

# From Drug Induced Mucosal Injury to Preventive Strategies: A Narrative Review on Gastrointestinal Complications, Medication Adherence and Gastroprotective Measures in Drug Therapy

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## ABSTRACT

Gastrointestinal complications arising from the chronic use of widely prescribed medications, including NSAIDs, corticosteroids, and antiplatelet drugs, represent a major source of patient morbidity and financial burden on the healthcare system. Medication adherence presents a clinical dilemma: non-adherence driven by GI discomfort can compromise treatment efficacy, whereas adherence without adequate gastroprotection elevates the risk of mucosal injury. While gastroprotective agents (GPAs) are effective, their clinical application is frequently suboptimal, characterized by under-prescription for high risk individuals and inappropriate use in low risk populations. This review identifies a critical deficit in research, especially within Indian tertiary care, where integrated data on adherence patterns and clinical outcomes is lacking. A dedicated epidemiological investigation is imperative to inform preventive strategies, optimize prescription protocols, and enhance patient safety.

**Keywords:** Gastrointestinal discomfort, Medication adherence, Gastroprotective agents, Prescribing patterns, Drug induced mucosal injury

## I. INTRODUCTION & BACKGROUND

The prolonged use of medications such as NSAIDs, corticosteroids, antiplatelet agents, oral hypoglycemic agents, oral iron supplements and certain antibiotics is frequently linked to gastrointestinal (GI) complications like nausea, vomiting, abdominal pain, dyspepsia, constipation, diarrhea, heart burn, peptic ulcers, indigestion, melena, GI bleeding.<sup>1,3</sup>

These drug-related complications contribute significantly to patient morbidity and increase hospital admissions and treatment costs, especially in tertiary healthcare settings.<sup>2</sup> Adherence to prescribed medications plays a vital role in determining both therapeutic effectiveness and the likelihood of adverse GI outcomes. Nonadherence often resulting from unpleasant side effects, complex dosing schedules, or a high number of medications can lead to greater mucosal damage and poor disease control.<sup>5,6</sup>

Conversely, patients who adhere to drugs without appropriate gastroprotective coverage face a significantly increased risk of GI complications, especially in the presence of comorbidities and polypharmacy.<sup>4</sup> To minimize these risks, the use of gastroprotective agents (GPAs) like proton pump inhibitors, H2-blockers, lactulose is advised for patients at elevated risk.<sup>7,8</sup> However, studies indicate that in real-world practice, the use of gastroprotective agents (GPAs) often deviates from guideline recommendations especially in resource limited settings resulting in preventable gastrointestinal (GI) complications.<sup>9</sup> This narrative review explores the connection between medication adherence, gastrointestinal complications, and the clinical implementation of gastroprotective measures in patients receiving long-term pharmacotherapy.

## DRUGS THAT COMMONLY IRRITATE THE GASTROINTESTINAL TRACT

Several medication classes are known to cause gastrointestinal (GI) injury through mechanisms such as direct mucosal irritation,

inhibition of protective prostaglandins, altered motility, and cytotoxic effects on epithelial cells. These adverse effects can occur anywhere along the GI tract from the esophagus to the colon leading to symptoms like dyspepsia and complications such as erosions, ulcers, bleeding, perforation, and strictures.

**Nonsteroidal anti-inflammatory drugs (NSAIDs)** and **low-dose aspirin** are the most frequent causes of drug-induced GI injury. By inhibiting cyclooxygenase (COX)-1 and COX-2, these drugs suppress prostaglandin synthesis, which diminishes mucus and bicarbonate secretion and compromises mucosal blood flow, making the mucosa more susceptible to injury. Risk is highest in elderly patients, those with *Helicobacter pylori* infection, and individuals using concurrent corticosteroids, anticoagulants, or antiplatelet drugs. Chronic use has also been linked to lower GI complications such as small and large bowel ulcerations even in patients on proton pump inhibitor (PPI) prophylaxis.<sup>10,11</sup>

**Antiplatelet agents** (e.g., clopidogrel, prasugrel, ticagrelor) and **anticoagulants** (e.g., warfarin, dabigatran, apixaban, rivaroxaban, edoxaban, heparin) heighten GI bleeding risk by impairing platelet aggregation or coagulation. When combined with NSAIDs or aspirin, the bleeding risk is synergistically increased.<sup>12,13</sup>

**Corticosteroids** hinder mucosal repair and decrease gastric mucus production, potentiating NSAID-induced damage. While the risk is relatively low with corticosteroid monotherapy, it rises significantly in patients taking other ulcerogenic medications or in those who are critically ill.<sup>14</sup>

**Bisphosphonates** (alendronate, risedronate, ibandronate) can cause caustic injury to the upper GI tract if tablets remain in contact with the mucosa, leading to esophagitis, ulceration, and gastritis. Taking the drug with a full glass of water and remaining upright for at least 30 minutes reduces this risk.<sup>15</sup>

Some **antibiotics**, particularly doxycycline, tetracycline, and clindamycin, may cause localized esophageal injury if pills are not swallowed properly. Broad-spectrum antibiotics can also disrupt gut microbiota, increasing the risk of diarrhea or *Clostridioides difficile* infection.

**Potassium chloride (KCl)** preparations especially sustained-release formulations—can cause corrosive injury to the esophagus or stomach, resulting in erosions, ulcerations, or bleeding.

**Oral iron supplements** (ferrous sulfate, ferrous fumarate, ferric citrate) may cause oxidative and

acidic injury to the mucosa, sometimes leading to strictures or ulceration, particularly when tablets become lodged in the esophagus.<sup>14</sup>

**Chemotherapeutic agents** such as 5-fluorouracil, methotrexate, irinotecan, and doxorubicin damage rapidly dividing GI epithelial cells, causing mucositis, ulcerations, diarrhea, and bleeding.

Although **Sodium-Glucose co-transporter-2 (SGLT2) inhibitors** (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) do not directly damage the GI mucosa, they are linked to gastrointestinal symptoms including nausea, diarrhea, constipation, and abdominal discomfort. Rarely, they have been associated with dehydration-induced ischemic colitis in older or volume-depleted patients. Additionally, the genitourinary infections associated with these drugs often require antibiotic therapy, which can further contribute to GI irritation.<sup>15,16</sup>

Given the variety of drugs capable of causing GI injury, it is important for prescribers to assess patient-specific risk factors, review concomitant therapies, and apply preventive strategies such as gastroprotective agents, proper drug administration techniques, and early monitoring for GI symptoms.

#### MEDICATION ADHERENCE TO GASTRIC IRRITANT DRUGS:

Medication adherence describes how closely patients follow the prescribed dose, schedule, and duration of therapy for drugs such as NSAIDs, low-dose aspirin, corticosteroids, bisphosphonates, and some antibiotics. Although adherence is necessary for optimal therapeutic benefit, it is frequently compromised by GI adverse effects like dyspepsia, abdominal discomfort, nausea, and reflux. These issues are a major cause of treatment discontinuation; for instance, bisphosphonate-related upper GI complications significantly decrease persistence in osteoporosis therapy, with about 28% of patients stopping treatment due to GI intolerance.<sup>17,18</sup> Long-term NSAID users, particularly those not on gastroprotective agents (GPAs), often demonstrate reduced adherence, and this challenge becomes more pronounced when NSAIDs are combined with corticosteroids or antiplatelets because the cumulative irritation increases discontinuation risk.<sup>19</sup> Interrupting therapy or using it inconsistently without GPA protection can result in mucosal damage, ulcers, and even GI bleeding, sometimes requiring hospitalization.<sup>20,22</sup> Predictors of poor adherence include advanced age with multiple illnesses, complex medication regimens, limited health literacy, lack of understanding of

long-term benefits, and financial barriers, which are especially relevant in resource-constrained settings.<sup>21,24</sup> Patient perceptions further influence adherence, as many view GI discomfort as dangerous, undervalue the consequences of stopping chronic therapy for conditions such as osteoporosis or cardiovascular disease, or are guided by cultural beliefs regarding medicines.<sup>25,26</sup> Vulnerable groups such as elderly polypharmacy patients, ICU patients, and post-surgical individuals are particularly susceptible to missed doses and therapy interruptions.<sup>27</sup> Strategies to improve adherence include simplified regimens such as once-weekly or monthly bisphosphonates or fixed-dose combinations—which reduce GI irritation and enhance persistence; comprehensive patient counseling on weighing therapeutic benefits against GI risks; consistent GPA co-prescription; and adherence-support interventions like refill monitoring and digital reminder tools to promote regular use and reduce GI-related complications.

#### **IMPACT OF ADHERENCE LEVEL ON GI COMPLICATION:**

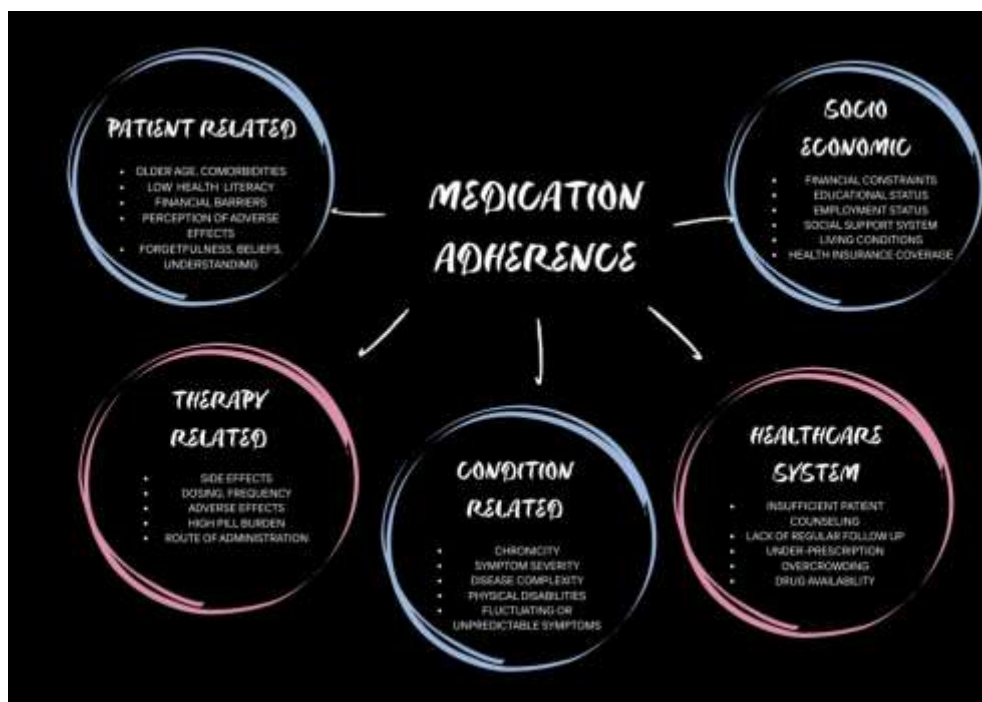
The relationship between adherence and gastrointestinal (GI) complications is largely determined by how consistently patients follow treatment regimens for both gastric irritant medications and prescribed gastroprotective agents (GPAs). Patients who regularly use drugs such as NSAIDs, aspirin, corticosteroids, or bisphosphonates but fail to take GPAs consistently face a much higher risk of peptic ulcers, upper GI bleeding, and mucosal damage.<sup>28,29</sup> Irregular or intermittent medication use interferes with the mucosa's adaptive processes, increasing the risk of acute injury and hospitalisation.<sup>30</sup> On the other hand, maintaining strong adherence to both gastric irritant drugs and GPAs significantly reduces the likelihood of complications, with studies showing that GPA adherence of 80% or higher can lower NSAID-induced ulceration and GI bleeding by as much as 50% (37). Despite this, many patients discontinue therapy due to GI symptoms like dyspepsia or reflux, which may exacerbate the underlying condition elevating cardiovascular risks for aspirin users or fracture risks for those on

bisphosphonates while resuming treatment without GPAs leaves them exposed.<sup>31</sup>

The risk is further increased in patients on multiple gastric irritant medications, as poor GPA adherence greatly raises the cumulative risk of mucosal injury.<sup>32,33</sup> Older adults, ICU patients, and individuals with a prior history of ulcers are especially vulnerable, often experiencing higher rates of bleeding, perforation, longer hospital stays, and increased healthcare costs when adherence to gastroprotective strategies is insufficient.<sup>34,35</sup>

#### **FACTORS AFFECTING ADHERENCE:**

A range of patient-related, treatment-related, and healthcare system factors can affect adherence to drugs. Older patients with multiple comorbidities often face complex regimens, and when these involve more than five daily medications, maintaining adherence becomes challenging.<sup>36</sup> High pill burden, frequent dosing schedules, and prolonged treatment durations tend to reduce persistence, while low health literacy and limited understanding of the long-term benefits of therapy further hinder compliance. Financial barriers, including high medication costs and restricted access in resource-limited settings, also contribute to poor adherence.<sup>37,38</sup> Adverse effects particularly GI symptoms such as dyspepsia, reflux, or abdominal discomfort are among the most common reasons for intentional discontinuation, as patients often perceive these symptoms as medication-induced harm. Cultural beliefs, negative past drug experiences, and mistrust in healthcare providers may further influence adherence behaviour.<sup>39</sup> From a system perspective, insufficient patient counselling, lack of regular follow-up, and under-prescription of gastroprotective agents (GPAs) in high-risk patients exacerbate non-adherence. These factors often act synergistically, placing vulnerable groups such as elderly polypharmacy patients, ICU admissions, and those with a history of GI complications at increased risk for inconsistent medication use and associated adverse outcomes.<sup>40</sup> A conceptual framework of factors influencing medication adherence are illustrated below in figure 1.



**Fig. 1:** A conceptual framework of factors influencing medication adherence

### ROLE OF GASTROPROTECTIVE THERAPY:

Proton pump inhibitors (PPIs) are widely recognized as the primary intervention for preventing drug-related gastrointestinal injury in patients at elevated risk, particularly those taking NSAIDs, dual antiplatelet therapy (DAPT), or oral anticoagulants. Evidence from a recent meta-analysis indicates that adding a PPI to DAPT can lower the incidence of upper gastrointestinal bleeding (UGIB) by nearly 60% and reduce all-cause mortality, without increasing major adverse cardiovascular events.<sup>41,42</sup> Similar benefits have been observed in large-scale real-world cohorts, including those involving post-myocardial infarction and ischemic stroke patients.<sup>43,44</sup> In individuals on oral anticoagulants, the impact of PPI co-therapy is less clear, with some studies reporting modest reductions in GI bleeding and others showing minimal differences, emphasizing the need for patient-specific risk evaluation.<sup>45</sup> Among NSAID users, PPIs, high-dose H2 receptor antagonists, and misoprostol are effective in reducing upper-GI injury, with PPIs favored for

better tolerability.<sup>46</sup> However, emerging evidence suggests that concurrent NSAID–PPI therapy may elevate the risk of lower-GI bleeding, highlighting the importance of balancing protective benefits with potential harms.<sup>48</sup> Current guidelines advise PPI co-therapy in those with risk factors such as advanced age, previous peptic ulcer or bleeding, *Helicobacter pylori* infection, or concurrent corticosteroid, anticoagulant, or SSRI use.<sup>47</sup> Concerns regarding PPI–clopidogrel interactions have limited clinical relevance, especially when pantoprazole is chosen due to its minimal CYP2C19 inhibition.<sup>49</sup> Despite robust supporting evidence, gastroprotective therapy remains underutilized, often prescribed for symptom relief rather than prevention. Integrating pharmacist-led screening, automated prescribing prompts, and patient education could improve targeted, evidence-based use.<sup>50</sup>

### PATTERNS OF GASTROPROTECTIVE AGENT PRESCRIPTION AND USE IN TERTIARY CARE:

In tertiary hospitals, the prescribing of gastroprotective agents (GPAs) frequently reflects two opposing challenges: underuse in patients who meet clinical criteria for prophylaxis and excessive use in those without valid indications.<sup>51,63</sup> Audit and survey data reveal that GPA co-prescription alongside NSAIDs or antithrombotics remains suboptimal, with notable variation between specialties often attributed to inconsistent application of risk assessment tools and limited awareness of guideline recommendations.<sup>52,62</sup> Overprescribing of proton pump inhibitors (PPIs) is also common, particularly when stress ulcer prophylaxis (SUP) initiated in intensive care units is unnecessarily continued on general wards or after discharge.<sup>53,54</sup> Strategies such as formulary controls, pharmacist-led interventions, and decision-support systems have proven effective in improving prescribing patterns by both reducing

missed prophylaxis in high-risk patients and curbing inappropriate use in low-risk groups.<sup>56,57</sup> Despite strong evidence supporting PPI use in high-risk populations such as patients on dual antiplatelet therapy (DAPT) or anticoagulants national data indicate that only about half of eligible cardiovascular patients receive appropriate gastroprotection, with substantial interdepartmental variation.<sup>58,61</sup> PPIs remain the most commonly used GPA, whereas H2 receptor antagonists and misoprostol are rarely prescribed, and prevention-focused use is inconsistently applied.<sup>64</sup> These findings highlight the need for systematic risk-based prescribing protocols, careful medication review at discharge to discontinue unnecessary SUP, and routine deprescribing initiatives to ensure GPA use remains evidence-based.<sup>59,60</sup> Clinical algorithm for prescribing gastroprotective agents are presented in figure 2.

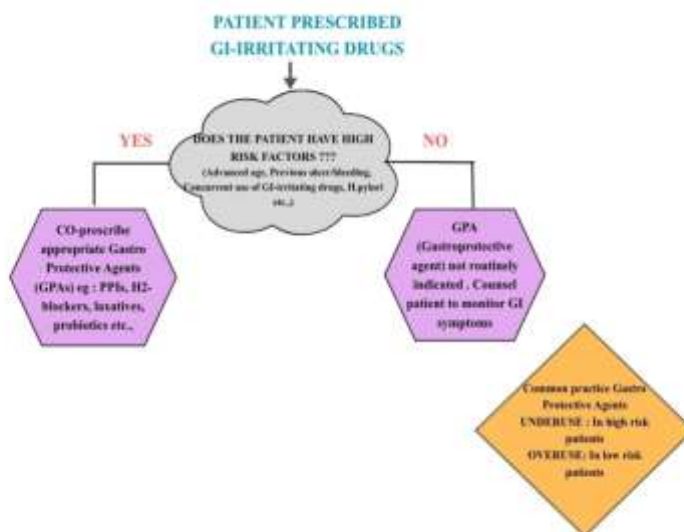


Fig. 2: Clinical algorithm for prescribing gastroprotective agents

**ADHERENCE TO GASTRIC IRRITANT DRUGS AND GPA USE:**

Adherence to gastric irritant drugs such as NSAIDs, antiplatelets, and oral anticoagulants as well as to prescribed gastroprotective agents (GPAs), remains inconsistent and directly affects clinical outcomes. Inadequate adherence to either the main therapy or the co-prescribed PPI/H2RA increases the risk of preventable upper GI bleeding, while early discontinuation of GPAs during ongoing risk periods removes necessary protection.<sup>66,72</sup> Barriers to adherence include

polypharmacy, complicated regimens, financial constraints, cognitive issues, negative beliefs about medicines, and system-related gaps such as insufficient counselling, low rates of co-prescription, and poor adherence to guidelines.<sup>65,67</sup> Evidence highlights that regular and continuous use of PPIs is essential to achieve meaningful reductions in gastrointestinal bleeding risk, especially in high-risk populations such as patients on dual antiplatelet therapy (DAPT) or anticoagulants; conversely, intermittent or on-demand use provides limited protection.<sup>68,70</sup> Real-

world studies frequently reveal underutilization of gastroprotection among eligible patients, with only about 50–60% receiving it. However, strategies such as pharmacist-led programs, medication reconciliation during discharge, clinical decision-support systems, and adherence tools like blister packaging have been shown to enhance both prescribing practices and long-term patient compliance.<sup>69,71</sup>

### SPECIAL POPULATIONS IN TERTIARY CARE HOSPITALS

Within tertiary hospitals, certain patient populations are at particularly high risk of gastrointestinal injury from commonly prescribed medications and therefore require tailored gastroprotective strategies. **Older adults** are especially vulnerable due to polypharmacy, multiple comorbidities, and physiological changes with aging, yet PPI prescribing in this group often falls short of guideline recommendations.<sup>73,74</sup> Similarly, **patients with chronic kidney disease (CKD)** face increased bleeding risk because of reduced renal clearance and frequent use of

NSAIDs, antiplatelets, and anticoagulants, but gastroprotective measures are not consistently implemented.<sup>75</sup> In **cardiovascular patients** on dual antiplatelet therapy (DAPT) or oral anticoagulants, evidence supports PPI co-therapy to significantly reduce upper GI bleeding, though uptake in clinical practice remains suboptimal.<sup>76,77</sup> **Critically ill patients** frequently receive stress ulcer prophylaxis (SUP) during ICU admission; however, continuation of SUP after transfer or discharge often leads to prolonged and unnecessary PPI use.<sup>78,79</sup> **Cancer patients**, who are often treated with corticosteroids, chemotherapy, or targeted agents, also carry a high GI risk, yet GPA prescribing is highly variable.<sup>80</sup> Improving care for these special populations requires systematic risk stratification, greater involvement of pharmacists, regular deprescribing strategies, and patient education to ensure rational and evidence-based GPA use in tertiary settings.<sup>81</sup> Primary GI risk factors of special population and their recommended management strategy are presented in table 1.

Table 1: GI risk factors and recommended management strategies in special populations

| SPECIAL POPULATION      | PRIMARY GI RISK FACTORS                                  | RECOMMENDED MANAGEMENT STRATEGY  |
|-------------------------|--|--|
| Older adults            | Polypharmacy, multiple comorbidities                     | Systematic risk stratification and guideline-based gpa use   |
| Patients with ckd       | Increased bleeding risk, frequent use of high risk drugs | Consistent implementation of gastroprotective measures   |
| Cardiovascular patients | Use of dapt or oral anticoagulants                       | Evidence -based ppi co-therapy to reduce upper gi-bleeding   |
| Critically ill patients | High risk of stress ulcers                               | Appropriate initiation of stress ulcer prophylaxis in icu and timely discontinuation upon transfer/discharge |

### PATIENT EDUCATION AND INTERVENTIONS TO IMPROVE ADHERENCE:

Improving adherence to gastroprotective agents (GPAs) in tertiary care requires both education-focused and system-driven interventions. Common causes of poor adherence include polypharmacy, complicated dosing regimens, limited patient understanding of therapy, and

insufficient counselling during clinical encounters.<sup>82</sup> Research highlights that personalized education through structured counselling, clear and simplified instructions, and the use of supportive tools improves persistence with PPIs, particularly in patients prescribed antithrombotics.<sup>83</sup> Pharmacist involvement through discharge counselling, medication reconciliation, and provision of adherence aids such as blister packs

has also been shown to enhance compliance and medication safety.<sup>84,85</sup> Technology-based solutions, including mobile applications, reminder systems, and electronic monitoring, further reinforce long-term adherence in chronic therapy.<sup>86</sup> Evidence from quality improvement programs indicates that combining direct patient education with hospital-level supports, such as electronic prescribing alerts and routine risk assessment, leads to more rational GPA use and stronger adherence outcomes. A comprehensive approach merging patient education, pharmacist engagement, and digital support can significantly improve adherence and reduce preventable GI complications in high-risk populations.<sup>87</sup>

### OVERUSE AND IRRATIONAL USE OF GASTROPROTECTIVE AGENTS

Gastroprotective agents (GPAs) such as proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), and misoprostol play an important role in preventing and managing drug-induced gastrointestinal (GI) injury, particularly in patients at elevated risk. While their clinical benefits in high-risk populations are well established, there is consistent evidence of widespread prescribing in situations where there is little or no medical indication. Several recent studies report that **30–60% of PPI prescriptions are inappropriate**, with the highest rates observed among hospitalized patients, nursing home residents, and chronic outpatient users.<sup>88</sup>

Patterns of irrational use include unnecessary prophylaxis for patients without GI risk factors, therapy continuation far beyond the recommended duration, duplicate therapy with both a PPI and an H2RA, and uncritical continuation of inpatient prescriptions at the time of discharge. Common drivers for this overuse are prescriber habit, defensive prescribing to prevent potential bleeding, limited awareness of updated guidelines, and the ease of over-the-counter access to PPIs in some countries.<sup>89</sup>

The long-term, unwarranted use of GPAs especially PPIs is linked to a range of adverse effects. Observational studies have associated chronic PPI use with *Clostridioides difficile* infection, vitamin B12 and magnesium deficiencies, chronic kidney disease, and an increased risk of bone fractures, although causality for some of these outcomes remains under debate. In addition to these potential harms, unnecessary use adds to healthcare costs, increases the burden of polypharmacy, and may delay the diagnosis of serious GI conditions by masking symptoms.<sup>90</sup>

To address these concerns, guidelines recommend **risk-based initiation** of GPAs, careful documentation of the clinical indication, and **regular reassessment for deprescribing** once the underlying need has resolved. Effective interventions include specifying duration at the time of initiation, pharmacist-led medication reviews, integrating clinical decision support systems (CDSS) into prescribing workflows, and engaging patients in shared decision-making to improve acceptance of deprescribing. Evidence from recent interventional studies shows that such measures can reduce inappropriate use significantly without increasing the incidence of GI complications.<sup>91</sup>

### ROLE OF CLINICAL PHARMACIST IN PROMOTING SAFE GI DRUG USE:

#### 1. Risk Assessment:

- Identify patients prescribed NSAIDs, antiplatelets, corticosteroids, bisphosphonates, or other GI-irritating medicines.
- Evaluate history for previous ulcers, GI bleeding, multiple medications, and comorbidities.<sup>92</sup>

#### 2. Optimising Gastroprotection:

- Review therapy and recommend appropriate gastroprotective agents (PPIs, H2 receptor antagonists, misoprostol) for high-risk patients.
- Ensure correct drug choice, dosage, and treatment duration in line with guidelines.

#### 3. Patient Education:

- Explain the importance of adhering to both primary medications and GPAs.
- Instruct on correct administration to minimise irritation (e.g., bisphosphonates with water, staying upright).
- Advise on recognising early symptoms of GI injury and when to seek care.<sup>93</sup>

#### 4. Reducing Barriers to Adherence:

- Simplify dosing regimens where possible.
- Address issues such as pill burden, financial constraints, or concerns about side effects.

#### 5. Preventing Drug-Related Problems:

- Monitor for drug–drug and drug–disease interactions that increase GI risk.
- Suggest therapy adjustments to improve safety.<sup>94</sup>

#### 6. Ongoing Monitoring:

- Use refill checks, follow-up calls, and digital reminders to sustain adherence.
- Regularly evaluate therapeutic outcomes and adverse effects.

#### 7. Audit and Policy Involvement:

- Participate in audits to measure compliance with gastroprotection protocols.
- Help develop and implement institutional prescribing policies.

#### 8. Training and Collaboration:

Educate and support healthcare professionals in evidence-based GI drug use and safe prescribing practices.<sup>95</sup>

#### GAPS AND RATIONALE FOR STUDY:

Although numerous international studies have demonstrated the association between gastric irritant drugs, gastroprotective agent (GPA) use, and GI complications, there is a clear lack of research evaluating these elements together in Indian tertiary care hospitals.<sup>96</sup> Much of the current literature focuses on individual drug classes, such as NSAIDs or aspirin, without assessing GPA co-prescription rates alongside actual patient adherence patterns.<sup>97</sup> Furthermore, the combined influence of patient-specific factors such as multiple comorbidities, polypharmacy, limited health literacy, and socioeconomic barriers

on adherence behaviour and resulting GI outcomes has received little attention.<sup>98</sup> Existing practice-based audits reveal that GPA prescribing for high-risk patients is often inadequate, yet comprehensive, region-specific data linking adherence to complication rates remain scarce.<sup>99</sup> This lack of integrated local evidence limits the ability to design targeted, evidence-based interventions to reduce preventable GI harm. Conducting a study that assesses adherence to gastroprotective agents, together with patient risk factors and documented GI events, would generate critical insights to guide clinical decision-making, optimise prescribing practices, and strengthen patient education in tertiary care settings.<sup>100</sup>

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