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Pharmacoeconomic Evaluation of an Olanzapine-Containing Quadruple Antiemetic Regimen for the Prevention of CINV: An Efficacy-Cost Analysis

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Abstract

This study systematically evaluates the efficacy, safety, and cost-effectiveness of an olanzapine-containing quadruple antiemetic regimen compared with the standard triple regimen for preventing chemotherapy-induced nausea and vomiting (CINV) associated with moderately to highly emetogenic chemotherapy. The aim is to provide evidence-based guidance for optimizing clinical CINV management. The quadruple regimen significantly improved the complete response rate for delayed-phase CINV to 83% – 86% and increased the overall no-nausea rate to 78.7%, demonstrating superior efficacy compared with the standard triple regimen. Adding olanzapine addressed the pharmacological limitations of the standard regimen by enhancing delayed-phase coverage and controlling refractory nausea through multi-receptor antagonism. Pharmacoeconomic analysis indicates that, despite the additional cost of olanzapine, the quadruple regimen reduces the need for rescue medications and complication management costs due to its enhanced efficacy, yielding cost savings of 300 – 500 yuan (RMB) per treatment cycle and a superior cost-effectiveness ratio. Incorporating low-dose olanzapine into the standard triple regimen offers a more effective and cost-efficient approach to preventing CINV in patients receiving moderately to highly emetogenic chemotherapy. Future research should focus on developing individualized predictive models and validating real-world effectiveness in diverse patient populations.

Keywords

chemotherapy-induced nausea and vomiting, olanzapine, antiemetic regimen, cost-effectiveness analysis, pharmacoeconomics

1. Introduction

Chemotherapy is a cornerstone of cancer treatment, significantly enhancing patient survival and quality of life. However, cytotoxic agents, while effective in targeting tumor cells, frequently cause substantial toxicity to healthy tissues. Among the most prevalent adverse effects are gastrointestinal toxicities, with chemotherapy-induced nausea and vomiting (CINV) representing a particularly distressing and common challenge for patients. Without appropriate prophylactic measures, the incidence of CINV can reach 70%–80%, and in cisplatin-based regimens, the incidence may approach 100%. Despite standardized prophylactic regimens,

chemotherapy-induced nausea and vomiting (CINV) affects approximately 60%–80% of patients. Prospective studies indicate that, even with antiemetic agents, CINV incidence ranges from 11.5% to 27.3%. Inadequately controlled CINV can lead to multiple complications: frequent vomiting disrupts normal nutritional intake, severe vomiting may cause esophageal mucosal injury or gastrointestinal bleeding, and dehydration can increase renal burden and exacerbate physical decline. Over time, patients may experience malnutrition, weight loss, and electrolyte imbalances (e.g., hypokalemia, hyponatremia), ultimately compromising immune function. Psychologically, persistent CINV can trigger fear of chemotherapy, anxiety, and depression, significantly impairing quality of life.

Early antiemetics were primarily dopamine D_2receptor antagonists (RAs), such as metoclopramide, which showed modest efficacy in mild cases but caused extrapyramidal side effects at higher doses. Phenothiazines, including chlorpromazine, were subsequently used but their clinical application was limited by frequent adverse effects. In the 1980s, 5-hydroxytryptamine type 3 receptor (5-HT_3R) antagonists were developed, followed in the early 21st century by neurokinin-1 receptor (NK-1R) antagonists. NK-1R antagonists are often used in combination with 5-HT_3R antagonists, resulting in more effective antiemetic regimens that significantly improve control of nausea and vomiting, especially those induced by highly emetogenic chemotherapy [1]. Although progress has been made in managing chemotherapy-induced nausea and vomiting (CINV), notable challenges and unmet clinical needs persist. Some patients experience breakthrough nausea or vomiting with standard prophylactic regimens, and available antiemetic agents may lead to additional side effects or financial strain. To address these challenges, this study examines current antiemetic combinations, evaluating their efficacy and cost-effectiveness to inform clinical decision-making.

2. Fundamentals and Developments in the Field

2.1 Mechanisms of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a complex phenomenon involving multiple factors and mechanisms. Its pathogenesis primarily encompasses three key aspects: direct stimulation of the gastrointestinal tract, activation of the chemoreceptor trigger zone (CTZ), and the influence of emotional factors on the cerebral cortex. Chemotherapeutic agents such as platinum compounds, anthracyclines, and nitrogen mustards can directly irritate the gastrointestinal mucosa, leading to the release of neurotransmitters such as 5-hydroxytryptamine (5-HT) from enterochromaffin cells. These neurotransmitters bind to their respective receptors, activating vagal afferent fibers that relay signals to the vomiting center in the medulla oblongata, thereby triggering the vomiting reflex. Concurrently, chemotherapy drugs and their metabolites can circulate through the bloodstream to affect the CTZ, a region rich in various neurotransmitter receptors, including dopamine and 5-HT receptors. When these receptors are activated by the drugs, neural impulses are transmitted to the vomiting center, resulting in vomiting. Furthermore, psychological elements such as anxiety and fear can modulate the vomiting center via the cerebral cortex, potentially initiating or intensifying symptoms of nausea and vomiting [2].

2.2 History of Antiemetic Drug Development

The evolution of antiemetic drug development can be broadly divided into distinct stages. Prior to the 1970s, effective treatments for chemotherapy-induced nausea and vomiting (CINV) were unavailable, with management relying primarily on agents such as antihistamines, anticholinergics, and phenothiazines. These agents, however, offered limited efficacy and were associated with significant adverse effects. The therapeutic landscape changed significantly in the 1980s with the recognition of 5-HT's pivotal role in CINV pathogenesis. This led to the emergence of the first-generation 5-HT_3 receptor antagonist (5-HT_3RA), ondansetron, which substantially improved antiemetic outcomes. Subsequent clinical introductions of agents like granisetron, tropisetron, and ramosetron further advanced CINV prevention and management [3].

The 21st century marked the advent of the Neurokinin-1 receptor antagonists (NK-1RAs), such as aprepitant. These agents exert their effect by blocking the binding of substance P to the NK-1 receptor and demonstrate particularly strong preventative efficacy against delayed-phase CINV. Current guidelines are based on emetogenic risk stratification: highly emetogenic chemotherapy (HEC) typically recommends a triple regimen (5-HT_3RA + NK-1RA + dexamethasone), while moderately to low emetogenic risk (MEC/LEC)

utilizes appropriately de-escalated antiemetic regimens (see Table 1) [4]. Nevertheless, interpatient variability and differences in drug metabolism still result in substantial heterogeneity in treatment efficacy. A subset of patients continues to experience breakthrough CINV, indicating that existing regimens require further optimization and refinement [1].

Table 1: Recommended Antiemetic Regimens for Chemotherapy with Different Emetogenic Risks

Emetogenic Level	Representative Drugs	Basic Regimen	Optimized Regimen
High Emetogenic Risk	Cisplatin, Carboplatin (AUC ≥ 4)	Triple: 5-HT$_3$ RA + NK-1 RA + Dexamethasone	Quadruple: Basic + Olanzapine 5-10 mg
Moderate Emetogenic Risk	Oxaliplatin, Carboplatin (AUC < 4)	Double: 5-HT$_3$ RA + Dexamethasone	Triple: Add NK-1 RA or Olanzapine
Low Emetogenic Risk	Paclitaxel, Gemcitabine	5-HT$_3$ RA or Dexamethasone [5]	

Note: AUC refers to the Area Under the Concentration-Time Curve, which measures the total drug absorption in the bo dy and serves as a key parameter for evaluating drug exposure.

3. Efficacy and Limitations of Current Standard Regimens

Currently, for highly emetogenic chemotherapy (HEC), the triple regimen consisting of a 5-HT$_3$ receptor antagonist (5-HT$_3$RA), an NK-1 receptor antagonist (NK-1RA), and dexamethasone has become the first-line antiemetic strategy. This approach performs well in controlling acute-phase vomiting, but its complete response rate (CRR) in the delayed phase remains only 65%-70%[1], highlighting a clear shortfall in long-term prevention of nausea and vomiting. The occurrence of breakthrough vomiting is linked to multiple factors, including Metabolic characteristics of the drugs, individual patient variations, and deviations in regimen adherence. For example, NK-1RAs have relatively short half-lives; taking aprepitant as an instance, its half-life is approximately 40 hours, which struggles to cover the peak periods of delayed vomiting, leading to diminished protective effects. Additionally, patient-specific factors such as being female, under 50 years old, or having a history of motion sickness can further reduce the CRR by 20%-30%. On the other hand, in clinical practice, dexamethasone is often dose-reduced or discontinued early due to its numerous adverse effects, which may lead to a 40% decline in the delayed-phase complete response rate [1].

In recent years, olanzapine, as a multi-receptor antagonist, has been incorporated into antiemetic regimens and demonstrated significant benefits [6]. Studies show that adding low-dose olanzapine (5-10 mg, days 1-4) to the traditional triple regimen to form a quadruple regimen can markedly elevate the delayed-phase CRR to 83%-86%, with the overall no-nausea rate increasing to 78.7%, representing a substantial improvement over the 65.6% seen with the triple regimen [1, 7]. Olanzapine is particularly effective against nausea symptoms that are difficult to control with conventional drugs, providing a promising option for patients with refractory CINV. Its mechanism of action involves blockade of multiple neurotransmitter pathways associated with emesis, exerting potent central inhibitory effects and thereby playing a pivotal role in the management of delayed-phase CINV. Notably, while the quadruple regimen offers remarkable efficacy, olanzapine itself may cause adverse reactions such as somnolence and metabolic disturbances. Therefore, in practical application, it is essential to weigh the benefits against the risks and individualize the dosage and duration of treatment.

4. Cost-Effectiveness Analysis of Different Antiemetic Regimens

Choosing cost-effective regimens is paramount for optimizing patient outcomes and ensuring healthcare system sustainability. In terms of direct drug costs, NK-1 receptor antagonists like aprepitant (125 mg/80 mg, 3-day course) are relatively expensive, with per-cycle costs ranging from approximately 480-580 yuan, and in many regions, they are not covered under medical insurance reimbursement, thereby increasing the economic burden on patients. Among 5-HT$_3$ receptor antagonists, palonosetron varies in price from 60-200 yuan per injection depending on formulation and brand. In contrast, olanzapine (5 mg × 4 days) costs less than 20 yuan, offering a significant price advantage and a favorable cost–benefit profile [1].

Further pharmacoeconomic analyses have shown that, relative to the traditional aprepitant-containing triple regimen, the olanzapine-containing triple regimen (olanzapine + 5-HT$_3$RA + dexamethasone) outperforms the traditional aprepitant-containing triple regimen not only in acute-phase vomiting relief rates (OR = 1.87, 95% CI: 1.08-3.27) but also in delayed-phase nausea control (OR = 2.78, 95% CI: 1.85-4.19), while reducing costs

per treatment cycle by 300-500 yuan [1]. Even when olanzapine is added to form a quadruple regimen, which incurs a modest cost increase, its substantial improvement in antiemetic efficacy leads to reduced rescue medication use (8.5% vs. 18.9%) and lower demands for complication management, ultimately decreasing overall healthcare expenditures [1, 8]. From a pharmacoeconomic perspective, olanzapine-containing regimens not only demonstrate clinical superiority but also alleviate economic pressures on both patients and medical insurance systems, making them particularly advantageous for implementation in resource-limited healthcare settings.

5. Unmet Clinical Needs and Future Research Directions

Although substantial progress has been made in antiemetic therapy, numerous unmet clinical needs persist. First, there is individualized prophylaxis remains insufficient. Current guidelines primarily recommend regimens based on the emetogenic classification of chemotherapy drugs, often overlooking patient-specific biomarker variations, such as plasma substance P concentrations and genetic polymorphisms (e.g., mutations in the 5-HT_3 receptor gene). These factors can influence the efficacy of antiemetic drugs and the risk of adverse reactions, resulting in some patients failing to benefit from standard regimens. In the future, integrating multidimensional data to develop predictive models will be essential for achieving more precise, personalized antiemetic treatments [5].

Second, antiemetic management strategies for special populations lack specificity. For instance, cancer patients with comorbid diabetes or psychiatric disorders may not tolerate high-dose dexamethasone or olanzapine, hightlighting the urgent need for novel non-hormonal, non-sedating antiemetic drugs or regimens to address these patients' unique requirements [8]. Additionally, the accessibility of long-acting antiemetic formulations remains low. For example, the netupitant/palonosetron fixed-dose combination capsule, with a half-life of up to 96 hours and a simplified dosing schedule, can improve patient adherence. However, its high cost limits widespread adoption. Future efforts should explore ways to enhance accessibility through policy adjustments, pricing negotiations, and insurance coverage strategies [4].

Finally, existing pharmacoeconomic evaluations are largely confined to comparisons of direct drug costs, lacking comprehensive consideration of health outcome metrics such as quality-adjusted life years (QALYs). Future studies should adopt a healthcare system perspective, employing more holistic economic evaluation methods to quantify the impact of optimized antiemetic regimens on patients' long-term quality of life and overall healthcare resource utilization [1].

Although antiemetic therapy has made considerable strides, numerous unmet clinical needs remain, and future research should further explore several key areas. First, the refinement of individualized prevention strategies. Current guidelines primarily base recommendations on the emetogenic classification of chemotherapy drugs, without fully incorporating patient-specific biomarker data, such as plasma substance P concentrations or 5-HT_3 receptor gene polymorphisms. Moving forward, efforts could focus on developing predictive models that integrate multi-omics data with clinical characteristics to identify subpopulations that respond best to particular antiemetic agents—for instance, screening patients with superior responses to ondansetron via 5-HT_3 receptor gene polymorphism testing, thereby enabling precision prescribing. Existing studies have already explored guiding antiemetic selection based on phenotypic classifications of the drug-metabolizing enzyme CYP2D6, offering an initial foundation for personalized therapy.

Additionally, in managing special populations, cancer patients with comorbidities like diabetes or psychiatric disorders often cannot tolerate high-dose dexamethasone or olanzapine, highlighting the need for intensified development of non-hormonal agents with minimal central inhibitory effects. For example, research has investigated the substitute potential of low-dose oxcarbazepine or mirtazapine in targeted populations, or examined the value of non-pharmacological approaches, such as behavioral interventions and acupuncture, as adjuncts to antiemetic care. Moreover, the accessibility and applicability of long-acting formulations require further enhancement. Take the netupitant/palonosetron fixed-dose combination capsule: despite its extended half-life and simplified dosing regimen, high costs have hindered widespread adoption. Future initiatives could involve pharmacoeconomic analyses grounded in real-world data to assess the long-term benefit-cost ratio, alongside promoting domestic generic drug development or adjustments in medical insurance policy to enhance clinical accessibility.

Finally, current pharmacoeconomic evaluations tend to emphasize direct drug costs while overlooking systematic assessments of health outcomes. In the future, incorporating comprehensive metrics like quality-adjusted life years (QALYs), from a healthcare system perspective, will be crucial to quantify how optimized antiemetic regimens affect patients' long-term quality of life, treatment adherence, and overall resource utilization—ultimately providing a more robust evidence base for clinical decisions and policy-making.

6. Conclusion

This article systematically reviews strategies for preventing and managing chemotherapy-induced nausea and vomiting (CINV), focusing on the efficacy and cost-effectiveness of a quadruple regimen that adds olanzapine to the standard triple regimen (5-HT_3 receptor antagonist, NK-1 receptor antagonist, and dexamethasone). The findings demonstrate that this quadruple regimen significantly improves outcomes for patients receiving moderately to highly emetogenic chemotherapy, particularly by increasing complete response and no-nausea rates during the delayed phase. These improvements address clinical challenges outlined in the introduction, including nutritional, physiological, and psychological complications arising from inadequate CINV control.

The regimen's significance lies in olanzapine's multi-receptor modulation, which translates into substantial clinical benefits, and its superior cost-effectiveness, as revealed through pharmacoeconomic analysis. By incorporating low-cost olanzapine, the quadruple regimen reduces overall healthcare costs by enhancing efficacy, decreasing breakthrough vomiting, and minimizing the need for rescue medications and complication management. These findings transcend simple drug cost comparisons, providing a robust framework for clinical decision-making that balances efficacy and resource utilization. The regimen offers a promising approach to improving patient quality of life while optimizing healthcare resource allocation, advancing effective and economical CINV management.

Despite these promising results, the study has certain limitations that warrant consideration. The primary conclusions rely on synthesized literature, which may be susceptible to publication bias. Variations in drug dosages, administration protocols, and patient baseline characteristics across studies may also limit result generalizability. Future research should validate the long-term efficacy and safety of the quadruple regimen in diverse real-world populations and develop tailored strategies for specific groups, such as patients with comorbid diabetes, to further enhance supportive care standards in oncology.

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Conflicts of Interest
The authors declare no conflict of interest.

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