Review Article

Comparative Analysis of Adverse Drug Reactions of Anti-Gastroenterology Agents in Patients with Comorbidities

Abstract: This study compares adverse drug reactions (ADRs) associated with anti-gastroenterology agents in patients with comorbidities. The research evaluates various classes of medications,including proton pumpinhibitors (PPIs), H2-receptor antagonists, 5-aminosalicylates, biologics, corticosteroids, immunosuppressants, prokinetics, and antacids. It highlights the frequency and severity of ADRs, Especially in patients with renal impairment, liver disease, osteoporosis, immunocompromised states, diabetes and cardiovascular diseases. The common adverse reactions of anti-gastroenterology agents were osteoporosis, hepatotoxicity and followed by renal impairment. The findings emphasize the need to carefully manage these agents to minimize risks and improve patient outcomes.
Keywords: Adverse drug reactions (ADRs), Comorbidities, Methotrexate, osteoporosis, liver disease.

Introduction*:* Gastroenteritis (GE) is an inflammation of the mucous membranes of the gastrointestinal tract, characterized by symptoms such as vomiting and diarrhoea, which can lead to significant dehydration, especially in children[1]. The most common causes of GE are viral infections, particularly from rotaviruses and adenoviruses, which are prevalent in infants and young children[2] While bacterial, protozoal, and helminthic infections can also cause GE, they are more common in developing countries[1]. The condition can result from various sources, including foodborne pathogens like Staphylococcus aureus, which can lead to food poisoning[3]. Outbreaks can occur due to environmental factors, such as water contamination, which can significantly impact community health and lead to economic losses due to sick leave[4]. Effective management primarily involves fluid replacement, as oral rehydration solutions are typically sufficient for most cases[1][5]

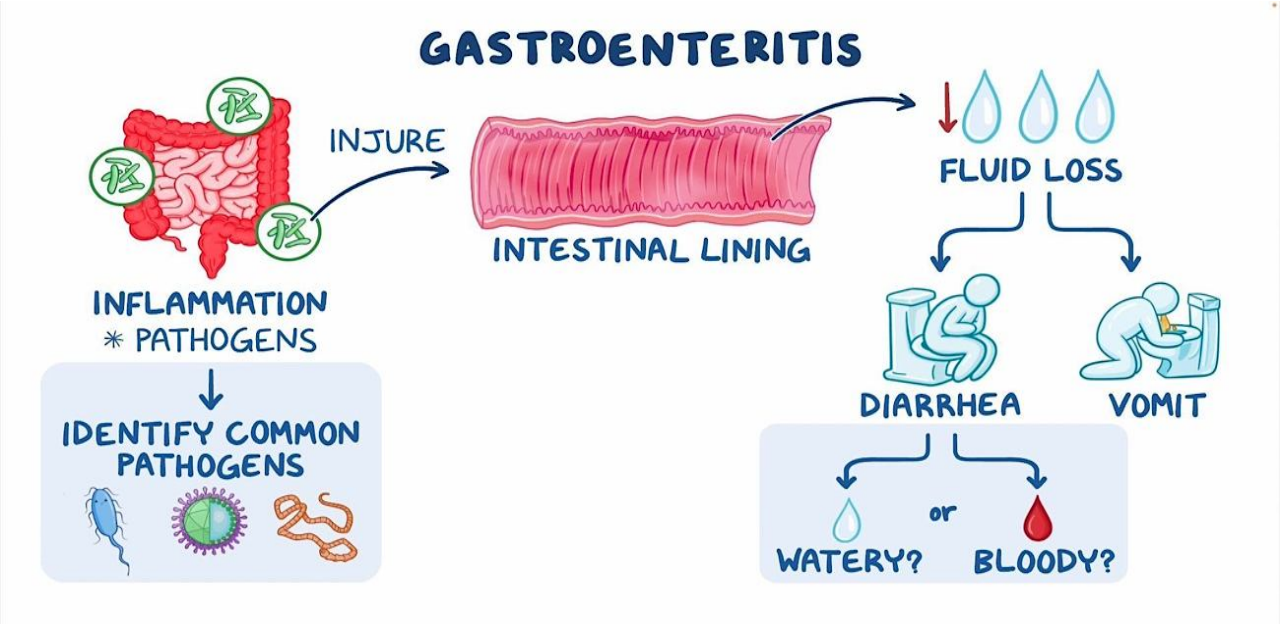

Figure No:01 . Gastroenteritis caused by a variety of viral, bacterial, and parasitic agents.

Gastroenteritis is primarily caused by a variety of viral, bacterial, and parasitic agents. In adults, bacterial infections are the leading cause, with diarrheagenic Escherichia coli (DEC) and Shigella spp. being significant contributors, exhibiting high rates of multi-drug resistance and extended spectrum-β-lactamase (ESBL) genes[6]. In children, enteric viruses account for approximately 70% of acute gastroenteritis cases, with rotavirus, adenovirus, and norovirus being the most prevalent pathogens[7][9]. Additionally, studies have shown that Giardia lamblia and Campylobacter spp. are notable parasitic and bacterial agents, respectively, particularly in younger populations[8]. The presence of co-infections, such as rotavirus with Giardia lamblia, further complicates the clinical picture[8] Overall, the diverse range of pathogens highlights the complexity of gastroenteritis and the need for targeted diagnostic and treatment strategies[7][10]. The study evaluates viral gastroenteritis agents in patients with gastroenteritis symptoms from 2017-2022 at Cerrahpaşa, focusing on viral etiology in gastrointestinal infections[11-13].

Gastroenteritis, primarily caused by viral agents like rotavirus and norovirus, is a significant health concern, especially in children under five, leading to severe diarrhea and dehydration[14][15], While most cases are viral and do not require antibiotics, bacterial gastroenteritis can arise from pathogens such as Salmonella, Shigella, and Campylobacter, which may necessitate antibiotic treatment in severe cases[14][16]. Probiotics have shown promise in mitigating viral gastroenteritis symptoms and enhancing immunity without side effects[15] Additionally, Moringa oleifera extracts exhibit antibacterial, anti-inflammatory, and antidiarrheal properties, making them a potential alternative therapy for bacterial gastroenteritis[16]. The development of antibiotic resistance among common bacterial pathogens is concerning, emphasizing the need for careful treatment selection and the potential role of natural remedies alongside conventional therapies[14][16].

Anti-gastroenterology drugs primarily include proton pump inhibitors (PPIs), H2 receptor blockers, and antacids, which are used to manage acid-dependent gastrointestinal diseases. PPIs are the most effective for reducing gastric acidity, but their overuse raises concerns about side effects, including potential links to food allergies and impaired gastrointestinal function due to reduced protein degradation[20]. Antacids, while less potent, provide symptomatic relief by buffering gastric acid and promoting mucosal protection through various mechanisms, such as stimulating bicarbonate and prostaglandin

synthesis[17]. Additionally, the use of non-steroidal anti-inflammatory drugs (NSAIDs) poses risks for gastrointestinal damage, which can be mitigated by combining them with antisecretory agents, although this may inadvertently increase small intestinal injury[19]. Emerging alternatives, such as H_2S-releasing NSAIDs, show promise for enhanced gastrointestinal safety[18].Overall, careful prescription practices are essential to balance efficacy and safety in gastroenterological treatments.

5-Aminosalicylate (5-ASA) is a crucial medication used primarily in the treatment of inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD)[21][22]. It functions as an antifolate, inhibiting bacterial folate biosynthesis, which is particularly effective against faster-growing, folate-dependent gut bacteria[21] While 5-ASA is generally well-tolerated, adverse events can occur, with a higher incidence reported in UC patients compared to those with CD[22] Recent studies have identified genetic biomarkers that may predict the risk of severe adverse events associated with 5-ASA treatment, enhancing personalized medicine approaches[22]. Additionally, a prognostic model has been developed to monitor 5-ASA toxicity, utilizing routine clinical data to inform monitoring intervals[23] Furthermore, innovative research is exploring hybrid compounds derived from 5-ASA for potential anticancer applications, indicating its versatile therapeutic potential[24-26].

Corticosteroids are often utilized in the management of gastrointestinal diseases, including gastroenteritis, due to their potent anti-inflammatory and immunosuppressive properties. They are particularly effective in treating conditions like inflammatory bowel disease (IBD), where they inhibit pro-inflammatory mediators and modulate gene transcription related to inflammation [29]. However, their use in gastroenteritis specifically is more nuanced, as glucocorticoids can lead to significant side effects, occurring in up to 80% of patients [28]. Long-term use without proper monitoring can result in complications that may outweigh their benefits [27]. While corticosteroids remain a cornerstone in treating various gastrointestinal conditions, including autoimmune and inflammatory diseases, careful consideration of the type, dose, and duration of therapy is essential to minimize adverse effects [29][28]. Newer corticosteroid analogues are being developed to reduce these complications, enhancing the safety profile of glucocorticoid therapy [29].

Biologic agents have shown promise in various gastrointestinal conditions, including gastroenteritis, by targeting specific pathways involved in inflammation and immune response. For instance, biologic therapies that target vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) have been effective in managing gastrointestinal malignancies, which may share inflammatory pathways with gastroenteritis [30][31]. Additionally, the use of biologic agents in treating acute graft-versus-host disease (GVHD) highlights their potential in addressing severe inflammatory responses in the gastrointestinal tract [32]. Furthermore, innovative biologic formulations aimed at improving intestinal flora, such as those containing lactic acid bacteria and dietary fibers, can help restore balance in gut microbiota, which is crucial for recovery from gastroenteritis [33-34].

Overall, while biologic agents are primarily recognized for their role in malignancies and inflammatory diseases, their application in gastroenteritis warrants further exploration. Immunosuppressants are primarily utilized in the management of various gastrointestinal diseases, including inflammatory bowel disease and autoimmune conditions, rather than directly treating gastroenteritis, which is often caused by infections. Their role is significant in conditions like systemic sclerosis, where gastrointestinal involvement can lead to severe morbidity [37] [38]. The use of immunosuppressive therapy can help manage symptoms and improve quality of life in patients with chronic gastrointestinal issues, but it also raises concerns about increased infection risk due to immune system suppression [36] [39]. Preventative strategies, such as vaccination and early recognition of infections, are crucial for patients undergoing immunosuppressive treatment [39]. While immunosuppressants can alleviate symptoms in chronic conditions, their application in acute gastroenteritis is limited, as the primary treatment focuses on addressing the underlying infectious cause rather than modulating the immune response [35] [36].

Prokinetics are pharmacological agents that enhance gastrointestinal motility and are primarily used for conditions like functional dyspepsia and gastroparesis, but their role in gastroenteritis is less clear. While prokinetics such as metoclopramide and itopride can improve gastric emptying and provide symptomatic relief in upper GI motility disorders, their effectiveness in treating gastroenteritis specifically is not well established[40][41].Recent studies indicate that prokinetics may have limited effectiveness as solo therapy for gastroparesis symptoms[42]. Moreover, the safety profile of prokinetics raises concerns, particularly regarding neurological and cardiovascular side effects, which necessitates careful selection based on individual patient risk factors[41][43]. Therefore, while prokinetics may offer some benefits in managing gastrointestinal symptoms, their application in gastroenteritis requires further investigation to determine efficacy and safety in this context[40][42].

Adverse drug reactions (ADRs) are defined as noxious and unintended responses to medicinal products, which can significantly impact clinical, economic, and humanistic outcomes, leading to increased morbidity and mortality, as well as elevated healthcare costs [44] [46]. ADRs can be categorized into mild and severe reactions, with management strategies varying based on the severity and individual patient circumstances, including drug withdrawal, dose adjustment, or symptomatic treatment [44] [45]. The mechanisms behind ADRs may involve immune responses and can manifest in various forms, such as cutaneous reactions 45. Effective pharmacovigilance systems are crucial for monitoring and reporting ADRs, as they help regulatory agencies identify safety signals and mitigate risks associated with drug use [46]. Despite the importance of reporting, under-reporting remains a significant challenge, necessitating increased involvement from patients, healthcare professionals, and regulatory bodies to enhance drug safety [46].

Adverse Drug Reaction (ADR) scales are essential for assessing the causality between medications and adverse events. Various scales have been developed, including the Naranjo algorithm, which is widely accepted for its effectiveness in determining the likelihood of ADRs [47] [49]. Other notable scales include the WHO-Uppsala Monitoring Centre system, the Liverpool Causality Assessment Tool (LCAT), and the Roussel Uclaf Causality Assessment Method (RUCAM) [47] [48]. Each of these tools has its advantages and limitations, and no single scale has achieved universal acceptance due to variability in expert assessments and the complexity of ADRs [48]. For instance, studies on antidiabetic drugs utilized multiple scales, revealing that a significant percentage of ADRs were categorized as probable or possible [51-52]. Additionally, the ADRROP scale was developed specifically for older adults to predict ADR risks based on various factors [50]. Overall, the choice of scale can significantly influence the assessment and management of ADRs. Adverse drug reactions (ADRs) can be classified based on severity into mild (1-3), moderate (4-6), severe (7-8), and very severe (9-10).

Method and materials: In this review articles, a systematic search from Pubmed, Scopus and Google Scholar and data extracted from the selected articles most common ADRs of anti-gastroenterology agents. The tools were used excel sheet for graphical presentation and data management analysis.

Discussion :

Table:01: classify symptomatically scale score.

Classification	Agent	Mild Scale(1-3)	Moderate Scale(4-6)	Severer Scale(7-8)	Very scale Severe (9-10)	Citation
Proton Pump Inhibitions	Omeprazole	Headache, Nausea	Hypomagnesemia	Osteoporosis (long-term use)	Clostridioides difficile and Stevens-Johnson Syndrome	Katz, P.

	Pantoprazole	Mild Diarrhea	Defiency of vitamin 12	Osteoporosis (long-term use)	Clostridioides difficile and Stevens-Johnson Syndrome	O., et al. (2013)[53].
H2-Receptor Antagonist	Ranitidine	Headache, Dizziness, Nausea	Diarrhea, Constipation, Fatigue	Hepatitis, Pancreatitis, Cardiac Arrhythmias	Anaphylaxis, Severe Skin Reactions (e.g., Stevens-Johnson Syndrome)	
	Cimetidine	Headache, Dizziness, Gastrointestinal discomfort, Fatigue.	Gynecomastia erectile dysfunction, Confusion, Rashes	Neutropenia, Drug interactions	**Hepatotoxicity,** Severe mental confusion and psychosis, Cardiac arrhythmias	Dobrilla, G., & Garofalo, R. (2020)[54].
Antacid	Aluminium hydroxide	Diarrhea Occasional, Nausea Mild stomach discomfort ,mild constipation	Abdominal pain Electrolyte imbalances, Muscle cramps or fatigue, Altered taste,TemporaryOsteomalacia, Phosphate depletion (Hypophosphatemia	Hypophosphatemia, Encephalopathy Intestinal obstruction,Renal impairment, Bone demineralization, Encephalopath	Aluminum toxicity, Severe hypersensitivity, Dialysis-related amyloidosis Rare,Chronic kidney disease exacerbation, Severe hypophosphatemia	
	Calcium Carbonate	Belching,**Constipation,** Nausea	Hypercalcemia, Milk-alkali syndrome, Kidney stones	Severe hypercalcemia, Gastrointestinal obstruction,	Life-threatening hypercalcemia, Milk-alkali syndrome (advanced)	Sakamoto, C., & Koyama, J. (2018)[55].
5-Aminosalicylate	Mesalamin	Headache, Nausea, Abdominal pain, Diarrhea	Rash, Fatigue, Fever, Dizziness	Pancreatitis, Hepatotoxicity, Colitis exacerbation, Renal impairment	AnaphylaxisToxic epidermal necrolysis (TEN)Steven-Johnson syndrome (SJS), Severe hypersensitivity reactions	
	Sulfasalazin	Headache, Nausea, Abdominal pain, Diarrhea	Electrolyte imbalances, Dehydration, Drowsiness, Abdominal distension, Photosensitivity, Reversible infertility in menElevated liver enzymes,**Blood dyscrasias**	Hepatotoxicity, AgranulocytosisInterstitial nephritis, Colitis exacerbation, Lupus-like syndrome	AnaphylaxisSteven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Severe hypersensitivity reactions	lichtenstein, g. r., et al. (2014)[56]
Corticosteroid	Prednisone	Increased appetite, Mild weight gain, Mood changes	Hypertension, Hyperglycemia, Gastrointestinal disturbances (e.g., nausea, dyspepsia)Skin changes (e.g., acne, easy bruising), Insomnia	Osteoporosis, Serious infections (due to immune suppression)Adrenal suppression, Significant mood disorders (e.g., severe depression or anxiety)	Cushing's syndrome Avascular necrosis (especially of the hip)Severe allergic reactions (e.g., anaphylaxis)Fulminant infections (e.g., septicemia)	
	Dexamethasone	Dry skin, Headache , Increased sweating, Facial puffiness,v	Gastric upset,**Muscle weakness,Electrolyte imbalance,** Delayed wound healing,**Menstrual irregularities**:	**Peptic ulcers,** Severe osteoporosis, Pancreatitis, Psychosis	Pulmonary embolism,**Heart failure,** Adrenal crisis, Infection-related death	Scully, M. (2018)[57]

Biologic Agent	Infliximab	Infusion reactions (e.g., fever, chills), Headache, Nausea, Fatigue,rashes	Increased risk of infections (e.g., upper respiratory infections)Rash or skin reactions, Elevated liver enzymes, Abdominal pain	Serious infections (e.g., tuberculosis, fungal infections), HepatotoxicityAllergic reactions (e.g., anaphylaxis), Congestive heart failure exacerbation, Bone marrow suppression	Malignancies (e.g., lymphoma), Severe hypersensitivity reactions, Neurological disorders (e.g., demyelinating diseases), Severe hematologic reactions (e.g., cytopenias), Demyelinating disorders.	
	Adalimuma	Mild headache, Nausea, Fatigue	Increased risk of infections (e.g., upper respiratory infections), Rash or skin reactions, Abdominal pain, Elevated liver enzymes	Serious infections (e.g., tuberculosis, bacterial infections), Allergic reactions (e.g., anaphylaxis), Heart failure exacerbation,Hepatotoxicity	Malignancies (e.g., lymphoma), Severe hypersensitivity reactions, Neurological disorders (e.g., demyelinating diseases),Severe hematologic reactions (e.g., cytopenias), Bone marrow suppression	Hanauer, S. B., et al.(2021)[58]
Immunosuppressant	Azathioprine	Nausea, Vomiting, Diarrhea,rash	Elevated liver enzymes, Bone marrow suppression, Diarrhea	Severe infections (e.g., sepsis, opportunistic infections), Hepatotoxicity Pancreatitis, Allergic reactions	Malignancies (e.g., lymphomas, skin cancer), Bone marrow suppression (severe cytopenias), Serious gastrointestinal complications (e.g., ulcers, perforation), Severe hypersensitivity reactions	Lichtenstein, G. R. et al.(2020)[59]
	Methotrexate	Nausea, VomitingOral mucositis, (mouth sores), Fatigue	Elevated liver enzymes,Gastrointestinal disturbances (e.g., diarrhea), Mild leukopenia (low white blood cell count), Rash	Severe hepatotoxicity, Pneumonitis (lung inflammation) Significantcytopenias (e.g., anemia, thrombocytopenia), Renal impairment	Bone marrow suppressionSevere infections (opportunistic infections) Malignancies (increased risk of lymphomas)Acute kidney injury	
Prokinetics	Metoclopramide	Drowsiness, FatigueNausea, Diarrhea	Extrapyramidal symptoms (e.g., restlessness, tremors), Increased prolactin levels (leading to breast tenderness or discharge), Dry mouth, Abdominal cramps	Extrapyramidal symptoms (e.g., restlessness, tremors), Increased prolactin levels (leading to breast tenderness or discharge) Dry mouth, Abdominal cramps	Life-threatening cardiac arrhythmias (especially with overdose), Severe extrapyramidal reactions requiring medical interventionAcute dystonic reactions (severe muscle contractions)	Ambika Nand Jha. Et.al.(2023)[60]
	Domperidone	Dry mouth,	Extrapyramidal	Severe	Tardive dyskinesia	

		Drowsiness, Nausea, Abdominal cramps	symptoms (e.g., restlessness, mild tremors), Increased prolactin levels (leading to breast tenderness or discharge), Fatigue	extrapyramidal symptoms (e.g., acute dystonia), Cardiac arrhythmias (especially in patients with underlying conditions), Allergic reactions (e.g., rash, anaphylaxis)	(risk with long-term use), Neuroleptic malignant syndrome (rare but serious), Severe cardiac events (e.g., sudden cardiac death in high-risk patients)	

Table:02.Review Agents with ADRs in comorbidities.

Agent	**Common ADRs**	**Comorbidities impacted**	**Drug ADRs comorbidities risks**
Proton Pump Inhibitors (PPIs) : Omeprazole, Pantoprazole	Hypomagnesemia **Osteoporosis** C. difficile infection	Renal impairment (worsens hypomagnesemia) - **Osteoporosis** (risk of fractures)	May exacerbate **osteoporosis** due to calcium malabsorption - Risk of kidney disease worsens hypomagnesemia
H2-Receptor Antagonists: Ranitidine, Famotidine	Dizziness B12 deficiency Confusion	Renal impairment (adjust dose) - Cardiovascular disease (rare arrhythmias)	Can cause confusion in elderly patients with dementia - Increased cardiac risks in patients with arrhythmias
5-Aminosalicylates (5-ASA): Mesalamine, Sulfasalazine	Abdominal pain Renal impairment Bone marrow suppression	Renal disease (worsened with nephrotoxic ADRs) - Liver disease (risk of hepatotoxicity)	Mesalamine can exacerbate renal disease - Sulfasalazine can worsen liver *function* in hepatic impairment
Biologics (TNF-alpha inhibitors) : Infliximab, Adalimumab	Infusion reactions **InfectionsHepatotoxicity**	Immunocompromised patients (risk of serious **infections**) - Liver disease (worsened **hepatotoxicity**)	Increased risk of serious **infections** in diabetes or HIV - **Hepatotoxicity** risks in chronic liver disease
Corticosteroids: Prednisone, Budesonide	**HyperglycemiaOsteoporosisHypertension**	Diabetes (exacerbates **hyperglycemia**) -**Hypertension** (worsens blood pressure control) - **Osteoporosis** (increases fracture risk)	Corticosteroids worsen diabetes control - Aggravate **hypertension** and **osteoporosis** in long-term use
Immunosuppressants: Azathioprine, Methotrexate	Bone marrow suppression **Hepatotoxicity** Increased **infections**	Liver disease (risk of **hepatotoxicity**) - Immunocompromised (**infection** risk)	Higher risk of **infections** in diabetes -**Hepatotoxicity** in liver disease
Prokinetics: Metoclopramide Domperidone	Drowsiness, Extrapyramidal symptoms, cardiac events	Neuroleptic malignant, chest pain	Neuroleptic malignant syndrome
Antacid: Calcium Carbonate, Aluminium hydroxide	Nausea	Osteomalacia, Chronic kidney, hypophosphatemia	Osteomalacia, Phosphate depletion Hypophosphatemia, Severe hypersensitivity

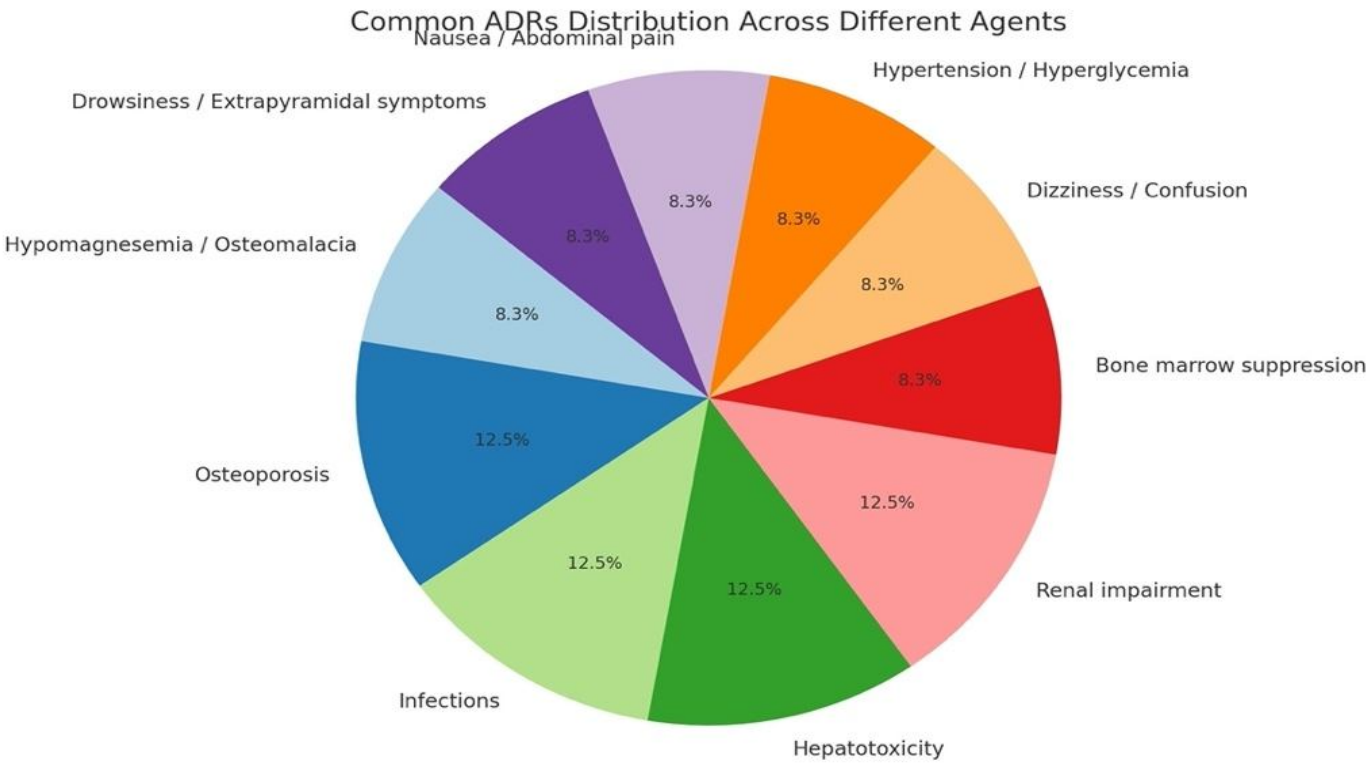

Figure No:02.Common ADRs(adverse reactions) across different agents

Figure no.02 pie chart indicates that common ADRS distribution across different anti-gastroenterology agents causes 12.5% of liver disease, renal impairment, osteoporosis and infection followed by 8.3% of other diseases.

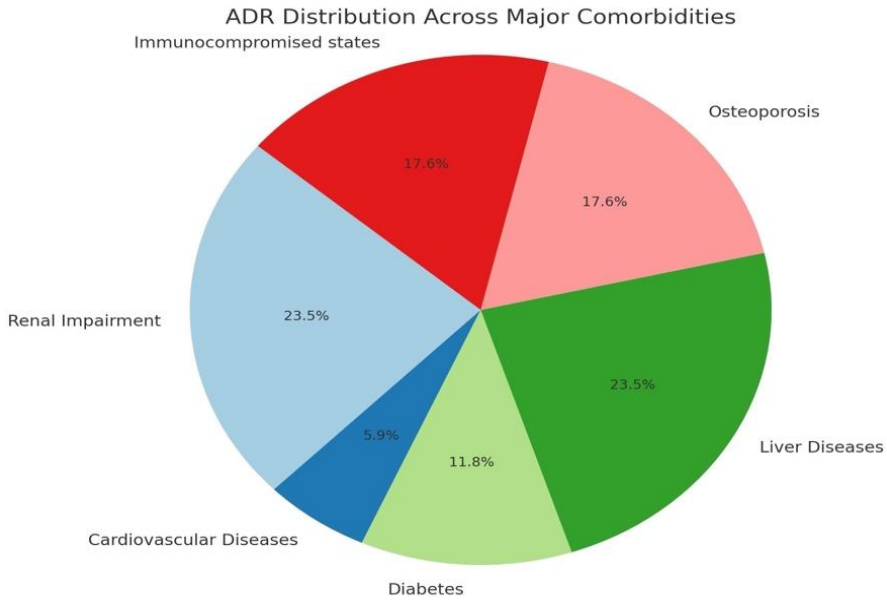

Figure No:03. ADRs (adverse reactions)distribution across comorbidities.

Figure no 03. Pie chart Identified Common Comorbidities were Renal Impairment, liver diseases, Osteoporosis, Immunocompromised states, Diabetes and Cardiovascular Diseases are common problems and liver disease agents have higher common ADRs impacted and ADRS risks.

Intervention Plan for Managing ADRs in Patients with Comorbidities:

Patients need to regularly assess all medications for nephrotoxic potential, adjust dosages of medications based on renal function (e.g., PPIs, 5-ASA), and Frequently check magnesium and potassium levels, especially for patients on PPIs. Implement EKG monitoring for patients on H2-receptor antagonists due to potential arrhythmias management,if needed encourage heart-healthy lifestyle changes (diet, exercise)and consider alternative medications with fewer cardiac risks.The regularly monitor blood glucose levels for patients on corticosteroids adjust diabetic medications as needed to manage hyperglycemia. Monitor liver function tests for patients on hepatotoxic medications (e.g., 5-ASA, immunosuppressants). Educate patients about signs of liver toxicity (e.g., jaundice, Consider safer alternatives for patients with significant liver impairment. Regularly evaluate fracture risk in patients taking corticosteroids and PPIs.Ensure adequate intake to mitigate bone density loss and implement fall prevention measures in the home and community settings. Infection Surveillance: Close monitoring for signs of infection in patients on biologics and immunosuppressants if required ensure up-to-date vaccinations (e.g., flu, pneumonia) for immunocompromised patients engage pharmacists, nurses, and physicians to collaborate on medication management and take advice.

Patient Education: Provide comprehensive education on the risks associated with medications and comorbidities, the schedule should be consistent follow-ups to reassess the patient's status and frequency of dose.

Conclusion: The analysis reveals that patients with comorbidities experience significant risks from anti-gastroenterology agents, Especially in patients with renal impairment, liver disease, osteoporosis, immunocompromised states, diabetes and cardiovascular diseases. Effective management strategies, including regular monitoring, dose adjustments, and patient education, are critical to mitigating these risks. Regular follow-ups and personalized intervention plans are needed to further improve health outcomes of comorbidities in gastroenterology.

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