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# Comprehensive Analysis Of Ranitidine Usage: Pharmacological Interactions, Safety In Polypharmacy And Effects On Disease Management

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**ABSTRACT**

**Background:** The selective histamine type 2 receptor antagonists/blockers (H2 blockers) are widely used in the treatment of acid-peptic disease, including duodenal and gastric ulcers, gastroesophageal reflux disease, and common heartburn.

**Aim And Objectives:** To comprehensively evaluate the indications, pharmacological interactions, and safety profile of ranitidine in polypharmacy prescriptions within the general medicine department.

**Methodology:**The six-month observational cross-sectional study was conducted in a tertiary care teaching hospital. Informed consent was collected from all the participants. All the patients (363) were monitored for drug interactions and adverse drug reactions.

**Results And Discussion:** Results showed that in this study, 54.2% of participants used ranitidine for non-labeled indications, exceeding the 45.7% who used it for approved purposes. Out of 363 study participants, 45.7% (166) were prescribed ranitidine for labeled indications (such as GI ulcers and GERD), aligning with approved uses for acid suppression. Rashes are the most frequent ADR, affecting 50.6% of patients, indicating a notable dermatological impact. Bradyarrhythmia, observed in 38.51% of cases, underscores the need for vigilant cardiac monitoring due to its serious nature. Out of 363, 204(56.19%) prescriptions are inappropriate polypharmacy, and among these, deprescribing is done in 56 prescriptions, and dose adjustment made in 20 prescriptions.

**Conclusion:** The comprehensive analysis of ranitidine usage reveals a high prevalence of conditions that may be affected by ranitidine therapy due to inappropriate use. This study highlights the importance of closely monitoring pharmacological interactions in polypharmacy, especially when using ranitidine among patients with complex health profiles.

***Keywords:*** *Ranitidine, Adverse drug reaction, GERD, Polypharmacy*

## 1. INTRODUCTION

Ranitidine is a histamine H2-receptor antagonist acts as a competitive and reversible inhibitor, blocking the effects of histamine released by enterochromaffin-like (ECL) cells at H2 Receptors on gastric parietal cells.[1] Introduced to the European market in 1981, ranitidine was widely used to treat acid-related conditions such as peptic ulcer disease, gastritis or duodenitis (with or without Helicobacter pylori infection), Zollinger-Ellison syndrome, gastroesophageal reflux disease (GERD), post-surgical ulcers, stress ulcer prevention, and chronic episodic dyspepsia. Before its withdrawal, ranitidine was available in both oral and injectable forms, as a prescription and an over-the-counter option for managing symptoms of

heartburn and non-ulcer Dyspepsia.[2]

In April 2020, the U.S. Food and Drug Administration (FDA) requested the withdrawal of all Ranitidine products from the market due to concerns over a contaminant known as N-nitrosodimethylamine (NDMA), which is classified as a probable human carcinogen. This contaminant was found in various ranitidine formulations, with levels increasing over time and under certain storage conditions.[3] Ranitidine's pharmacokinetic interactions with other drugs can occur during absorption, Metabolism, or renal excretion. Generally, these interactions are minor and of low clinical Significance. These interactions may arise from ranitidine's effects on hepatic metabolism or on the absorption of drugs taken concurrently.[4]

Polypharmacy is the concurrent use of multiple medications. Polypharmacy is often defined as the routine use of five or more Medications. This includes over-the-counter, prescription and/or traditional and complementary Medicines used by a patient. The goal should be to reduce inappropriate polypharmacy (irrational prescribing of too many Medicines) and to ensure appropriate polypharmacy (rational prescribing of multiple medicines Based on best available evidence and considering individual patient factors and context).[5,6] Since ranitidine become common drug in prescription, it is recommended to comprehensively review the treatment chart to check its appropriateness and to promote deprescribing in the lights of evidence based practice for the safe use of medications.

## 2. METHODOLOGY

This was a six-month cross-sectional observational study conducted in the general medicine department of a tertiary care hospital in Erode, Tamil Nadu.

**Inclusion criteria:** Inpatients of both genders, Age 18 years and above, polypharmacy prescription containing ranitidine (IV/Oral)

**Exclusion Criteria:** Incomplete case sheet. Patients not willing to participate. Patients admitted other than General Medicine department

**Sample size:** Sample size was calculated by RAOSOFTWARE and found to be 280.

## 3. ETHICAL CONSIDERATION

Institutional Review Board of J.K.K.Nattraja College of Pharmacy, IEC certificate No: JKKNCP/TEC-CER/0417124/MP

## 4. RESULTS AND DISCUSSION

363 study patients were included in this research study with prescription containing ranitidine either IV or oral dosage form. From this we categorized the patients according to their age, indications, interactions with other co-prescribed drugs, severity of their interactions and to find out the appropriate polypharmacy from inappropriate and accelerate deprescribing when needed.

| Sl No. | Age group (years) | No. of Patients (N=363) | Percentage |
|---|---|---|---|
| 1 | 18-27 | 28 | 7.7 |
| 2 | 28-37 | 26 | 7.1 |
| 3 | 38-47 | 40 | 11.0 |
| 4 | 48-57 | 47 | 12.9 |
| 5 | 58-67 | 52 | 14.3 |
| 6 | 68-77 | 78 | 21.4 |
| 7 | >78 | 92 | 25.3 |

**Table 1: Age-wise distribution of study participants**

Table 1 shows the age distribution of patients in this study on Ranitidine usage reveals that the largest group is above 78 years old patients, mainly due to their multiple disease conditions. This usage in older patients highlights the importance of age specific safety and efficacy of ranitidine usage due to polypharmacy which can influence drug interactions and adverse effects.

| S.No | Ranitidine + Drug | Reaction | No. of Patients (N=363) | Percentage (%) |
|---|---|---|---|---|
| I | **SEVERE** | | | |
| a. | Carbamazepine | Increased carbamazepine exposure | 21 | 5.78 |
| b. | Alprazolam | Increased alprazolam exposure and an increased risk of alprazolam-related adverse reactions. | 3 | 0.82 |
| c. | Warfarin | Increased warfarin exposure, an increased INR and an increased risk of bleeding | 4 | 1.10 |
| d. | Budesonide | Increased budesonide exposure inhibition of CYP3A4mediated metabolism of budesonide | 11 | 3.03 |
| e. | Clozapine | Increased clozapine exposure by inhibition of CYP3A4-mediated clozapine metabolism | 2 | 0.55 |
| f. | Domperidone | Increased domperidone exposure and an increased risk of QT prolongation**.** | 3 | 0.82 |
| g. | Tramadol | Increased tramadol exposure and an increased risk of seizures, serotonin syndrome and opioid toxicity by inhibition of CYP3A4-mediated tramadol metabolism | 9 | 2.47 |

| | | | | |
|---|---|---|---|---|
| h. | Colchicine | Increased colchicine exposure and an increased risk of colchicine-related toxicity by inhibition of CYP3A4-mediated metabolism of colchicine | 28 | 7.71 |
| i. | Risperidone | Result in increased risperidone bioavailability. | 5 | 1.37 |
| II | **MODERAT E** | | | |
| a. | Itraconazole | Reduced gastrointestinal absorption of itraconazole due to suppression or neutralization of gastric pH | 8 | 2.20 |
| b. | Glipizide | Increased glipizide absorption due to ranitidine-induced alterations in gastric pH | 11 | 3.03 |
| c. | Glimepiride | Increased risk of hypoglycemia | 16 | 4.40 |
| d. | Cefpodoxime | It may result in decreased cefpodoxime effectiveness by reduced absorption. | 27 | 7.43 |
| e. | Midazolam | Increased midazolam bioavailability due to decreased gastric pH induced by ranitidine. | 14 | 3.85 |
| f. | Procainamide | Procainamide and high doses of ranitidine may leads to increased serum concentrations of procainamide due to competition for active tubular secretion, thereby decreasing renal clearance of procainamide. Monitor for potentially increased adverse effects of procainamide (cardiac arrhythmias, hypotension, CNS depression) | 10 | 2.75 |
| III | | **MINOR** | | |

| | | | | |
|---|---|---|---|---|
| a. | Aspirin | It may result in reduced salicylate plasma levels and decreased antiplatelet effect of aspirin. | 25 | 6.88 |
| b. | Phenytoin | It may result in increased phenytoin concentrations by reduced metabolism of phenytoin. | 7 | 1.92 |
| c. | Theophylline | It may result in theophylline toxicity (nausea, vomiting, palpitations, seizures) by reduced metabolism | 11 | 3.03 |
| d. | Bisacodyl | It may result in decreased effectiveness of bisacodyl. | 16 | 4.40 |

**Table 2: List of Potential Ranitidine Interaction among study participants**

Table 2 shows several significant interactions between ranitidine and other drugs among participants, emphasizing the need for cautious use, especially in patients on multiple medications. Notably, 7.71% of patients on colchicine and 5.78% on carbamazepine faced increased exposure to these drugs due to ranitidine's effect on CYP3A4 metabolism, heightening toxicity risks. Glimepiride interactions (4.40%) also posed hypoglycemia risks, while tramadol (2.47%) increased the likelihood of serotonin syndrome and seizures. Additionally, aspirin (6.88%) and theophylline (3.03%) saw reduced effectiveness due to ranitidine's impact on absorption and metabolism. These findings underscore the importance of monitoring drug levels and considering alternative therapies for patients using ranitidine with these medications, especially in light of recent safety concerns regarding NDMA contamination

| **S. No** | **Ranitidine indication** | **No. of patients (N=166)** | **Percentage (%)** |
|---|---|---|---|
| **1** | **Labeled indication** | **138** | **83.13** |
| a. | GI ulcer | 75 | 54.3 |
| b. | GERD | 26 | 18.8 |
| c. | Zollinger Ellison Syndrome | 3 | 1.8 |
| d. | Erosive esophagitis | 5 | 3.62 |
| e. | Indigestion- non ulcer | 21 | 15.2 |

| | | | |
|---|---|---|---|
| f. | Stress ulcer | 8 | 5.79 |
| **2** | **Non- Labeled indications** | **28** | **16.86** |
| a. | Pneumonia | 12 | 42.8 |
| b. | Asthma | 16 | 57.14 |

**Table 3: Categorization of patients based on Ranitidine indication (Labeled/non labeled)**

In this study, 83.13% of ranitidine prescriptions were for labeled indications, primarily conditions directly associated with acid suppression, such as GI ulcers (54.3%) and GERD (18.8%), where ranitidine effectively reduces gastric acid secretion, supporting ulcer healing and symptom relief. Less common labeled indications included Zollinger-Ellison syndrome (1.8%), erosive esophagitis (3.62%), non-ulcer indigestion (15.2%), and stress ulcers (5.79%), each benefiting from acid suppression to prevent gastric and esophageal damage. Conversely, 16.86% of ranitidine prescriptions were for non-labeled indications, particularly for asthma (57.14%) and pneumonia (42.8%), suggesting the drug's hypothesized role in reducing respiratory symptoms potentially linked to reflux. Acid reflux has been associated with exacerbations in respiratory conditions like asthma and increased pneumonia risk by affecting respiratory mucosa.

| S. No | Ranitidine indication | No. of study participants (N=363) | Percentage (%) | Severity classification | No. of patients |
|---|---|---|---|---|---|
| 1 | Labeled | 138 | 45.7 | Severe | 7 |
| | | | | Moderate | 10 |
| | | | | Minor | 0 |
| 2 | Non labeled | 28 | 7.1 | Severe | 24 |
| | | | | Moderate | 27 |
| | | | | Minor | 11 |
| 3 | Not indicated | 197 | 54.2 | Severe | 59 |
| | | | | Moderate | 49 |
| | | | | Minor | 48 |

**Table 4: Distribution of study participants on Ranitidine indication and severity classification of ranitidine drug interaction**

Table 4 indicates 54.2% of participants used ranitidine for non-labeled indications, exceeding the 45.7%who used it for approved purposes. This reflects a broader trend of off-label drug use, where medications are prescribed beyond FDA-approved indications to manage related symptoms. While off-label use offers treatment flexibility, it raises concerns about efficacy and patient safety due to the lack of rigorous FDA testing for these applications. Research indicates a higher likelihood of adverse drug events with off-label use, highlighting the need for careful monitoring and evidence-based approaches. Notably, 54.2% (197) had no clear indication for ranitidine use, suggesting gaps in adherence to clinical guidelines and possible reliance on ranitidine for unverified symptom relief or prophylaxis. This pattern underscores the need for better prescribing practices and clinician education, especially considering recent NDMA contamination concerns (FDA, 2019).

The study shows a notable frequency of severe and moderate drug interactions with ranitidine, particularly among patients with **non-labeled** and **not-indicated** uses. Severe interactions comprised **38% (90)** of cases, primarily in the not-indicated

group, with increased risks for toxicity involving drugs like carbamazepine and tramadol. Moderate interactions made up **36.1% (86)**, common in not-indicated uses, where drugs like glimepiride and midazolam saw increased adverse effects due to ranitidine's effects on absorption. Minor interactions, at **24.8% (59)**, were mostly in not-indicated cases, impacting drugs like aspirin and theophylline. These findings emphasize the importance of restricting ranitidine use to evidence-based indications to reduce potential risks.

**Table 5: Adverse Drug reactions of ranitidine (Fast IV Bolus) among patients**

The data on adverse drug reactions (ADRs) reveals significant findings. Rashes are the most frequent ADR, affecting 50.6% of patients, indicating a notable dermatological impact. Bradyarrhythmia, observed in 38.51% of cases, underscores the need for vigilant cardiac monitoring due to its serious nature. Although cardiac arrest is less common (4.05%), its critical severity necessitates a thorough safety evaluation. Headaches, reported in 6.75% of cases, while less severe, can affect patient compliance and quality of life. The presence of non-labeled and not indicated ADRs highlights the importance of continuous pharmacovigilance and updating safety information. Overall, a comprehensive review of the drug's safety profile, including a benefit-risk assessment, is essential to ensure patient safety and effective management.

| Sl.No | Adverse drug reactions | Total number of ADR (n=148) | Percentage (%) |
|---|---|---|---|
| 1 | Certain | 87 | 58.78 |
| 2 | Probable/likely | 33 | 22.29 |
| 3 | Possible | 28 | 18.9 |

**Table 6: WHO UMC- Causality assessment of Ranitidine ADR**

The analysis of the WHO UMC causality assessment of ranitidine adverse drug reactions (ADRs) among participants shows that 58.78% of ADRs were classified as certain, indicating a high level of confidence that ranitidine caused these reactions. Additionally, 22.29% of ADRs were considered probable or likely, suggesting a moderate level of certainty, and 18.9% were possible, indicating a lower level of confidence. This high percentage of certain ADRs highlights the critical need for close monitoring of ranitidine use. The presence of probable and possible ADRs also underscores the necessity for ongoing vigilance and further research to fully understand the potential adverse effects of ranitidine.

| S. No | Type | Number of patients(N=363) | Management opted | Percentage (%) N=204 |
|---|---|---|---|---|
| 1 | **Appropriate polypharmacy** | 159 | - | - |
| 2 | **Inappropriate polypharmacy** | 56 | **Deprescribing** | 27.45 |
| | | 20 | **Dose Adjustment** | 9.80 |
| | | 128 | **No action** | 62.74 |

**Table 7: Polypharmacy classification of Ranitidine prescription**

The analysis of polypharmacy among 363 study participants revealed that 43.8% were on appropriate polypharmacy, while 56.2% were on inappropriate polypharmacy. This high prevalence of inappropriate polypharmacy indicates significant issues with over prescribing or unnecessary medication use, potentially leading to adverse drug events, increased healthcare costs, and reduced quality of life. Regular medication reviews are essential to ensure that all prescribed drugs are necessary and

beneficial, which can help mitigate inappropriate polypharmacy and improve patient outcomes. Patient education and involvement in the decision-making process are crucial for adherence to prescribed regimens and early reporting of issues. Healthcare providers must be vigilant in prescribing, considering potential drug interactions and adverse effects, and prioritize deprescribing when appropriate. Implementing clinical guidelines and policies for medication reviews, deprescribing protocols, and patient-centered care can help standardize the approach to polypharmacy. Further research is needed to identify factors contributing to inappropriate polypharmacy and develop effective interventions to reduce its prevalence, focusing on specific patient populations and the efficacy of different deprescribing strategies.

## 5. CONCLUSION

This study highlights the importance of closely monitoring pharmacological interactions in polypharmacy, especially when using ranitidine among patients with complex health profiles. This high percentage of certain ADRs highlights the critical need for close monitoring of ranitidine use. The presence of probable and possible ADRs also underscores the necessity for ongoing vigilance and further research to fully understand the potential adverse effects of ranitidine. Study emphasize the importance of continuous pharmacovigilance and revaluation of its safety profile. These findings reinforce the need for healthcare professionals to be vigilant in prescribing and monitoring this medication to ensure patient safety.

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