

## Olanzapine: The Game-Changer “Antiemetic”

### Abstract

Chemotherapy-induced nausea and vomiting (CINV) is significantly debilitating and worsens the quality of life. Olanzapine, an atypical antipsychotic drug, also has an antiemetic potential. Studies have shown that olanzapine-based regimens have similar efficacy as compared to aprepitant in patients receiving highly emetogenic chemotherapy (HEC). National Comprehensive Cancer Network guidelines also recommends olanzapine-based regimen in HEC. Olanzapine, palonosetron, dexamethasone regimen is a cost-effective option in resource-limited settings in patients receiving HEC.

**Keywords:** Chemotherapy-induced nausea and vomiting, highly emetogenic chemotherapy, olanzapine

### Introduction

Chemotherapy-induced nausea and vomiting (CINV) is debilitating and worsens the quality of life. Acute CINV occurs within 24 h of chemotherapy, and delayed CINV is predominant during 24–48 h until 5 days. The prevention strategies for highly emetogenic chemotherapy (HEC) include corticosteroids, serotonin (5-HT<sub>3</sub>) receptor antagonists, and neurokinin 1 receptor antagonists. Olanzapine is an antipsychotic drug of thienobenzodiazepine class that is used in the management of schizophrenia and bipolar disorder. This drug has also shown to have high antiemetic potential.

### Mechanism of Action

Olanzapine acts as an antagonist on multiple receptors including dopaminergic (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>), serotonergic (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub>), adrenergic (alpha 1), histaminic (H<sub>1</sub>), and muscarinic (M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, and M<sub>4</sub>) receptors.

### Discovery

In 1954, chlorpromazine was shown to be effective in controlling CINV in patients with advanced cancer.<sup>[1]</sup> Subsequently, in 1960, preclinical studies proved that haloperidol has antiemetic properties.<sup>[2]</sup> In 1992, Fuller and Snoddy showed that, in rats, olanzapine blocks serotonin and

dopamine receptors better than clozapine and could be a potential antipsychotic drug.<sup>[3]</sup> It was termed novel “atypical” antipsychotic as it has additional anticholinergic properties that have lesser extrapyramidal symptoms.<sup>[4]</sup> In 1995, olanzapine showed efficacy in patient with schizophrenia with lower incidence of extrapyramidal symptoms.<sup>[5]</sup> In 2000, a case report highlighting the antiemetic properties of olanzapine was published.<sup>[6]</sup> This led to the development of various clinical trials with olanzapine.

### Approval

It is United States Food and Drug Act approved in the management of schizophrenia and bipolar disorder. Olanzapine is approved by the Drugs Controller General of India for the treatment of schizophrenia and resistant depression. It is currently not approved for use as antiemetic.

### Highly Emetogenic Chemotherapy

The National Comprehensive Cancer Network (NCCN) defined HEC (>90% risk of emesis): cisplatin, carboplatin  $\geq$ AUC 4, adriamycin-cyclophosphamide (AC), cyclophosphamide >1500 mg/m<sup>2</sup>, ifosfamide >2 g/m<sup>2</sup> per dose, adriamycin >60 mg/m<sup>2</sup>, epirubicin >90 mg/m<sup>2</sup>, and dacarbazine.

### Olanzapine Dose

- Tablet olanzapine 10 mg D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>.

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**Table 1: Phase 3 trials comparing olanzapine versus other antiemetic regimen in patients receiving highly emetogenic chemotherapy**

Study	Olanzapine-based regimen	Aprepitant-based regimen	Acute (0-24 h) CINV	Delayed (25-120 h) CINV
Navari <i>et al.</i> <sup>[17]</sup>	OPD	APD	CR (no rescue) 97% versus 87%, $P>0.05$	CR (no rescue) 77% versus 73%, $P>0.05$
Navari <i>et al.</i> <sup>[7]</sup>	OAPD	APD	CR 85.7% versus 64.6%, odds ratio 0.30, $P<0.001$	CR 66.9% versus 52.4%, odds ratio 0.55, $P=0.007$
Tan <i>et al.</i> <sup>[18]</sup>	OAD	AD	No difference in acute CINV	CR 69% versus 30%, $P<0.05$

OPD – Olanzapine, palonosetron, dexamethasone; OAPD – Olanzapine, aprepitant, palonosetron, dexamethasone; APD – Aprepitant, palonosetron, dexamethasone; AD – Azasetron, dexamethasone; CR – Complete response; CINV – Chemotherapy-induced nausea and vomiting; OAD – Olanzapine, azasetron, dexamethasone

### Olanzapine, Palonosetron, Dexamethasone Regimen

- Tablet olanzapine 10 mg D1–D4
- Injection palonosetron 0.25 mg D1
- Injection dexamethasone 12 mg intravenous D1.

### Why Olanzapine-Based Regimen Is Better Than Other Regimens?

Navari *et al.* showed that olanzapine, palonosetron, dexamethasone (OPD) regimen has similar control over nausea and vomiting as compared to aprepitant, palonosetron, dexamethasone (APD) regimen in patients receiving HEC. The second study showed that regimen olanzapine, APD (OAPD) had a superior efficacy as compared to APD regimen.<sup>[7]</sup> A prospective study also demonstrated that APD regimen was as effective as OPD for patients with breast cancer who received AC chemotherapy.<sup>[8]</sup> [Table 1] In a recent study, olanzapine proved to be effective in patients who failed aprepitant-based regimen while receiving HEC.<sup>[9]</sup> Mini OPD regimen (tablet olanzapine 5 mg D1 and D2 along with palonosetron and dexamethasone) has shown to be cost-effective in patients receiving weekly cisplatin for carcinoma cervix.<sup>[10]</sup> Addition of olanzapine to palonosetron and dexamethasone significantly reduces nausea and the need for rescue medications in patients receiving moderately emetogenic chemotherapy.<sup>[11]</sup> A meta-analysis revealed that olanzapine is more effective than other antiemetics for controlling CINV in delayed and overall phase and 5 mg is equally as effective as 10 mg dose.<sup>[12]</sup> A systematic review and meta-analysis from Japan revealed that olanzapine, when substituted instead of aprepitant in the APD regimen, can be hugely cost-effective.<sup>[13]</sup> Although the newer antiemetics (fosaprepitant,<sup>[14]</sup> netupitant,<sup>[15]</sup> and rolapitant<sup>[16]</sup>) have shown to be effective in HEC, they are less effective in controlling nausea and are more expensive.

### Guidelines

- The NCCN 2019 antiemetic guidelines recommends OPD regimen for the treatment of HEC
- The ASCO 2018 antiemetic guidelines recommends addition of olanzapine to antiemetic regimen in patients receiving HEC

- The Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology 2016 antiemetic guidelines recommends OPD as an effective antiemetic regimen.

### Toxicity

The side effect of olanzapine is sedation (severe in 5%<sup>[7]</sup>). If patients experience sedation, the dose can be reduced to 5 mg/day.

### Olanzapine, Palonosetron, Dexamethasone Failure

Patients who have breakthrough emesis while on olanzapine can be treated with aprepitant-based regimen.

### Cost-effectiveness

Olanzapine (6 cycles, Rs. 170/-) is priced 50 times lower as compared to aprepitant (6 cycles, Rs. 9000/-). A recent study from Southeast Asia showed olanzapine-based regimen to be very cost-effective.<sup>[19]</sup>

### Conclusion

OPD regimen should be the preferred antiemetic schedule for all patients receiving HEC as it has similar efficacy with minimal toxicity as compared to APD regimen. The NCCN 2019 antiemetic guidelines recommends OPD regimen for HEC. Further considering the low cost of therapy, it is an attractive, cost-effective option in a resource-limited setting.

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### Conflicts of interest

There are no conflicts of interest.

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