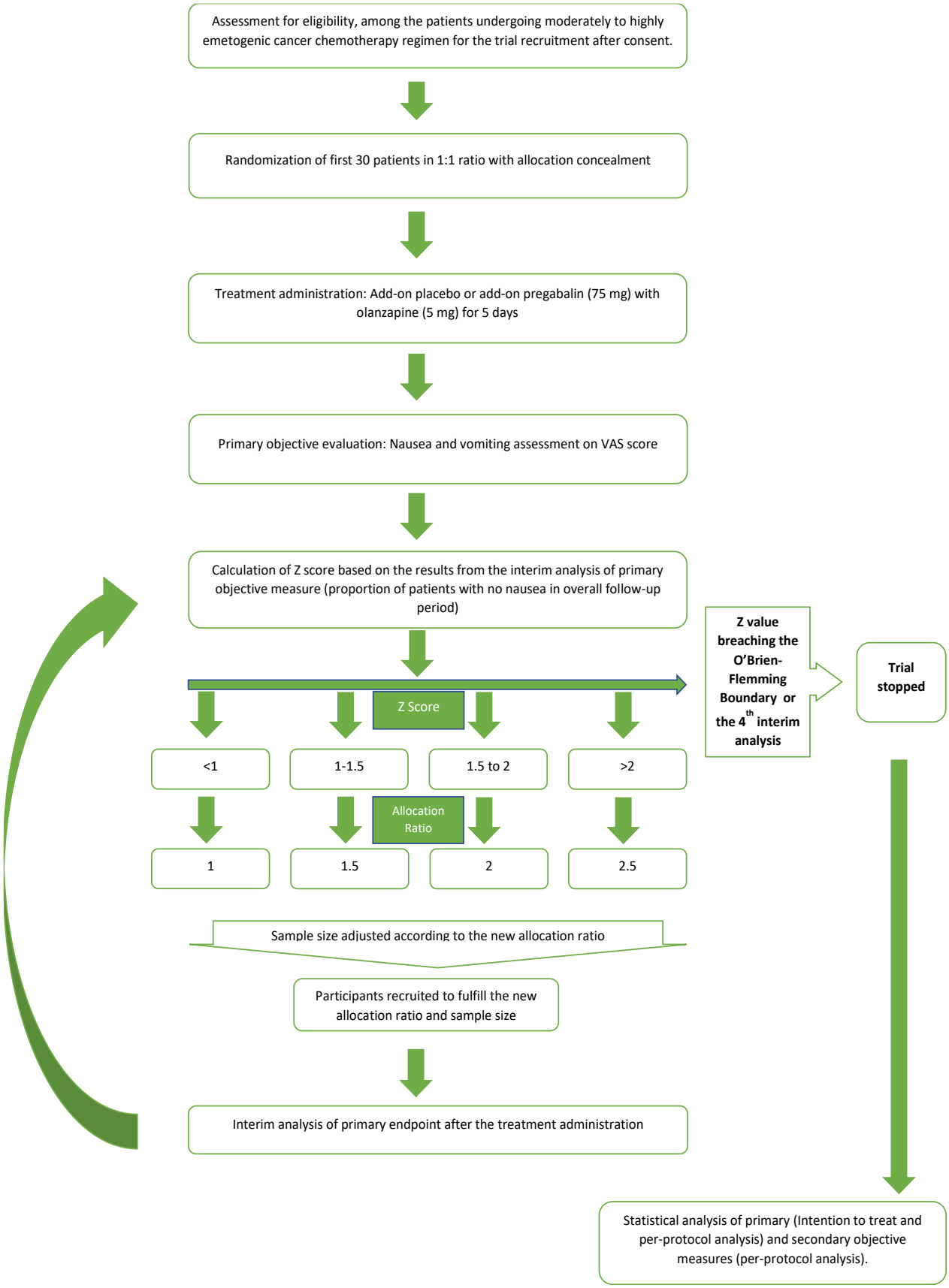

Figure 3) Flowchart demonstrating the trial methodology and analysis plan.

4.12 Blinding and allocation concealment

This study was a double-blinded, randomized clinical trial. Blinding was maintained by using a similar-looking placebo. The assessor was blinded regarding the groups of allocation of the participant. The assessor was not involved in data analysis and interpretation of results. Allocation concealment was done by allotting numbers to the randomization chart generated. These numbers were labelled on the drug containers.

4.13 Participant recruitment and treatment administration

Once the participant who has planned for highly emetogenic cancer chemotherapy consents to the study, an assessment of eligibility was done by

- History and physical examination
- ECOG performance status
- Liver & renal function tests and serum electrolytes

Based on the allocation, either a placebo or a combination of pregabalin 75mg plus olanzapine 5mg was given along with the standard of care (inj. ondansetron 8 mg IV and inj. dexamethasone 12 mg IV) to the participant for one hour before the administration of chemotherapeutic agents. The participants were given the experimental drugs or similar-looking placebo formulations once daily at night for the next four days, along with oral dexamethasone 8 mg (days 2 to 4) in both groups.

4.14 Assessment of outcomes

After 24 hours, the patients were contacted over the phone and enquired about the nausea severity (Visual analog scale (VAS) score), vomiting episodes, rescue medication use, undesired sedation, increased appetite, and disturbance in vision. This process was repeated for four more days. At the end of the fifth day, the patients were enquired about treatment compliance and administered the FLIE questionnaire to assess the effect of the intervention on the patient’s quality of life.

4.15 Assessment of Adverse event

Initially, the participant was asked about any adverse event with a non-leading question, followed by leading questions to assess the specific adverse events pertaining to the experimental drugs.

- Undesired sedation and increased appetite were assessed daily in terms of VAS scoring.
- Any disturbance in vision was also enquired about.

4.16 Contact and interview schedule.

Domains of the interview schedule for the investigator

a) Demographic characteristics of participants
b) Clinical history with diagnosis and type of chemotherapy agents used.
c) Baseline vitals and laboratory parameter assessment
d) Baseline FLIE and nausea VAS score assessment
e) Telephonic assessment of vomiting episodes, rescue medication intake, nausea VAS score, sedation scores and adverse event assessment.

Table 4) Study schedule and outcome assessment

SNO	Parameters	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
1	Nausea and vomiting questionnaire	✓	✓	✓	✓	✓	✓
2	Serum electrolytes	✓	-	-	-	-	-
3	Renal function tests	✓	-	-	-	-	-
4	Liver function tests	✓	-	-	-	-	-
5	FLIE questionnaire	✓	-	-	-	-	✓
6	Adverse event monitoring	-	✓	✓	✓	✓	✓

4.17 Statistical analysis

The statistical analysis was done using R 4.1. The continuous data, like VAS score, age, etc., are expressed as mean (SD). The categorical variables, like the presence or absence of nausea/vomiting, gender, etc., are represented as proportions. The difference in the response rate was analysed with the two sample Z tests for proportions (one-sided), which provided the Z-scores for interim analyses for both efficacy and futility. These Z-scores were used to assess boundary breaches in the O'Brien-Fleming (OBF) analysis and to determine the allocation ratio (to implement adaptive randomization) for the forthcoming interim/final analysis. The boundaries for the OBF analysis were defined to evaluate the efficacy and futility (refer to protocol). The continuous outcomes were assessed for normality using the Shapiro–Wilk test. If normally distributed, an unpaired t-test was used to assess the significance of the difference between the groups. If skewed, the Wilcoxon rank-sum test was used for the same. The VAS scores for nausea over five days were assessed using mixed ANOVA. As we had no missing data, we proceeded without conducting separate intention-to-treat and per-protocol analyses. Adverse events were analyzed using Fisher's exact test. Subgroup analysis was performed to evaluate the efficacy in terms of gender, age, previous history of nausea and vomiting, and history of alcohol consumption. Linear regression was performed to analyze the association between the substance-P levels and the VAS scores.

4.18 Ethical Consideration

The study followed the National ethical guidelines for biomedical and health research involving human participants established by ICMR in 2017. The declaration of Helsinki, the benefits and harms of participating in the research, and the freedom to withdraw from the study at any moment were explained to participants. From each participant, full voluntary written informed consent was obtained. The study subjects were recruited after obtaining written permission from the IEC (Institutional Ethics Committee). The study was registered with the Clinical trial registry of India (CTRI) CTRI/2021/08/035.

5 Results

The current study is a group-sequential, response-adaptive, randomized, double-blinded, placebo-control clinical trial. The study aimed to evaluate the safety and efficacy of the add-on combination of olanzapine plus pregabalin for the prevention of CINV in patients receiving highly emetogenic chemotherapeutic agent in a daycare setting in the Department of Radiotherapy in collaboration with the Department of Pharmacology of All India Institute of Medical Sciences, Bhubaneswar.

5.1 Study initiation and completion

After obtaining approval from the institutional ethics committee and the registration of the clinical trial in CTRI (CTRI/2021/08/035451), the recruitment of the participants for the study started in August 2021, and the follow-up of the last patient recruited ended in December 2022.

5.2 Patient recruitment and randomization for the study

A total of 187 participants were assessed for eligibility, of which 54 (30 in stage 1st and 24 in the 2nd stage) were included in the study (figure 4). Since it is a group-sequential design, the first 30 eligible patients were randomized to a 1:1 ratio to receive a placebo or combination of olanzapine 5mg plus pregabalin 75 mg by computer-generated random sequence. After the completion of the study for 30 patients as defined for the first interim analysis, a blinded interim analysis was conducted for the primary objective. The Z score of 1.73 obtained for efficacy did not breach the predetermined OBF boundary. As per the protocol, the allocation ratio was changed to 2:1, with more participants in the group showing a favorable response, and the study continued through the next stage. During the second blinded interim analysis after the completion of the study for 54 participants, the Z score of 2.42 obtained breached the efficacy OBF boundary. So, the trial was stopped for the early attainment of primary outcome measures (no nausea).

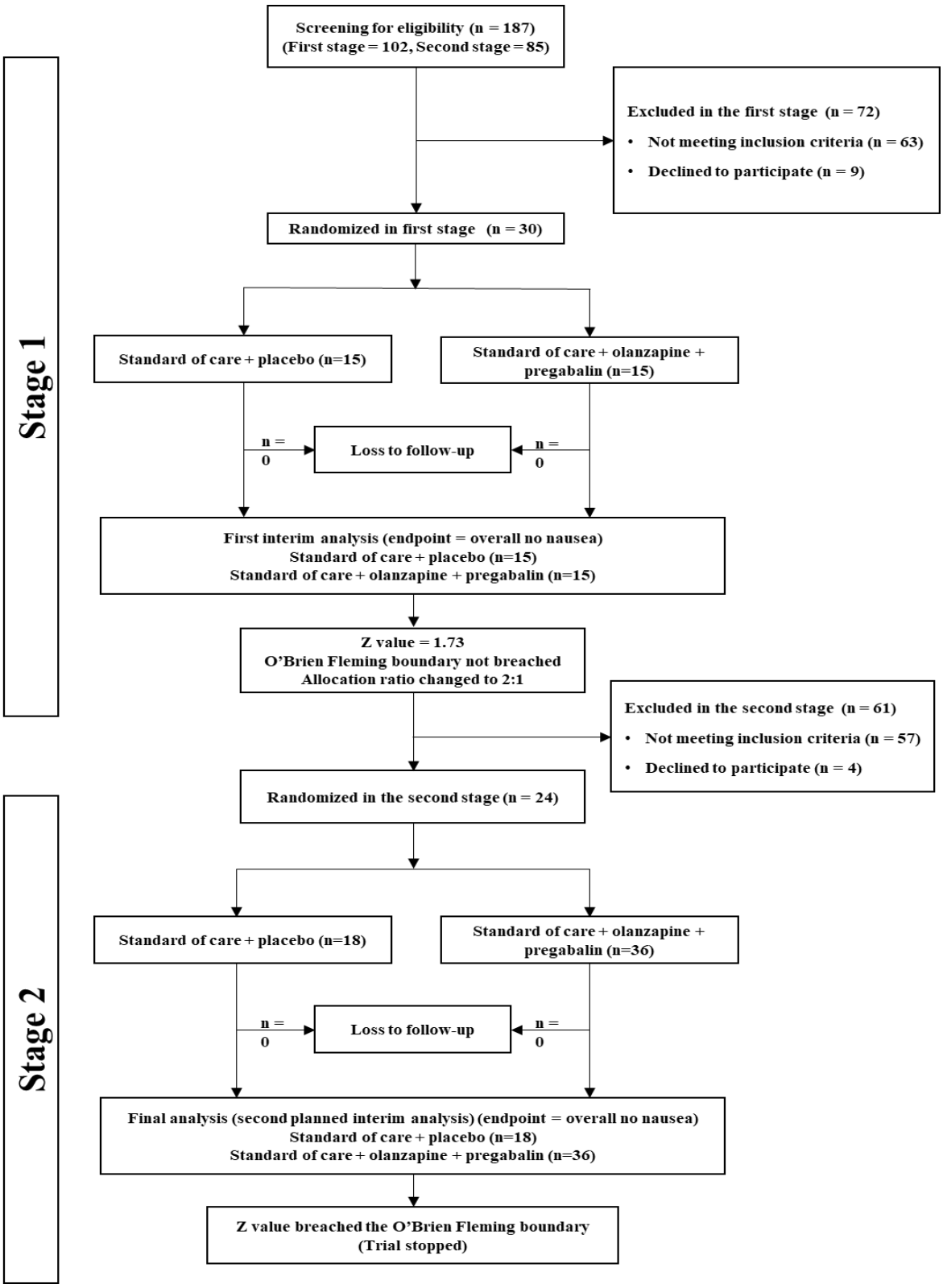

Figure 4) CONSORT flowchart depicting the flow of the group-sequential, response-adaptive randomized clinical trial.

5.3 Baseline characteristics

The baseline demographic characteristics and clinical parameters showed no significant difference between groups. A summary of the baseline characteristics of both groups is presented in Table 5.

Table 5) Baseline characteristics of participants in the experimental and the control group

Characteristics	Experimental (n=36)	Control (n=18)	p-value
Age in years (mean±SD)	44.50 ±9.29	44.78 ±11.54	0.924
Gender (number (%))			0.822
Male	9(25.0%)	4 (22.2%)	
Female	27 (75.0%)	14 (77.8%)	
Education status (number (%))			0.801
High school	34 (94.4%)	17(94.4%)	
Graduate	2 (5.6%)	1(5.6%)	
Cancer site (number (%))			0.613
Breast	22 (61.1%)	12 (66.6 %)	
Gall bladder	6 (16.7%)	4 (22.2 %)	
Head and neck	3 (8.3%)	2 (11.1%)	
KUB	3 (8.3%)	0 (0.0%)	
Lung	1 (2.8%)	0 (0.0%)	
Ovary	1 (2.8%)	0 (0.0%)	
Breast	22 (61.1%)	12 (66.6 %)	
Gall bladder	6 (16.7%)	4 (22.2 %)	
Chemotherapeutic drugs (number (%))			0.836
Adriamycin+cyclophosphamide	21 (58.3%)	10 (55.5%)	
Adriamycin+cyclophosphamide+cisplatin	0 (0.0%)	1 (5.6%)	
Carboplatin+paclitaxel	1 (2.8%)	1 (5.6%)	
Cisplatin	2 (5.6%)	1 (5.6%)	
Cisplatin + adriamycin	1 (2.8%)	0 (0.0%)	

Cisplatin+gemcitabine	9 (25.0%)	4 (22.2%)	
Epirubicin+cyclophosphamide+5-fluorouracil	2 (5.6%)	1 (5.6%)	
Adriamycin+cyclophosphamide	21 (58.3%)	10 (55.5%)	
Adriamycin+cyclophosphamide+cisplatin	0 (0.0%)	1 (5.6%)	
Adjuvant or adjuvant (number (%))			0.439
Adjuvant	31 (86.1%)	14 (77.8%)	
New adjuvant	5 (13.9%)	4 (22.2%)	
Cycle number (mean±SD)	1.75 (0.77)	1.94 (0.73)	0.377
History of morning sickness (number (%))	19 (52.8%)	7 (38.9%)	0.305
History of motion sickness (number (%))	5 (13.8%)	3 (16.6%)	0.786
History of nausea and vomiting in the previous cycle (number (%))	20 (55.6%)	12 (66.7%)	0.433
History of alcohol consumption (n (%))	0.11 (0.32)	0.17 (0.38)	0.596
Serum urea (mg/dl) (mean±SD)	20.25±11.73	19.16±5.04	0.707
Serum creatine (mg/dl) (mean±SD)	0.77±0.19	0.66±0.19	0.069
Serum bilirubin (mg/dl) (mean±SD)	1.63±4.63	0.58±0.32	0.341
Serum AST (mean±SD)	26.41±14.20	28.92±13.85	0.539
Serum ALT (mean±SD)	29.86±21.80	29.04±19.20	0.892
Serum ALP (mean±SD)	92.19±41.65	91.56±58.28	0.963
Hb (g/dl) (mean±SD)	11.12±1.37	11.56±1.04	0.236
Platelet count (mean±SD)	2.91±1.01	3.24±1.05	0.270
White cell count (mean±SD)	7312±3470	7708±3151	0.685
Neutrophils count (mean±SD)	209±860	62±10	0.475
Random blood sugar (mg/dl) (mean±SD)	123.88±16.58	117.56±18.96	0.214
Serum sodium (mean±SD)	139.02±3.31	139.17±4.19	0.891
Serum potassium (mean±SD)	4.24±0.37	4.19±0.26	0.577
Serum chloride (mean±SD)	101.01±3.26	101.61±3.70	0.547
Serum substance-P (mean±SD)	389.26±129.05	410.36±227.71	0.633

5.4 Follow- Up

Patients were followed up for five days after receiving moderately to highly emetogenic agents.

5.5 Change in Outcome variables.

5.5.1 Primary outcome measure

Fifty-four participants were followed up for five days after receiving highly emetogenic agents. The proportion of patients with no nausea in the overall period of CINV in the add-on combination of pregabalin 75mg and olanzapine 5mg group was significantly higher than the placebo group (41.6% vs. 5.5%, p =0.008) (figure 2). The difference in the proportion of the participants with "overall no nausea" between the experimental and control group was 35.4% (95% CI = 12.7% to 59.5%).

Table- 6) The difference in the percentage of patients with no nausea in the acute (0 hrs to 24 hrs of post-chemotherapy period and delayed (24hrs to 5 days) and overall (0-120 hours) period of CINV.

Variable	Experimental (n=36)	Control (n=18)	P value
0-120 hrs after chemotherapy			
No nausea (VAS=0)	15 (41.7%)	1 (5.6%)	0.006
Nausea	21	17	
0-24 hrs after chemotherapy			
No nausea	29 (80.6%)	7 (38.8%)	0.002
Nausea	11	17	
24- 120 hrs after chemotherapy			
No nausea	20 (55.5%)	2 (11.1%)	0.002
Nausea	16	16	

5.5.2 Secondary outcome analysis

5.5.2.1 The difference in the percentage of patients with no nausea in the acute (0 hrs to 24 hrs of post-chemotherapy) period and delayed (24hrs to 5 days) period of CINV.

The results are summarised in table- 6. For the acute period, the response in the experimental group is 80.55 (29/36), and the control group is 38.88% (7/18). They differ significantly as the p-value is 0.002. For the delayed period, the response in the experimental group is 55.55% (20/36) vs. the control group of 11.11% (2/18), which is statistically significant (p-value is 0.002).

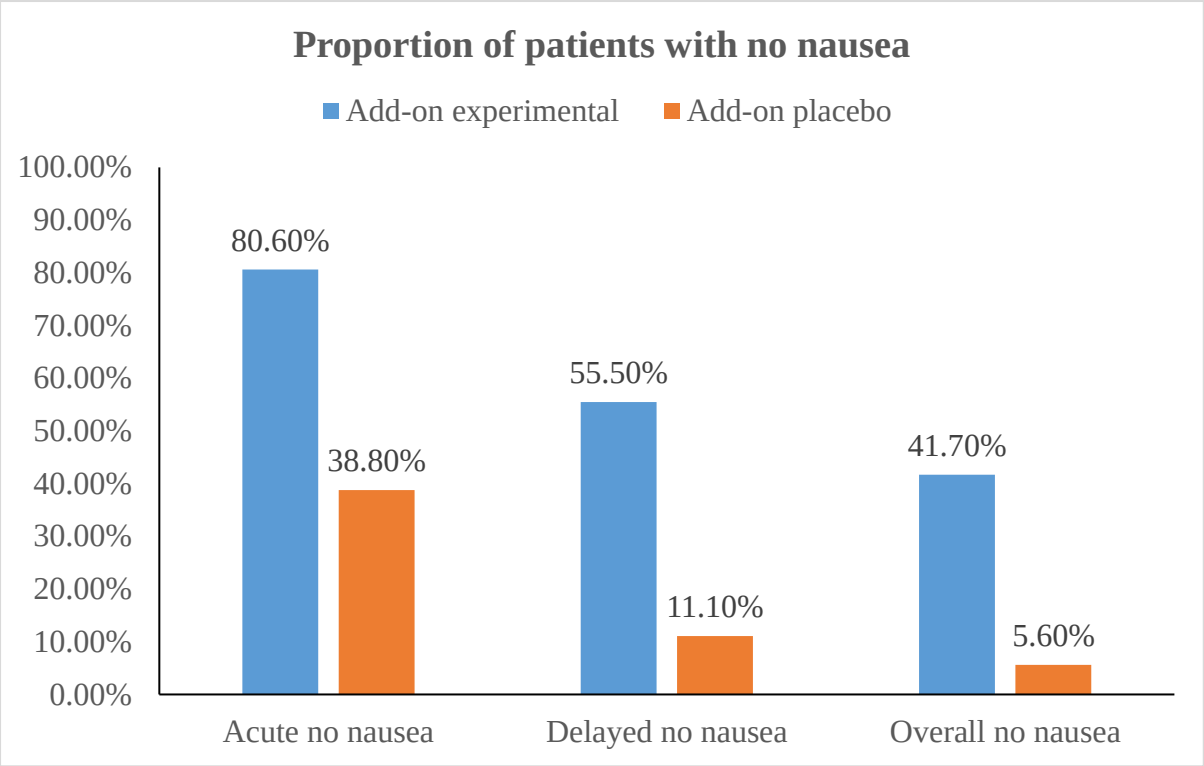

Figure 5) The proportion of patients with "no nausea" (VAS = 0) in the overall, acute, and delayed periods in the experimental and control groups. The proportion of responders was significantly (p(overall) = 0.008, p(acute)= 0.006, p(chronic)= 0.005) more in the experimental group than in the control groups in all periods.

5.5.2.2 The difference in the percentage of patients with no significant nausea (VAS ≤ 25mm) in acute (0 hrs to 24 hrs of post-chemotherapy) periods, delayed (24hrs to 5 days) periods, and overall periods.

No significant nausea (VAS<2.5) significantly differs between the control and experimental groups for all three periods, as shown in the table-7 below.

Table-7) The difference in the percentage of patients with no significant nausea (VAS ≤ 25mm) in acute (0 hrs to 24 hrs of post-chemotherapy) periods, delayed (24hrs to 5 days) periods, and overall periods.

No nausea (VAS<2.5mm)	Experimental (n=36)	Control (n=18)	P value
0-120 hrs after chemotherapy (%)	23 (63.8%)	3 (16.6%)	0.001
0-24 hrs after chemotherapy (%)	34 (94.4%)	9 (50%)	< 0.001
24- 120 hrs after chemotherapy (%)	24 (66.7%)	4 (22.2%)	0.002

5.5.2.3 The difference in the percentage of patients without vomiting in acute, delayed, and overall periods.

The result is presented in Table-9. Our study showed a significant difference in no vomiting response between the groups in acute, delayed, and overall periods.

Table-8) The difference in the percentage of patients with no vomiting in acute, delayed, and overall periods

No vomiting	Experimental (n=36)	Control (n=18)	P value
0-120 hrs after chemotherapy (%)	24 (66.6%)	4 (22.2%)	0.002
0-24 hrs after chemotherapy (%)	32 (88.8%)	9 (50%)	0.002
24- 120 hrs after chemotherapy (%)	26 (72.2%)	5 (27.8%)	0.002

5.5.2.4 The difference in the percentage of patients with rescue medication use.

The following Table-9 compares rescue medication use between two groups. It shows the rescue medication use is significantly lower in the experimental group than in the control group.

Table-9) The difference in the percentage of patients with rescue medication use.

Rescue medication use	Experimental (n=36)	Placebo (n=18)	P value
Yes (%)	13 (36.6%)	14 (77.7%)	P= 0.004
no (%)	23 (63.4 %)	4 (82%)	

5.5.2.5 Differences in the percentage of patients with complete response (no vomiting /no rescue medication use) and complete control (no vomiting /no nausea with no rescue medication use) in the acute period (0 hrs to 24 hrs of post-chemotherapy), delayed (24hrs to 5 days) period, and overall periods.

The results are summarised in Table- 10. Complete response (CR) and complete control (CC) were significantly more in the experimental group than in the control group.

Table-10) Differences in the percentage of patients with complete response (no vomiting /no rescue medication use) and complete control (no vomiting /no nausea with no rescue medication use) in the acute period (0 hrs to 24 hrs of post-chemotherapy), delayed (24hrs to 5 days) period, and overall periods.

Complete response	Experimental (n=36)	Control (n=18)	P value
Overall complete response (number (%))	19 (52.7%)	3 (16.6%)	0.02
Acute complete response (number (%))	19 (52.7%)	3 (16.6%)	0.02
Delayed complete response (number (%))	23 (63.8%)	3 (16.6%)	0.001
Overall complete control (number (%))	16(44.4 %)	1 (5.5%)	0.01
Acute complete control (number (%))	19 (52.7%)	3 (16.6%)	0.02
Delayed complete control (number (%))	20 (55.5%)	1 (5.5%)	<0.001

5.5.2.6 VAS scores for nausea in acute, delayed, and overall periods.

Visual analog scale scores for the experimental group are lower than in the placebo group in all assessment periods, as shown in the Table. The mixed-ANOVA analysis showed a significant effect of the experimental group and period of assessment independently on vas scores with significant interaction between the two parameters.

Table 11) VAS scores in acute, delayed, and overall periods.

Time period	Experimental (mean + SD)	Placebo (mean + SD)	p-value
Overall VAS score (mean±SD)	0.92 ±1.35	3.76±2.22	<0.001
Acute VAS score (mean±SD)	0.47±1.48	4.22±3.44	<0.001
Delayed VAS score (mean±SD)	1.04±1.50	3.65±2.408	<0.001

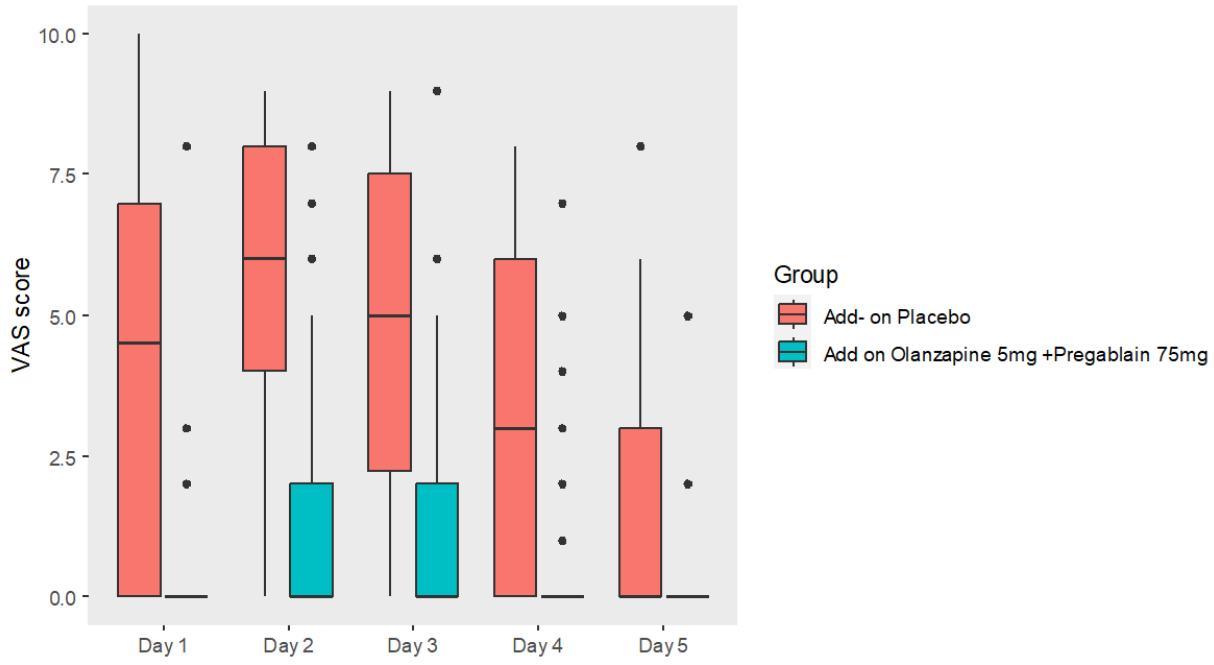

Figure 6) VAS score for nausea through the five days in the experimental and control groups. Apart from the significant difference between the groups over all the days of follow-up, an interaction between the group and the day of follow-up was also observed in the mixed ANOVA analysis.

5.5.2.7 Effectiveness of the intervention on improvement of patient Quality of life using the FLIE questionnaire

At the end of day five, the FLIE score obtained was summarised in the following Table. The mean FLIE scores were 109 in the treatment group and 84.51 in the placebo group. Patients with FLIE score >108 were 58.3% (21/36) in the treatment group and 16.6 % (3/18) in the placebo group, representing no or minimal impact on their daily life with statistically significant(p=0.005). The median nausea FLIE domain was 59 in the treatment and 31.2 in the placebo group. The median vomiting FLIE domain was 63 in the experiment and 38 in the placebo. Our experimental group had significantly higher FLIE scores than the control. Moreover, a higher proportion of patients with FLIE scores>108 was observed in the experimental group, representing a better quality of life in the experimental group.

Table-12) Effectiveness of the intervention on improvement of patient Quality of life using the FLIE questionnaire.

FLIE	Experimental	placebo	P value
Baseline FLIE	126	126	1.000
FLIE total day 5 FLIE (mean±SD)	109.00±21.06	84.51±22.80	<0.001
FLIE nausea domain (mean±SD)	51.87±12.7	39.75 ±11.39	0.001
FLIE domain (mean±SD)	57.14±9.92	44.75±12.40	<0.001
No or minimal impact on daily life (FLIE>108) ((number (%))	21 (58.3%)	3 (16.6%)	0.005

5.5.2.8 Overall treatment-emergent adverse events

In our study, the experimental group experienced significant sedation (72.2% vs. 22.2%, p=<0.001) and dizziness (36% vs. 5.5 %, p= 0.04) compared to the placebo group. Incidence of other adverse events such as headache, postural hypotension, diarrhea, constipation, febrile neutropenia, increased appetite, and difficulty in vision was similar between the groups.

Table-13: Adverse events

Adverse events	Experimental (n= 36)	Placebo (n = 18)	P value
Sedation	26 (72.2%)	4 (22.2%)	< 0.001
Headache	4 (11.1%)	2 (11.1%)	0.972
Dizziness	13 (36%)	1 (5.5%)	0.056
Loose motion	2 (5.5%)	1 (5.5%)	1.000
Constipation	6 (16.6%)	1 (5.5%)	0.252
Febrile neutropenia	0	0	1.00
Increase in appetite	0	0	1.00
Difficulty in vision	0	0	1.00

5.5.3 Subgroup analysis

Our subgroup analysis showed that the treatment would work irrespective of chemo regimens, number of chemotherapy cycles, previous history of morning sickness, alcohol consumption, female sex, and history of motion sickness.

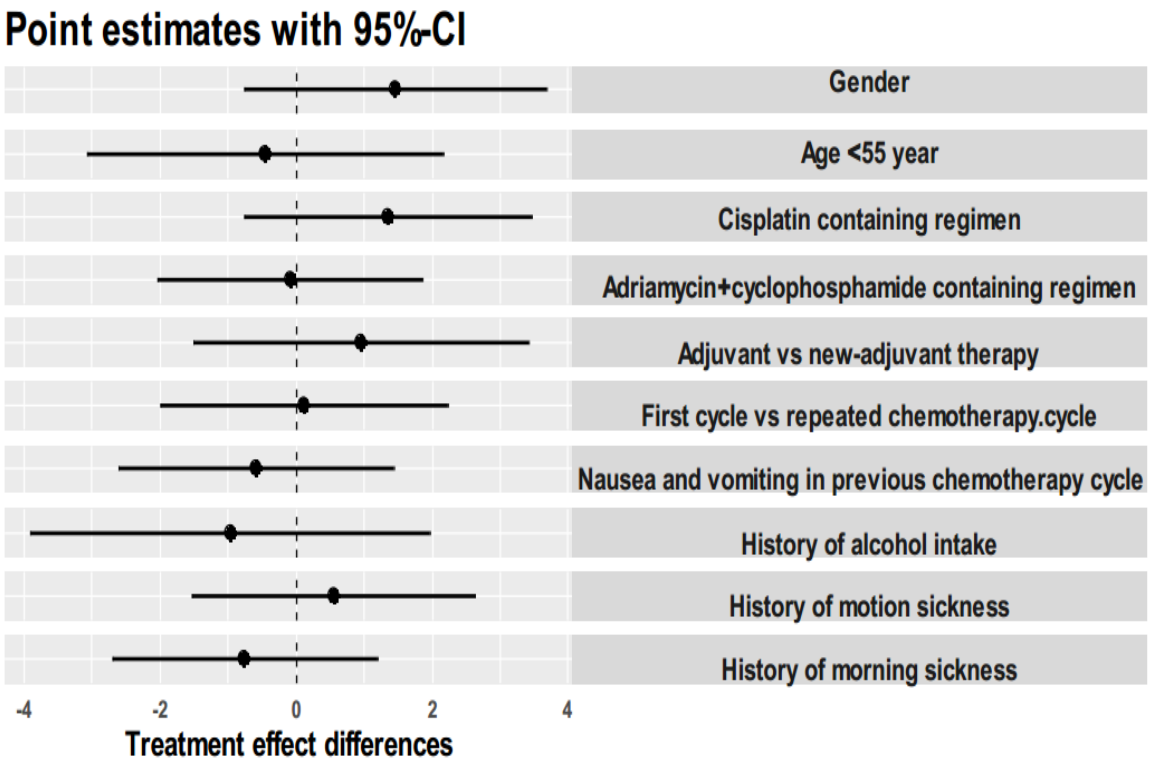

Figure-7) Subgroup analysis of various CINV risk factors depicting the treatment effect difference in terms of VAS score for nausea for the respective subgroups.

6 Discussion

This group sequential response-adaptive randomized double-blinded study demonstrated that administration of olanzapine 5mg in combination with pregabalin 75 mg along with the standard of care as preventive prophylaxis resulted in better control of nausea and vomiting compared to standard of care alone. There was a significant reduction in the use of rescue medication, the incidence of acute nausea, the incidence of delayed nausea, the incidence of acute vomiting, the incidence of delayed vomiting, the overall mean VAS score, and the acute and delayed VAS score in the experimental group. The current trial is the first study to evaluate the addition of olanzapine with pregabalin to prevent nausea and vomiting in patients who cannot afford aprepitant therapy. The subgroup analysis showed that the treatment would work irrespective of gender, age <55, type of chemotherapy agent, number of chemotherapy cycles, previous history of morning sickness, motion sickness, and alcohol consumption.

The results of our study aligned with the studies done with olanzapine to prevent CINV. Several studies (9, 10, 25, 29, 30, 45) explored the role of olanzapine in preventing CINV. The proportion of patients who achieved “overall no nausea” in our study was 41.7% with add-on olanzapine plus pregabalin, whereas in a similar study by Tienchaiananda et al. (31) the proportion of patients who achieved “overall no nausea” with add-on olanzapine alone was 30%. This may show a potential benefit of the combination over olanzapine alone which has to be explored further in clinical trials. Similarly, the role of pregabalin has been evaluated in the context of postoperative nausea and vomiting by many clinical trials , and a meta-analysis by Grant et al. (12) suggested the inclusion of pregabalin in the preoperative period to prevent PONV. However, the role of add-on pregabalin in managing CINV is not adequately explored. A study by Rossi C et al. (13) showed that adding pregabalin alone to the standard of care does not significantly improve the CR rates (53.7% vs. 48.8%) compared with the standard of care alone. However, in our study, the addition of pregabalin to olanzapine along with standard of care has been found to be beneficial.

In the current study, the add-on experimental group had a 36 % more CR rate than the standard of care alone, whereas a study by Hesketh et al. (46) showed that add-on aprepitant had only a 20.4 % more CR rate than the standard of care alone. This shows that there may be a potential benefit of using the add-on olanzapine plus pregabalin over the add-on aprepitant alone, which has to be further evaluated in clinical trials.

The combination of pregabalin (which blocks the release of neurotransmitters) and olanzapine (which blocks the action of neurotransmitters) may be synergistic in preventing nausea and vomiting, which has neither been explored in a mechanistic study nor in a clinical trial. Since the combination has not been explored, we planned to design a study such that the exposure to ineffective treatment will be minimal, along with early termination of the trial. So we used the group-sequential response adaptive randomization design to explore the role of the current combination in preventing CINV. The group-sequential design allowed us to complete the study in less time and with fewer participants. Moreover, the adaptive randomization part of the study design reduced the exposure of a less effective regimen to the participants. However, the synergistic effect between the two agents has to be confirmed using factorial clinical trials in the future.

The significant adverse effect of this combination was sedation and dizziness, which were anticipated for olanzapine and pregabalin, respectively. A previous study that explored the role of add-on olanzapine at 10 mg or 5mg doses demonstrated better tolerability of olanzapine 5 mg with reduced sedation without compromising efficacy (47). Based on this study, to minimize the sedation, we used a 5 mg dosage. However, because of the combination of pregabalin and olanzapine, the incidence of sedation was higher. Hence, we scheduled the dosing at bedtime so that the drowsiness or sedation would minimally affect the patient’s daily functions. Moreover, the advantage of better management of CINV using the experimental combination would reduce the incidence of CINV complications, such as dehydration and electrolyte imbalance, ultimately reducing the need for hospitalization.

The quality of life explored using the FLIE questionnaire (for both nausea and vomiting domains) indicated that the experimental arm had a significantly better quality of life which is comparable to the study done by Ithimakin et al. (33). Hence, using olanzapine in combination with pregabalin improves the patient’s quality of life and reduces non-adherence to the subsequent cycles of chemotherapy.

In our study, the baseline substance P levels did not predict the incidence of nausea and vomiting in the patients receiving HEC, irrespective of the cycle number. In contrast, the study done by Park HS et al. 34 showed that high baseline substance P levels were significantly associated with patients' experience of nausea and vomiting (odds ratio 1.72). This may be due to the study population in the study done by Park HS et al., which included

the patients receiving only the first cycle of chemotherapy. So, the role of substance P in predicting nausea and vomiting has to be explored further.

7 Limitations of our study

- Due to the low socio-economic status of the participants, our study had limitations as we were unable to use aprepitant as a part of the standard of care. This was partially offset by adopting the group-sequential design with adaptive randomization to limit the number of participants requiring less effective therapy.
- Our study follow-up was only five days, but recent evidence suggests CINV can occur after five days. Hence, in future studies, we should plan to observe this late, delayed nausea and vomiting.

8 Recommendations

1) Since in the present study, patients receiving 5mg of olanzapine experienced significant sedation, it is proposed to reduce the dose of olanzapine to 2.5 mg when combined with pregabalin in future studies.
2) A factorial trial for checking the interaction effect of pregabalin plus olanzapine will be helpful in exploring the synergism between the two drugs.
3) A non-inferiority trial with olanzapine plus pregabalin combination vs aprepitant can be planned to explore efficacy in CINV.

9 Conclusion

Olanzapine 5mg plus pregabalin 75mg add-on (days 1 to 5) to injection ondansetron 8mg + injection dexamethasone 12mg on day one followed by oral dexamethasone 8mg on days 2 to 4 will significantly prevent the incidence of CINV compared to the combination of dexamethasone and ondansetron alone in patients of low socioeconomic status receiving HEC. However, the combination is associated with significant sedation and dizziness as adverse events anticipated with olanzapine and pregabalin, respectively.

10 Impact of the research in the advancement of knowledge or benefit to mankind

Our study represents a significant contribution to the field of oncology, specifically addressing the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapeutic regimens, particularly those from low socioeconomic backgrounds who often face additional challenges in accessing effective treatments for CINV.

Innovative Clinical Design: The unique aspect of our research lies in the utilization of an adaptive design for an investigator-initiated clinical trial. This design allows us to limit the number of participants requiring less effective therapy, ultimately enhancing patient outcomes.

Scientific Insight Enrichment: By rigorously assessing the safety and efficacy of the Olanzapine-Pregabalin combination, the trial potentially unveils novel insights into the mechanisms of CINV, steering future treatment avenues.

Clinical Protocol Refinement: The trial's findings can significantly influence clinical protocols and guidelines for managing CINV. This impact resonates beyond the trial's scope, shaping comparable studies and influencing medical practices worldwide.

Healthcare Cost Alleviation: Successful outcomes of trial could reduce healthcare costs associated with managing CINV, addressing a critical concern of medical affordability. This financial impact aligns with the broader objective of making medical interventions accessible to all.

Patient-Centric Care Promotion: By focusing on outpatient settings for chemotherapy administration, the trial aligns with evolving healthcare trends, aiming to deliver effective treatments with minimal hospitalization. This approach optimizes healthcare resources and enhances patient convenience.

11 Research summary

Background

The patients on cancer chemotherapy experience chemotherapy-induced nausea and vomiting (CINV) even with antiemetic prophylaxis. Pregabalin, which has been shown to work in postoperative nausea and vomiting, has been evaluated in the current trial along with olanzapine in combination for managing CINV.

Methods

In this group sequential, response adaptive randomized double-blinded clinical trial, patients received olanzapine 5 mg plus pregabalin 75 mg or placebo orally for five days add-on to standard antiemetic therapy (injection ondansetron 8mg + injection dexamethasone 12mg on day one followed by oral dexamethasone 8mg on days 2 to 4). The primary outcome was the difference in the proportion of patients with "overall no nausea" between groups. The allocation ratio changed depending on each interim analysis result, and more patients were allocated to the well-performing arm.

Results

Initially, 30 patients were equally randomized into two groups. As the experimental group performed well in the interim analysis, the allocation ratio was changed to 2:1 for the subsequent period. A total of 54 patients completed the study. The experimental group performed better in terms of "overall no nausea" (41.7% vs. 5.6%, p value-0.0077). Similar results were obtained in the acute and delayed phases of CINV. Sedation and dizziness were significantly more in the experimental group.

Conclusions

Olanzapine 5mg plus pregabalin 75mg add-on (days 1 to 5) to the standard of care will significantly prevent the incidence of CINV compared to the standard of care alone. However, the combination is associated with sedation and dizziness as adverse events.

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13 Appendix

1. PARTICIPANT INFORMATION SHEET (PIS)
2. Participant Informed Consent Form
3. Case Record Form (CRF)
4. Eastern Cooperative Oncology Group (ECOG) performance status (ECOG)
5. IEC approval
6. CTRI registration
7. ICMR Financial Assistance
8. CONSORT Checklist
9. Certificate for Plagiarism/Similarity

13.1 Participant Information Sheet

(PIS)

Principal Investigator: Dr. Anand Srinivasan

Co-Investigators: Dr. Saroj Kumar Das

Dr. Mathan Kumar

Date-

Study Title: A Group sequential, response adaptive randomized double-blinded clinical trial to evaluate the safety and efficacy of an add-on combination of olanzapine and pregabalin for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapeutic regimen in a daycare setting.

We request you to participate in this study to evaluate the effects of a combination of olanzapine and pregabalin in preventing chemotherapy-induced nausea and vomiting. This study will be conducted in the Department of Radiotherapy and Department of Pharmacology, AIIMS, Bhubaneshwar.

Details of the study.

You will be receiving cancer chemotherapy agents for your condition that may cause nausea and vomiting. To prevent nausea and vomiting, you will be given certain medicines (ondansetron and dexamethasone) as a standard of care treatment. Despite this, you may get nausea and vomiting. To prevent this nausea and vomiting, we will test if the addition of a combination of pregabalin (75 mg/day) and olanzapine (5 mg/day) can further reduce nausea and vomiting. These drugs are relatively safe, and their side effects are also less in the doses administered.

You will receive two capsules, either two starched-filled capsules or a capsule of pregabalin 75 mg and a capsule of olanzapine 5mg. This will be given 30 mins before administering chemotherapy agents, along with the other vomiting-reducing drugs. Then you have to take one of each capsule per day before going to bed, starting from today up to the next four days. If you get nausea and vomiting during the study period, you could take the prescribed medication (ondansetron 8mg). During these five days, you will be contacted by phone call daily to remind you to take medication and to ask about the vomiting episode and nausea severity. After five days, you have to report to the Department of Pharmacology.

Your participation is voluntary. By taking part in this study, your symptoms of nausea and vomiting may be reduced, and it will provide evidence to use this combination to

prevent CINV in future patients. This combination may cause sedation and drowsiness. So, you should avoid activities that require mental alertness, like a machine operating for the study period (5 days). You will be given a copy of this form. You can decide after a discussion with your family. Your records and details of the participants will be maintained confidential. You can withdraw from the study at any time without penalty or loss of benefits to which the subject would otherwise be entitled.

If you want to further discuss this study, please contact the Department of Pharmacology, AIIMS, Bhubaneshwar.

Ph -8110807347

Signature of the investigator.

ସହଭାଗୀ ସୂଚନା ପତ୍ର (PARTICIPANT INFORMATION SHEET)

ତାରିଖ:

ମୁଖ୍ୟ ଅନ୍ୱେଶକ: Dr. ଆନନ୍ଦ ଶ୍ରୀନିବାସନ
ସହ ଅନ୍ୱେଶକ: Dr. ସରୋଜ କୁମାର ଦାସ ମଜୁମ୍ଦାର
Dr. ମଦନ କୁମାର

ଅନୁସନ୍ଧାନର ଶୀର୍ଷକ :ଏ ଗ୍ରୁପ ସିକ୍ୱେନ୍ସିଆଲ ରେଷ୍ପନ୍ସ ଆଦପ୍ତିଭ ରାଣ୍ଡୋମାଇଜ୍ଡ ଡବଲ ବ୍ଲାଇଣ୍ଡେଡ କ୍ଲିନିକଲ୍ ଟ୍ରାଏଲ୍ ଟୁ ଇଭାଲୁଏଟ୍ ଦ ସେଫ୍ଟି ଏଣ୍ଡ ଇଫିକେସି ଅଫ ଏଡ୍- ଓନ କମିନେସନ ଅଫ ଓଲାନଜାପିନ ଏଣ୍ଡ ପ୍ରିଗାବାଲିନ ଫର୍ ଦ ପ୍ରୀଭେନ୍ସନ ଅଫ କେମୋଥେରାପି ଇଣ୍ଡୁସେଡ୍ ନୌସେଆ ଏଣ୍ଡ ଭୋମିଟିଂ ଇନ୍ ପେସେଣ୍ଟ୍ ରିସିଭିଂ ମୋଡରେଟଲି ଟୁ ହାଏଲି ଏମେଟୋଯେନିକ କିମୋଥେରାପେଉଟିକ୍ ରେଜୀମେନ୍।

ଏହି ଗବେଷଣାରେ ଓଲାନଜାପିନ ଏବଂ ପ୍ରିଗାବାଲିନ ଦ୍ୱାରା କର୍କଟ ରୋଗ ପାଇଁ ଦିଆ ଯାଉ ଥିବା ଔଷଧ ଜନିତ ବାନ୍ତି କିମ୍ବା ବାନ୍ତି ର ଅନୁଭୂତିର ନିବାରଣ ପରୀକ୍ଷା କରା ଯିବ । ଆମେ ଆପଣଙ୍କୁଏହି ଗବେଷଣାର ଭାଗ ନେବା ପାଇଁ ଅନୁରୋଧ କରୁଛୁ, ଯାହା AIIMS ଭୁବନେଶ୍ୱର ର ବିକିରଣ ଚିକିତ୍ସା ବିଭାଗ ଏବଂ ଫାର୍ମାକୋଲଜୀ ବିଭାଗରେ କରା ଯିବ ।

ଏହି ଗବେଷଣା ର ମୂଳ ଲକ୍ଷ ଏବଂ ପ୍ରଣାଳୀ: ଆପଣଙ୍କ କର୍କଟ ରୋଗ ପାଇଁ ଯାହା ଔଷଧ ଦିଆ ଯିବ ସେହା ବାନ୍ତି କିମ୍ବା ବାନ୍ତି ର ଅନୁଭୂତି କରେଇ ପାରେ। ଏହି ବାନ୍ତି ର ନିବାରଣ ପାଇଁ ଔଷଧ ଦେବା ସତ୍ତ୍ୱେ (ଓଣ୍ଡନସେଟ୍ରୋନ ଏବଂ ଦେକ୍ସାମେଥସନ୍) ଏହି ଆପଣଙ୍କୁ ବାନ୍ତି କିମ୍ବା ବାନ୍ତି ର ଅନୁଭୂତି ହେଇ ପାରେ। ଏହି ସମସ୍ୟା ର ନିବାରଣ ପାଇଁ ଆମେ ପ୍ରିଗାବାଲିନ (୭୫ ମିଗି/ଦିନ) ଏବଂ ଓଲାନଜାପିନ (୫ ମିଗି/ଦିନ) ଔଷଧ ର ପରୀକ୍ଷା କରିବୁ। ଆପଣଙ୍କୁ ଗୋଟିଏ କେପସୁଲ ଦିଆ ଯିବ ଯାହା ଭିତରେ ଓଲାନଜାପିନ- ପ୍ରିଗାବାଲିନ ଔଷଧ କିମ୍ବା ଷ୍ଟାର୍ଚ୍ଚ ଥାଇ ପାରେ। କର୍କଟ ରୋଗ ଔଷଧ ଦେବା ର ୩୦ ମିନିଟ୍ ପୂର୍ବରୁ ଏହି କେପସୁଲ ଅନ୍ୟ ବାନ୍ତି କମେଇବା ର ଔଷଧ ସହିତ ଦିଆ ଯିବ। ଏହା ପରେ ଆଜି ଠାରୁ ଆରମ୍ଭ କରି ଚାରି ଦିନ ପର୍ଯ୍ୟନ୍ତ ପ୍ରତି ଦିନ ରାତି ରେ ଏହି କେପସୁଲ ଗୋଟେ ଲେଖା ଖାଇବେ। ଏହି ସମୟରେ ଯଦି ବାନ୍ତି କିମ୍ବା ବାନ୍ତି ର ଅନୁଭୂତି ହୁଏ ତାହେଲେ ବାନ୍ତି ପାଇଁ ଦିଆ ଯାଇ ଥିବା ଅନ୍ୟ ଔଷଧ (ଓଣ୍ଡନସେଟ୍ରୋନ ୮ ମିଗି) ର ସେବନ କରନ୍ତୁ। ଏହି ୫ ଦିନରେ ଆପଣଙ୍କୁ ସବୁ ଦିନ ଫୋନ୍ ଦ୍ୱାରା ଔଷଧ ସେବନ ପାଇଁ ମନେ ପକେଇ ଦିଆ ଯିବ ଏବଂ ବାନ୍ତି କିମ୍ବା ବାନ୍ତି ର ଅନୁଭୂତି ର ଗମ୍ଭୀରତା ବିଷୟରେ ପଚରା ଯିବ। ପାଞ୍ଚ ଦିନ ପରେ ଆପଣ ଫାର୍ମାକୋଲଜୀ ବିଭାଗରେ ଆମ ସହିତ ଦେଖା କରିବେ।

ଏହି ଅନୁସନ୍ଧାନ ରେ ଆପଣଙ୍କର ଯୋଗଦାନ ପୂର୍ଣତଃ ସ୍ୱଇଚ୍ଛାରେ। ଏହି ଗବେଷଣାରେ ଯୋଗ ଦେଲେ ଆପଣଙ୍କର ବାନ୍ତି କିମ୍ବା ବାନ୍ତିର ଅନୁଭୂତି କମି ଯାଇ ପାରେ ଯାହା ଦ୍ୱାରା ଆମେ ଏହି ଔଷଧ ଗୁଡା ଅନ୍ୟ କର୍କଟ ରୋଗୀ ମାନଙ୍କର ବାନ୍ତି କମେଇବା ପାଇଁ ବ୍ୟବହାର କରି ପାରିବୁ। ଏହି ଔଷଧ ମାନଙ୍କ ଦ୍ୱାରା ନିଦ ବେଶୀ ଲାଗିବାର ସମ୍ଭାବନା ଅଛି। ତେଣୁ ଔଷଧ ଖାଉଥିବା ୫ ଦିନ ରେ ଆପଣ ଏମିତି କୌଣସି କାମ କରିବେନି ଯୋଉଥିରେ କି ଅଧିକ ମାନସିକ ସତର୍କତାର ଦରକାର ହେବ ଯଥା ଜନ୍ତ୍ରୋପଚାର। ଆପଣଙ୍କୁ ଏହି ସୂଚନା ପତ୍ର ର ଏକ ପୃଷ୍ଠା ଦିଆ ଯିବ। ଆପଣଙ୍କର ପରିବାର ସହିତ ଆଲୋଚନା କରି ଆପଣ ଆମକୁ ଆପଙ୍କର ନିଷ୍ପତ୍ତି ବିଷୟରେ ସୂଚିତ କରି ପାରିବେ। ଏହି ଗବେଷଣାରେ ବ୍ୟବହୃତ ହୋଉଥିବା ସମସ୍ତ ଦସ୍ତାବେଜ ଗୋପନୀୟ ରଖାଯିବ I ଅନୁସନ୍ଧାନରେ ସହଯୋଗୀ ସ୍ୱଇଚ୍ଛାରେ ଯୋଗ ଦେଇ ପାରିବେ କିମ୍ବା ଓହରି ଯାଇ ପାରିବେ I ଅନୁସନ୍ଧାନରୁ ଓହରି ଗଲେ ଏହା ରୋଗ ର ଚିକିତ୍ସା ଉପରେ କୌଣସି ପ୍ରଭାବ ପକାଇବ ନାହିଁ।

ଏହି ଅନୁସନ୍ଧାନ ବିଷୟରେ ଯଦି ଆପଣଙ୍କ ପାଖରେ କିଛି ପ୍ରଶ୍ନ ଅଛି ତାହେଲେ ଦୟା କରି ଫାର୍ମାକୋଲଜୀ ବିଭାଗ, AIIMS ଭୁବନେଶ୍ୱର ରେ ସମ୍ପର୍କ କରନ୍ତୁ।

ଟେଲିଫୋନ ନଂ ୮୧୧୦୮୦୭୩୪୭

(ମୁଖ୍ୟ ଅନୁସନ୍ଧାନ କାରୀ ଙ୍କ ଦସ୍ତଖତ(

13.2 Participant Informed Consent Form (PICF)

Participant identification number for this study: _____

Title of Thesis: **A Group sequential, response adaptive randomized double-blinded clinical trial to evaluate the safety and efficacy of an add-on combination of olanzapine and pregabalin for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapeutic regimen.**

Name of Principal Investigator: Dr. Anand Srinivasan. Tel.No(s).9216996577

Name of Co-Investigator: Dr. Saroj Kumar Das Majumdar

Dr. Mathan Kumar Tel.No-8110807347

The contents of the information sheet dated …….. that was provided have been read carefully by me / explained in detail to me in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions. The nature and purpose of the study and its potential risks/benefits, and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected. I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS, Bhubaneswar. I permit these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:
(Signatures / Left Thumb Impression) Place:

Name of the Participant :
Son / Daughter / Spouse of : _____
Complete postal address : _____

This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date:
Place:

Witness

Signatures

Name:

Address:

ଜ୍ଞାପିତ ସ୍ୱୀକୃତୀପ୍ରାରୂପ (PARTICIPANT INFORMED CONSENT FORM)

ଅନୁସନ୍ଧାନ ନଂ _____

ଅନୁସନ୍ଧାନ ରେ ପରିଚୟ ପାଇଁ ନଂ _____

ଅନୁସନ୍ଧାନ ର ଶୀର୍ଷକ: ଏ ଗ୍ରୁପ ସିକ୍ୱେନ୍ସିଆଲ ରେସ୍ପନ୍ସ ଆଦପ୍ତିଭ ରାଣ୍ଡୋମାଇଜ୍ଡ ଡବଲ ବ୍ଲାଇଣ୍ଡେଡ କ୍ଲିନିକଲ୍ ଟ୍ରାଏଲ୍ ଟୁ ଇଭାଲୁଏଟ୍ ଦ ସେଫ୍ଟି ଏଣ୍ଡ ଇଫିକେସି ଅଫ ଏଡ୍- ଓନ କମିନେସନ ଅଫ ଓଲାନଜାପିନ ଏଣ୍ଡ ପ୍ରିଗାବାଲିନ ଫର୍ ଦ ପ୍ରୀଭେନ୍ସନ ଅଫ କେମୋଥେରାପି ଇଣ୍ଡୁସେଡ୍ ନୌସେଆ ଏଣ୍ଡ ଭୋମିଟିଂ ଇନ୍ ପେସେଣ୍ଟ୍ ରିସିଭିଂ ମୋଡରେଟଲି ଟୁ ହାଏଲି ଏମେଟୋଯେନିକ କିମୋଥେରାପେଉଟିକ୍ ରେଜୀମେନ୍ ।

ମୁଖ୍ୟ ଅନ୍ୱେଶକ: Dr. ଆନନ୍ଦ ଶ୍ରୀନିବାସନ ଟେଲିଫୋନ ନଂ ୯୨୧୬୯୯୬୫୭୭

ସହ ଅନ୍ୱେଶକ: Dr. ସରୋଜ କୁମାର ଦାସ ମଜୁମ୍ଦାର

Dr. ମଦନ କୁମାର ଟେଲିଫୋନ ନଂ ୮୧୧୦୮୦୭୩୪୭

ଏହି ଅନୁସନ୍ଧାନ ବିଷୟରେ ସୂଚନା ପତ୍ର ରେ ଯେଉଁ ସୂଚନା ଉଲ୍ଲେଖ କରାଯାଇଛି ସେହା ସବୁ ମୁଁ ସଠିକ୍ ଭାବରେ ପଢିଛି (_____ ତାରିଖରେ)। ମୋତେ ସବୁ ବିସ୍ତୃତ ଭାବରେ ଓ ସାବଲୀଳ ଭାଷାରେ ଠିକ୍ ଭାବରେ ବୁଝାଇ ଦିଆଯାଇଛି। ଏହି ସନ୍ଦର୍ଭରେ ବା ବିଷୟରେ ପ୍ରଶ୍ନ ପଚାରିବା ପାଇଁ ମୋତେ ସୁଯୋଗ ବା ଅନୁମତି ଦିଆଯାଇଛି।
ଏହି ଅନୁସନ୍ଧାନ ର ବିଷୟ ବସ୍ତୁ, ଏହାର ମୁଖ୍ୟ ବିପଦ ଆଶଙ୍କା, ଲାଭ ଏବଂ ଏହାର ପ୍ରତ୍ୟାଶିତ ସମୟ ଏବଂ ଅନ୍ୟ ସମସ୍ତ ଉଚିତ ବିଷୟ ବସ୍ତୁ ମୋତେ ବିସ୍ତାରିତ ଭାବରେ ବୁଝାଇ ଦିଆଯାଇଛି। ଏହି ଅନୁସନ୍ଧାନ ରେ ମୁଁ ସ୍ୱଇଚ୍ଛା ରେ ଯୋଗଦାନ କରୁଛି। ଯେ କୌଣସି ସମୟରେ, କୌଣସି ସ୍ପଷ୍ଟୀକରଣ ନ ଦେଇ ମୁଁ ଏହି ଗବେଷଣା ରୁ ବାହାରି ଯାଇ ପାରିବି। ଏହା ଦ୍ୱାରା ମୋର କୌଣସି ପ୍ରକାର ନ୍ୟାୟିକ ଅଧିକାର କିମ୍ବା ଯତ୍ନ ବ୍ୟବସ୍ଥା ହ୍ରାସ ପାଇବ ନାହିଁ।

ମୁଁ ବୁଝୁଛି ଯେ ଏହି ଅନୁସନ୍ଧାନ ରେ ମୋ ଠାରୁ ଏବଂ ମୋର ସ୍ୱାସ୍ଥ୍ୟ ସମ୍ବନ୍ଧିତ ଫାଇଲ୍ ରୁ ଯାହା ତଥ୍ୟ ସଂଗ୍ରହ କରାଯିବ ତାହା AIIMS ର ଦାୟିତ୍ୱ ସମ୍ପନ୍ନ ବ୍ୟକ୍ତିଙ୍କ ଦ୍ୱାରା ନିରୀକ୍ଷଣ କରା ଯିବ। ମୋର ସ୍ୱାସ୍ଥ୍ୟ ସମ୍ବନ୍ଧିତ ଫାଇଲ୍ ନିରୀକ୍ଷଣ କରିବା ପାଇଁ ମୁଁ ସ୍ୱୀକୃତି ପ୍ରଦାନ କରୁଛି।

ମୁଁ ଏହି ଅନୁସନ୍ଧାନ ରେ ସହଯୋଗ କରିବା ପାଇଁ ସହମତି ଦେଉଛି।

_____ ତାରିଖ:
(ଦସ୍ତଖତ/ବାମ ବୁଢ଼ା ଆଙ୍ଗୁଠି ଟିପ) ଜାଗା:

ସହଯୋଗୀଙ୍କ ନାମ:
ବାପା/ମାଁ/ସ୍ୱାମୀ ଙ୍କ ନାମ:
ସମ୍ପୂର୍ଣ ଠିକଣା:
ଉପରୋକ୍ତ ସହମତି ପତ୍ର ମୋର ଉପସ୍ଥିତି ରେ ସ୍ୱାକ୍ଷରିତ ହୋଇଛି।

_____ ତାରିଖ:
(ମୁଖ୍ୟ ଅନୁସନ୍ଧାନ କାରୀ ଙ୍କ ଦସ୍ତଖତ) ଜାଗା:

୧) ପ୍ରଥମ ସାକ୍ଷୀ	୨) ଦ୍ୱିତୀୟ ସାକ୍ଷୀ
_____	_____
ଦସ୍ତଖତ	ଦସ୍ତଖତ
ନାମ:	ନାମ:
ଠିକଣା:	ଠିକଣା

13.3 Case record form

(CRF)

Enrolment No	Date	Patients Initial

A Group Sequential, Response Adaptive Randomized Double-Blinded Clinical Trial to Evaluate the Safety and Efficacy of Add-on Combination of Olanzapine and Pregabalin for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Highly Emetogenic Chemotherapeutic Regimen in a Daycare Setting

Investigator's Name	
Study Site	

GENERAL INSTRUCTIONS

1. A CRF must be completed for each study participant who is successfully enrolled
2. Please fill the CRFs with a black ballpoint pen.
3. Answer every question explicitly: don't use ditto marks.
4. Do not leave any question unanswered. If the answer to a question is unknown, write NK (not known). If the requested test has not been done, write ND (not done). If a question is not applicable, write NA (not applicable).
5. Errors should be lined out, and new entries should be made on the same sheet with initials and dates. Correction fluid should not be used.
6. The date in the CRFs should be entered as Day / Month /Year.

The CRFs must be complete in every respect.

Case Record Form

Name of the patient				OPD.NO	
Age		Sex		Allocation code	
Address with mobile number					

Diagnosis :

Chemotherapeutic regimen :

New adjuvant / Adjuvant :

Cycle number :

ECOG performance status :

Body weight :

Height :

BMI :

H/O nausea and vomiting within 24 hrs : Yes/No

H/O seizure disorder, severe cognitive disturbance, psychiatric disturbance : Yes/No

H/O Parkinson's disease, primary or secondary CNS malignancy : Yes/No

H/O dementia-related psychosis : Yes/No

H/O uncontrolled diabetes : Yes/No

H/O cardiac failure, cardiac arrhythmia or myocardial infarction within 6 months : Yes/No

H/O antipsychotic drug intake : Yes/No

H/O pregabalin/olanzapine intake : Yes/No

H/O hypersensitivity to olanzapine /pregabalin : Yes/No

H/O current pregnancy/ lactation : Yes/No

H/O condition that cause upper GIT obstruction : Yes/No

H/O risk factors for CINV

Parameters	**Yes**	**No**
Nausea vomiting in the previous cycle		
Alcohol intake >6 units*/week		
Motion sickness		
Morning sickness		
*Alcohol units =strength *volume/1000		

EXAMINATION

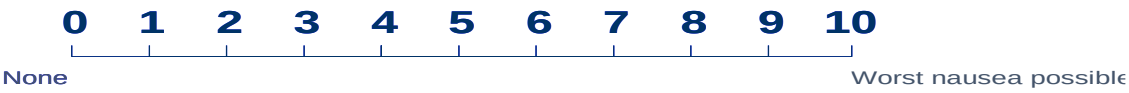
BP: PR:

Blood investigation

Test	**Parameter**	**Value**	**Unit**
RFT	Urea		
	Creatine		
LFT	Serum bilirubin		
	AST		
	ALT		
	ALP		
CBC	Hb		
	Platelet count		
	Total WBC		
	Neutrophils		
Blood glucose	Random blood glucose		
Serum electrolytes	Sodium		
	Potassium		
	Calcium		

Baseline -Nausea and vomiting questionnaire **Date:**

The scales provided in the questionnaire rates issues from 0 to 10, where 0 is no trouble at all and 10 denotes the worst trouble possible for the particular issue in question.

1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No
4) If nausea was present, please rate as per the scale given. How severe was nausea in the past 24 hours?  	
5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided.  	
6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided.  	
7) Was there any visual disturbance in the past 24 hrs?	Yes /No

Baseline – FLIE Nausea and vomiting questionnaire score	

DAILY TELEPHONE CONTACT

Day 1
Date of telephone contact or attempt to contact was made _____
Were you able to contact the patient? Yes/ No

Verify the following with the subject:

Study medication taken	Yes	No

If "No", provide a reason

_____

Has rescue Medication taken? *(check one)* (If yes)	Yes	No

Agent Name	Dose

Nausea and Vomiting during the first 24 hrs after chemotherapy,

1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No
4) If nausea was present, please rate as per the scale given. How severe was nausea in the past 24 hours? 0 1 2 3 4 5 6 7 8 9 10 None Worst nausea possible	
5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None Severely debilitating	
6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None Severely increased	
7) Was there any visual disturbance in the past 24 hrs?	Yes /No

DAILY TELEPHONE CONTACT

Day 2
Date of telephone contact or attempt to contact was made _____
Were you able to contact the patient? Yes/ No

Verify the following with the subject:

Study medication taken	Yes	No

If "No", provide a reason

_____

Has rescue Medication taken? *(check one)* (If yes)	Yes	No

Agent Name	Dose

Nausea and Vomiting during last 24 hrs

1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No
4) If nausea was present, please rate as per the scale given. How severe was nausea in the past 24 hours? 0 1 2 3 4 5 6 7 8 9 10 None — Worst nausea possible	
5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None — Severely debilitating	
6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None — Severely increased	
7) Was there any visual disturbance in the past 24 hrs?	Yes /No

DAILY TELEPHONE CONTACT

Day 3
Date of telephone contact or attempt to contact was made _____
Were you able to contact the patient? Yes/ No

Verify the following with the subject:

Study medication taken	Yes	No

If "No", provide a reason

_____

Has rescue Medication taken? *(check one)* (If yes)	Yes	No

Agent Name	Dose

Nausea and Vomiting during last 24 hrs

1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No
4) If nausea was present, please rate as per the scale given. How severe was nausea in the past 24 hours? 0 1 2 3 4 5 6 7 8 9 10 None — Worst nausea possible	
5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None — Severely debilitating	
6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided. 0 1 2 3 4 5 6 7 8 9 10 None — Severely increased	
7) Was there any visual disturbance in the past 24 hrs?	Yes /No

DAILY TELEPHONE CONTACT
Day 4
Date of telephone contact or attempt to contact was made _____
Were you able to contact the patient? Yes/ No

Verify the following with the subject:

Study medication taken	Yes	No

If "No", provide a reason.

_____

Has rescue Medication taken? *(check one)* (If yes)	Yes	No

Agent Name	Dose

Nausea and vomiting during last 24 hrs

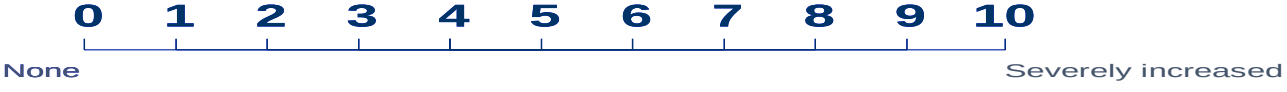
1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No

4) If nausea was present, please rate as per the scale given.

How severe was nausea in the past 24 hours?

5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided.

6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided.



7) Was there any visual disturbance in the past 24 hrs?	Yes /No

DAILY TELEPHONE CONTACT

Day 5

Date of telephone contact or attempt to contact was made _____
Were you able to contact the patient? Yes/ No
Verify the following with the subject:

Study medication taken	Yes	No

If "No", provide a reason _____

Has rescue Medication taken? *(check one)* (If yes)	Yes	No

Agent Name	Dose

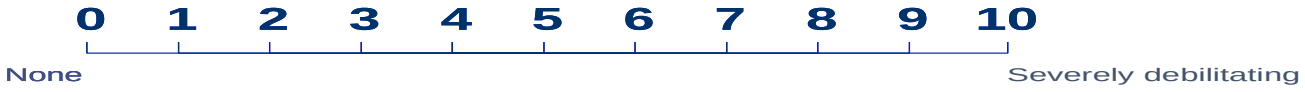
Nausea and Vomiting during last 24 hrs

1) Was there any vomiting episode in the past 24 hours?	Yes/No
2) If vomiting was present in the past 24 hrs, how many times did it happen?	
3) Was there any nausea in the past 24 hours**?**	Yes/No

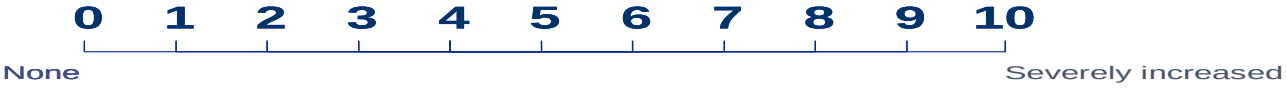
4) If nausea was present, please rate as per the scale given.

How severe was nausea in the past 24 hours?

5) If there was any undesired sedation in the past 24 hours, please rate it as per the scale provided.



6) If there was any undesired appetite increase in the past 24 hours, please rate it as per the scale provided.



7) Was there any visual disturbance in the past 24 hrs?	Yes /No

Day 5 FLIE Nausea and vomiting questionnaire score	

FLIE Nausea and vomiting questionnaire score	
Baseline	**Day 5**

Adverse Events Monitoring

DAY	**Adverse Events with duration** (to be mentioned other than sedation, increased appetite, visual disturbance)	**Severity** 4-point verbal scale (none-mild-moderate-severe.)	**Relationship to study medication**	**Action taken**
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				

13.4 Eastern Cooperative Oncology Group (ECOG) performance status (ECOG)

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.
5	Dead

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

13.5 IEC Approval

INSTITUTIONAL ETHICS COMMITTEE
(Registration No. ECR/534/Inst/OD/2014/RR-20)

All India Institute of Medical Sciences Bhubaneswar
Level 3 Academic Block, AIIMS Bhubaneswar (At Sijua)
Bhubaneswar 751019, Odisha
Email: iec@aiimsbhubaneswar.edu.in **Phone**: 0674-2476083

Date: June 26, 2021

Dr Mathan Kumar
Post Graduate Student
Department of Pharmacology,
AIIMS, Bhubaneswar

Ref Number: IEC/AIIMS BBSR/PG Thesis/2021-22/06

Through Guide: Dr Anand Srinivasan

Subject: A Group Sequential, Response Adaptive Randomized Double-Blinded Clinical Trial to Evaluate the Safety and Efficacy of Add-on Combination of Olanzapine and Pregabalin for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Moderately to Highly Emetogenic Chemotherapeutic Regimen in a Day Care Setting.

Dear Dr Mathan Kumar

This is regarding above-mentioned **post graduate thesis protocol** which was discussed and reviewed in the Institutional Ethics Committee, AIIMS Bhubaneswar meeting held on June 19, 2021 and your subsequent letter dated June 25, 2021 responding to queries raised during IEC meeting.

The protocol has been approved from ethical angle prospectively with effect from **June 26, 2021** till the entire period of the conduct of study according to the study duration mentioned in the protocol under guidance of Dr Anand Srinivasan, thesis guide.

Student and guide are responsible for following requirements

1. All co-guides must be kept informed of the status of the project
2. No significant change to the protocol should be made and implemented without prior intimation and approval of the IEC
3. IEC should be reported about all Serious Adverse Events (SAEs) occurring during the study.
4. Only approved informed consent form and participant information sheet to be used for enrolment of the participants. All consent forms and other documents must be archived safely with PI for IEC audit
5. A six-monthly study progress report of the project must be submitted to IEC
6. It is hereby confirmed that neither you nor any of the study team members have participated in the voting/ decision making process of Institute Ethics Committee of AIIMS Bhubaneswar related to this study.

Member Secretary
(IEC AIIMS Bhubaneswar)

सदस्य सचव / Member Secretary
संस्थागत आचार समिति
Institutional Ethics Committee
एम्स, भुवनेश्वर / AIIMS,Bhubaneswar

13.6 CTRI registration

CTRI No	**CTRI/2021/08/035451** [Registered on: 05/08/2021] **Trial Registered Prospectively**
Acknowledgement Number	REF/2021/07/045884
Last Modified On:	04/08/2021
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Evaluating the Antiemetic Role of Add on Combination of Pregabalin plus Olanzapine in Chemotherapy Induced Nausea and Vomiting using Adaptive Clinical Trail Designs
Scientific Title of Study	"A Group Sequential, Response Adaptive Randomized Double-Blinded Clinical Trial to Evaluate the Safety and Efficacy of Add-on Combination of Olanzapine and Pregabalin for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving Moderately to Highly Emetogenic Chemotherapeutic Regimen in a Day Care Setting".
Trial Acronym	
Secondary IDs if Any	**Secondary ID**: NIL; **Identifier**: NIL
Details of Principal Investigator or overall Trial Coordinator (multi-center study)	**Name**: Dr Anand Srinivasan **Designation**: Associate Professor **Affliation**: All India Institute of Medical Sciences **Address**: Room no- 105, Department of pharmacology, academic block, AIIMS HOSPITAL Sijua,Patrapada,Po-dumduma, Bhubaneswar. Khordha ORISSA 751019 India **Phone**: 9216996577 **Fax**: **Email**: anandsrinivasan@aiimsbhubaneswar.edu.in **Email**: anandsrinivasan@aiimsbhubaneswar.edu.in

13.7 ICMR Financial Assistance

ICMR
INDIAN COUNCIL OF MEDICAL RESEARCH

भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग, स्वास्थ्य और परिवार कल्याण मंत्रालय, भारत सरकार

Indian Council of Medical Research
Department of Health Research, Ministry of Health and Family Welfare, Government of India

No.3/2/June-2021/PG-Thesis-HRD (01) Date: 20/09/2021

MD21JUN-0045
Dr. Mathan Kumar,
Department of Pharmacology,
All India Institute of Medical Sciences,
Bhubaneswar, Odisha- 751019

Subject: Award of ICMR Financial Support for the MD/MS/DM/MCh/DNB/DrNB/MDS thesis for the June, 2021 batch- reg.

Dear Dr. Mathan Kumar,

This is in reference to your application seeking financial assistance from the ICMR for MD/MS/DM/MCh/DNB/DrNB/MDS thesis entitled **"A group sequential, response adaptive randomized double-blinded clinical trial to evaluate the safety and efficacy of add-on combination of olanzapine and pregabalin for the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately to highly emetogenic chemotherapeutic regimen in a day care setting".**

I am glad to inform you that, based on the recommendation of Expert Committee, the Director General, ICMR has approved your application for the financial support of **Rs. 50,000/- (Fifty thousand only)** for the thesis as stated above, which will be disbursed in two/three installments. Initial amount of **Rs. 30,000/-** will be released after receipt of the Undertaking as per the guidelines and remaining amount of **Rs. 20,000/-** on receipt of the electronic copy and summary of work done of your thesis duly approved by the University/Institute along with one publication in an indexed journal. Mandatory requirement to avail this opportunity is to provide us with an Undertaking duly forwarded through the Guide, to the undersigned, enabling us to release the grant.

The amount will be released after submission of the UNDERTAKING, GUIDE DETAILS as well as the MANDATE FORM (available on ICMR website) along with a photocopy of a Cancelled Cheque (please ignore, if already submitted) latest by 15th October, 2021 for receiving e-payment for purpose of verification of the concerned bank account where money is to be remitted.

Yours faithfully

(Bal Ugrin Sah)
Administrative Officer-HRD
For Director General

Copy to:
1. Guide: Dr. Anand Srinivasan, Associate Professor, Department of Pharmacology, All India Institute of Medical Sciences, Bhubaneswar, Odisha-751019

वी. रामलिंगस्वामी भवन, पोस्ट बॉक्स नं. 4911,
अंसारी नगर, नई दिल्ली - 110 029, भारत
V. Ramalingaswami Bhawan, P.O. Box No. 4911,
Ansari Nagar, New Delhi - 110 029, India

Tel. +91-11-26588895 / 26588980 / 26589794
+91-11-26589736 / 26588707
Fax. +91-11-26588662 | icmr.nic.in

13.8 CONSORT 2010 checklist for a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Cover page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	56
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	22
	2b	Specific objectives or hypotheses	25
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	28
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	28
	4b	Settings and locations where the data were collected	28
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	30
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	25
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	30
	7b	When applicable, explanation of any interim analyses and stopping guidelines	31
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	31
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	31
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	33
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	33

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	33
	11b	If relevant, description of the similarity of interventions	33
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	35
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	35
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	37
	13b	For each group, losses and exclusions after randomisation, together with reasons	37
Recruitment	14a	Dates defining the periods of recruitment and follow-up	37
	14b	Why the trial ended or was stopped	37
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	39
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	39
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	41
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	41
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	48
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	47
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	52
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	52
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	50
Other information			
Registration	23	Registration number and name of trial registry	83
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	84

13.9 Certificate for Plagiarism/Similarity

ALL INDIA INSTITUTE OF MEDICAL SCIENCES

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Dr. Anand Srinivasan
Additional professor
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PRIMARY SOURCES

1	Calcagnile, S., C. Lanzarotti, M. Gutacker, V. Jakob-Rodamer, K. Kammerer, and W. Timmer. "Evaluation of the effect of food and age on the pharmacokinetics of oral netupitant and palonosetron in healthy subjects: A randomized, open-label, crossover phase 1 study", Clinical Pharmacology in Drug Development, 2015. Crossref	25 words — 3%
2	www.dovepress.com Internet	21 words — 3%
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4	Senri Yamamoto, Hirotoshi Iihara, Ryuji Uozumi, Hitoshi Kawazoe et al. "Effects of adding a neurokinin-1 receptor antagonist to 5mg olanzapine, a 5-hydroxytryptamine-3 receptor antagonist, and dexamethasone	12 words — 2%