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EPIDEMIOLOGICAL STUDIES IN THE TREATMENT OF PEPTIC ULCER DISEASE

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Abstract: Through monitoring illness prevalence, describing the disease's natural history, and identifying determinants or causes of the disease, epidemiologic studies serve as the cornerstone for disease control and prevention. Peptic ulcer, Gastric ulcer, ulcerative colitis and other GI ulcers is one the most prevailing disease in this running time. The major reason for this is un-healthy life style, alcohol and tobacco consumption, junk eating, and many other life style related activities beside the bacterial infection, any physiological body change and disease induced. Treatment include usage of many drugs, herbal products and many other home remedies. And where the concept of drug use arises, concept of ADR (Adverse Drug Reaction) arises itself. ADR is a reaction to a drug which is toxic and unintended and which occurs at doses normally used in man for disease prevention, diagnosis, or treatment, or for the modification of physiologic function. Many ADRs remains undetected or hidden during the clinical studies so a post marketing surveillance and a continuous epidemiological study is required for the detection of ADR so desired action can be taken and patients reliance, safety can be maintained. More than 100 patients were counseled during the survey and a data of about 52 patients were collected, presented, analyzed, interpreted and concluded about their diseases specifically seeking GI ulcer like abdominal ulcer, peptic ulcer, duodenal ulcer and related disorders like ulcerative colitis, Zollinger-Ellison, piles, any disease and drug induced GI ulcer patients. They were counseled about the treatment they were receiving, their satisfaction and any ADR if suspected, detected, or reported.

Index Terms **- ADR, Peptic ulcer, herbal treatment, Epidemiological studies, Drugs, Gastric ulcer, Ulcerative colitis, GI ulcers.**

1. PEPTIC ULCER

1.1.Introduction

An "ulcer" is a wound that is open. The word "peptic" denotes a problem that has its origins in acid. The term "ulcer," as used by gastroenterologists, primarily refers to a peptic ulcer. The two most common types of peptic ulcers are "gastric ulcers" and "duodenal ulcers." These names identify the location of the ulcer. Around the world, peptic ulcers are a chronic illness that affects up to 10% of individuals. Gastric juice pH and a loss in mucosal defenses both have an impact on the formation of peptic ulcers. Non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori (H. pylori) infection are the key variables impacting the mucosal resistance to injury. Peptic ulcer disease (PUD) is characterized by discontinuity in the GI tract's inner lining because to pepsin or gastric acid release. It passes through the muscularis propria layer of the stomach epithelium. Typically, the proximal duodenum and stomach are impacted. The distal duodenum, jejunum, or lower esophagus might all be impacted. In contrast to duodenal ulcers, which often begin to hurt 2-3 hours after eating, patients with stomach ulcers typically report epigastric discomfort within 15–30 minutes of eating. Two popular treatments for peptic ulcers, proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have been proven to have adverse effects, relapses, and a number of pharmacological interactions. Medicinal plants, on the other hand, may be used to treat and prevent a wide range of diseases because of the chemical compounds they create. Thus, this overview presents the typical medicinal herbs that may be used for the treatment or prevention of peptic ulcers. Even while ulcer sickness has a modest frequency, the pain, suffering, and expenditure that go along with it are extremely expensive [1]. The term "peptic ulcer disease" (PUD) refers to a discontinuity in the GI tract's inner lining caused by the discharge of pepsin or gastric acid. It passes through the muscularis propria layer of the stomach epithelium. Typically, the proximal duodenum and stomach are impacted. The distal duodenum, jejunum, or lower esophagus might all be impacted. Patients with duodenal ulcers often suffer discomfort two to three hours after eating, but patients with gastric ulcers typically have epigastric pain 15 to 30 minutes after eating. Helicobacter pylori testing should be performed on all individuals with peptic ulcer disease [2]. Some people, especially those who experience unsettling symptoms, might require an endoscopy to confirm the diagnosis. The majority of patients may now be treated with a triple-drug regimen based on proton pump inhibitors (PPI).

1.2.Signs and symptoms

A peptic ulcer may show one or more of the following signs and symptoms:

- Epigastric stomach pain, which is typically associated with mealtimes. When a person has a duodenal ulcer, the discomfort usually awakens them from sleep three hours after eating
- Bloating and a feeling of fullness in the abdomen
- Water brash (a surge of saliva after a regurgitation episode to neutralize the acid in the esophagus, although this is more frequently linked to gastro esophageal reflux disease)
- Nausea and frequent vomiting
- Loss of appetite and weight loss in cases of gastric ulcers
- Weight increase in cases of duodenal ulcers since eating reduces pain
- Hematemesis (blood vomiting), [3] which can result from esophageal injury brought on by severe or persistent vomiting or by bleeding straight from a gastric ulcer. Rarely, an ulcer can result in a stomach or duodenal

perforation, which causes acute peritonitis and extremely painful stabbing attacks that necessitate emergency surgery

- Melena (tarry, foul-smelling feces caused by the presence of oxidized iron from hemoglobin) [4].

1.3.Causes of peptic ulcer

The two factors that make up the majority of the aetiology of PUD are PUD associated with NSAIDs and PUD associated with Helicobacter pylori [5].

NSAIDs, NSAID-associated stomach ulcers, and uncommon conditions like Zollinger-Ellison Stressors include severe illness, burns, concussions, lymphomas, gastric/lung cancer, viral infection, vascular insufficiency, radiation therapy, and Crohn's disease.

90% of duodenal ulcers and 70% to 90% of stomach ulcers are caused by PUD by the gram-negative bacteria Helicobacter Pylori. People with lower socioeconomic position are more likely to have the infection H. pylori, which is usually picked up during childhood. The bacteria can adhere to the stomach's mucosal epithelial cells and lead to inflammation.

Individual vulnerability is significant at the start of mucosal injury since only a small percentage of those with H. pylori or using NSAIDs develop peptic ulcer disease. Peptic ulcers and functional polymorphisms in many cytokinin genes are related. For instance, polymorphisms of interleukin 1 beta (IL1B) alter the mucosal production of interleukin 1, resulting in gastroduodenal disorders linked to H. pylori [6]. On the other hand, NSAID users—and aspirin users in particular—have had a four-fold rise in the difficulty of peptic ulcer [7]. Upper gastrointestinal hemorrhage is more likely when aspirin, NSAIDs, and other medications such corticosteroids and selective serotonin reuptake inhibitors are used together [8]. The role of NSAIDs and aspirin in the aetiology of peptic ulcer disease is still debatable, despite the fact that many patients who use them also have H. pylori infections. According to a meta-analysis of observational studies, the use of NSAIDs, aspirin usage, and H. pylori infection all independently raise the chance of developing peptic ulcer disease [9]. About one-fifth of instances with peptic ulcer disease, which is categorized as an idiopathic ulcer and is H. pylori negative, NSAID negative, and aspirin negative [10], can be detected. The pathogenic processes that underlie the onset of an idiopathic peptic ulcer are yet unclear, although it is believed that there is an imbalance between factors that support mucosal integrity and aggressive results [11]. According to a thorough investigation, psychological stress may make peptic ulcers more common [12]. Numerous different aetiologies are taken into account, including ischemia, medication side effects, radiation, infections, histaminic responses, eosinophilic infiltration, gastric bypass surgery, and metabolic abnormalities [13].

1.4.Pathogenesis

1.4.1. Mechanism of gastric acid secretion

The stomach is mostly used for digesting food. When stimulating food is present, the stomach releases acid and enzymes. When food is present, the mechano-sensitive and chemoreceptors in the stomach are stimulated, causing specific reactions. Gastrin, Histamine, and Ach binding to G-protein coupled receptors, activating the second messenger pathway [14].

The parietal cell of the stomach secretes acid. An essential aspect in stomach acidity is the physiological regulation of acid output by parietal cells. The secretion of parietal acid is done by three vital pathways:

1. The neural system is stimulated by the Vagus nerve.

2. Localized histamine release that is paracrine-stimulated via enterochromaffin-like cells.
3. Antral G cells that have been induced by the endocrine gland to release gastrin. Via parietal cells on the basolateral membrane, muscarinic M3 receptors in the neural system activate the vagal nerve, which releases acetylcholine, and the stomach, which secretes acid.

The CNS is thought to be the primary factor instigating the secretion of gastric acid as a response to food anticipation. From gastric antrum G cells via gastrin and fundus possessing enterochromaffin-like histamine and their release activation by indirectly acetylcholine. ECL cells were the main sources of the gastric histamine that was secreted by the parietal cells. Histamine is released from HCL activated by the paracrine binding to the H2 receptor in parietal cells. Gastrin is primarily found in antral G cells. The regulation of central neural, chemical, and local gastric content distension leading to the release of gastrin [15]. The effect of gastrin and vagal stimulation on mast cell and paracrine-ECL cell effects production of histamine. Increase the amount of intracellular Ca2+ through cyclic AMP and the release of acid by Ach/gastrin via histamine [16]. The final stage of acid secretion is stimulated by H+/K+ ATPase. Which is additionally known as gastric proton pump. cAMP or Ca2+ ion-dependent pathways activation or H+/K+ ATPase activation from parietal cells [17].

1.4.2. Pathophysiology of peptic ulcer

Recent developments have improved our knowledge of the pathophysiology of peptic ulcers. An imbalance between pepsin, acid, and mucosal digestion inactivity results in ulcer disease. The three groups of possible etiologies for peptic ulcers.

1. A massive hyper secretion of peptic acid occurred in Zollinger-Ellison Syndrome.
2. By the use of non-steroidal anti-inflammatory drugs (NSAIDs).
3. The ulcer is associated with the *Helicobacter pylori* infections. The number of acid secretions was abnormal in the duodenal ulcer patient, which is a universal fact. The parietal cell mass increases by 1.5 to 2 times [18].

A. Pepsin: Pepsinogen 1 (PG1) is the origin of peptic ulcer disease [19]. This led to the discovery of superficial gastritis originating from *Helicobacter pylori* [20]. In children, *H. pylori* treatment resulted in PG1-level serum depletion. However, it was not known that depletion leads to a decrease in serum PG1 levels of luminal pepsin activity. In some patients with duodenal ulcer, looking at the fluid consisting of gastric contents, gastric acid overcame its ability to neutralize duodenal acid and determined the abnormality [21].

B. Acid: Acid secretion under normal conditions was dependent on neural (vagal), gastrin (endocrine), and histamine (paracrine limb). The frequency of pepsin and acid secretion increases after food ingestion due to cephalic activation via the Vegal nerve and gastric secretion of parietal cells. It lowers duodenal and gastric pH to baseline for acid secretion and inhibits gastric release [22].

C. Mucosal protection: The digestive enzymes pepsin and acid have potent anti-inflammatory and protective actions on the gastrointestinal mucosa [23]. Maintain the duodenal and gastric pH at or above 6 when the luminal pH is around 1.5. The epithelial cell influences gastric destruction and is acid resistant. To stop acid from penetrating, tight junctions were used to link the gastric epithelial cells. For four hours at pH 2, the surface of a gastric mucosa apical cell's monolayer was complied with trans-membrane electrical potential and acid flow sustained by an in vivo consist variability [24]. Mucosal breaches that occur are followed by epithelial passage through the basement membrane [25].

D. Abnormal mucus: Duodenal ulcers in patients with peptic ulcers have mucus-lined gastric and duodenal epithelium. The number of ulcer disease patients has risen in the low molecular weight dextrans section, which results in thinner mucus [26]. The physical characteristics of the gastric mucus differ between ulcer patients and controls. Gastric mucus's hydrophobicity was measured using goniometry. In patients with stomach ulcers, duodenum and dyspeptic management, groups of ulcer disease patients have significantly less hydrophobicity. A significant decrease in hydrophobicity controls is brought on by *H. Pyloric* gastritis [27]. Prostaglandin synthesis is critical for mucus depletion. In mucus, endogenous synthesis of prostaglandins and mediators takes place [28].

E. Blood flow: Blood movement is crucial for maintaining the health of any organ, including the gastro-duodenal. It is debatable whether the decrease in epithelial blood flow is therapeutically necessary for the treatment of ulcer disease. When an acute lesion forms, the gastro-duodenal epithelium of the animal exhibits significant evidence due to the reduction in blood supply. Rat stomach ischemia is more resistant to the duodenum. The presence of a gastric lesion cannot be detected until the flow falls below a threshold of basal 40%. In the absence of a threshold level, the flow has linearly declined since the formation of the duodenal lesion and the hemorrhagic mucosal lesion. Pretreatment with sodium thiosulfate or dimethyl PGE2 can stop the vascular alterations without boosting basal flow [29].

2. TREATMENT OF ULCERS

Treatment for peptic ulcer disease aims to reduce symptoms, repair craters, halt complications, and prevent recurrences. Medical therapy should include drug therapy, which should have the following objectives: Prostaglandin analogue, environmental factors such NSAIDs and smoking removal, and emotional stress reduction. Reduce stomach acidity by actions that limit or neutralize acid production. To prevent acid and pepsin from reaching the ulcer base (in a subgroup of individuals), cover ulcer craters.

Simple ulcer: For individuals with simple ulcers, 14 days of treatment with a PPI (such as omeprazole 20 mg twice day) combined with an antibiotic regimen to treat H. pylori is usually enough to promote healing.

A complex ulcer is one that has bleeding, perforation, penetration, or obstruction of the stomach outlet. All patients with such ulcers should have an intravenous PPI. Once patients are able to tolerate oral medications, they should switch to an oral PPI at a high dose twice day (for example, omeprazole 40 mg twice daily) to hasten the healing process. In many cases, the dosage should be decreased to once daily after four weeks. However, patients who are bleeding might be shifted to a lower oral dose of the PPI (such as 20 mg omeprazole once daily).

When treating H. pylori, the first antibiotic regimen should be chosen while taking into account the possibility of penicillin allergy and risk factors for macrolide resistance. For first therapy, we suggest triple therapy for 14 days in patients without macrolide resistance risk factors (Grade 2B) using a proton pump inhibitor (PPI), amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily). Only in those who are penicillin allergic, as metronidazole resistance is common and can reduce the effectiveness of treatment.

Starting with bismuth triple treatment is what we advise for people who have risk factors for macrolide resistance. Bismuth is utilized in quadruple therapy as a PPI.

All NSAIDs, including aspirin, should be stopped or lowered in PUD patients. Wherever possible, other medicines like acetaminophen or a non-acetylated salicylate (like salsalate) should be used. Patients with

NSAID-associated ulcers should take a PPI (such as omeprazole 20 to 40 mg daily) for four to eight weeks, depending on the size of the ulcer. In peptic ulcer patients who must continue taking NSAIDs or aspirin, maintenance anti-secretory therapy with a PPI (such as omeprazole 20 mg daily) can reduce the risk of ulcer complications or recurrence [30].

2.1.Classification of drugs:

A. Gastric acid secretion inhibitors:

- H_2 Antihistamines: Cimetidine, Ranitidine, Famotidine, Roxatidine, Lafutidine
- Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium
- Proton pump inhibitors: Omeprazole (Prototype), Pantoprazole, Esomeprazole, Lansoprazole, Rabeprazole, Dexrabeprazole, Ilaprazole
- Prostaglandin analogue: Misoprostol

B. Gastric acid neutralizers (Antacid):

- Systemic: Sodium bicarbonate, Sodium citrate
- Non systemic: Mag. Hydroxide, Mag. Trisilicate, Alumin. Hydroxide, Magaldrate, Calcium carbonate

C. Ulcer protectives: Sucralfate, Colloidal bismuth subcitrate (CBS)

D. Anti *H, pylori* drugs: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline, CBS

2.2.Gastric acid secretions inhibitors

2.2.1. H2- Antihistamines

A. Cimetidine: First H2 blocker to be introduced clinically, described as 'prototype' drug. All clinically used H2 blockers are competitive antagonist of histamine except famotidine. These drugs block histamine- induced gastric acid secretions. Inhibit acid production by reversible competing with histamine for binding with H2 receptor on the basolateral membrane of parietal cells. Suppress acid production by 70%. Inhibit basal acid secretions and nocturnal secretion also.

- **Pharmacokinetic:** Absorbed orally, bioavailability is 60-80% due to first pass hepatic metabolism. It crosses placenta and reaches milk, but poorer blood brain barrier. About 2/3rd drug is excreted unchanged in urine and bile. The t1/2 is of 2-3hr, but duration of action is longer.
- **Side effects:**

➢ Diarrhea, headache, drowsiness, fatigue, constipation.
➢ Confusion, delirium, hallucinations, and slurred speech.
➢ Rebound hyperacidity.
➢ Thrombocytopenia.
➢ Pancytopenia, neutropenia, anemia.

- **Uses:** Peptic ulcer, non-ulcer dyspepsia, urticaria, GERD (gastro esophageal reflux disease), bleeding from stress ulcers and erosive gastritis.
- **Drug interactions**: Inhibit the metabolism of many drugs: Theophylline, Phenytoin, Warfarin, Carbamazepine, and Metronidazole

B. Ranitidine: Non-imidazole H2 blocker. 5 times more potent than cimetidine. Longer duration of action, with greater 24hr acid suppression is obtained. Less penetration in brain, less inhibition of hepatic metabolism of other drugs.

- **Side effects:** Headache, diarrhea, constipation.
- **Uses:** Used in peptic ulcer, GERD and urticaria.

C. Famotidine: Thiazole ring containing H2 blockers which bind tightly with H2 receptors and exhibit longer duration of action. Some inverse agonistic action has been demonstrated. 5-8 times more potent than cimetidine. Oral bioavailability is 40-50 %. It is excreted trough kidney 70% in unchanged form.

- **Side effects:** Dizziness, bowel upset, headache, rashes
- **Uses:** Peptic ulcer, GERD.

D. Roxatidine: Same mechanism of action, pharmacokinetics and side effects to that of ranitidine. It is twice more potent and longer acting.

E. Lafuatidine: This is second generation H2 blocker. It acts by preventing gastric acid secretions. It also activates calcitonin gene related peptide, resulting in the stimulation of nitric oxide (NO) and regulation of gastric mucosal blood flow, increases somatostatin levels also resulting in less gastric acid secretion. Side effects: Constipation, diarrhea, drug rash, nausea, vomiting and dizziness.

- **Uses:** Exact uses are not known but it can be used for gastric ulcers and duodenal ulcers, gastritis and chronic gastritis.

2.2.2. Proton pump inhibitors (PPIs)

This the most commonly used class of acid suppressants.

A. Omeprazole: It is prototype member of benzimidazoles which inhibit the final step of gastric acid secretions. It is a powerful inhibitor of gastric acid. It has dose dependent suppression of gastric acid secretion without blocking any receptor. After absorption of pro-drug, it gets activate tetracyclic sulfonamide cation. This activated form then binds to sulfhydryl groups of cysteine in the H+ k+ ATPase, irreversibly inactivating the pump molecule. Especially when two molecule of omeprazole reacts with one molecule of the enzyme. It also inhibits gastric mucosal carbonic anhydrase.

- **Pharmacokinetics:** All PPIs are enteric coated to protect the drug from molecular transformation in the acidic gastric juice. It is administered orally. Oral bioavailability is about 50% due to acid liability. Bioavailability of all PPI are reduced by food. So they should be taken in empty stomach, because 10% of proton pumps are active. Omeprazole is highly plasma protein bound drug. Rapidly metabolized in liver by CYP2C19 and CYP3A4. Plasma t1/2 is of 1hr. Metabolites are excreted in urine.
- **Side effects:** These are very safer drugs. Some side effects are nausea, loose stools, headache, and dizziness.
- **Interactions:** Inhibits oxidation of certain drugs like Diazepam, Phenytoin, and Warfarin, reduced gastric acidity decreases absorption of Ketoconazole, iron salts, Clarithromycin inhibits omeprazole metabolism.
- **Uses:** Peptic ulcer, bleeding peptic ulcer, GERD, Zollinger-Ellison Syndrome, Stress ulcers, Aspiration pneumonia.

B. Pantoprazole: It has same potency like omeprazole. It is more stable and has higher oral bioavailability. Affinity for CYP450 is lower than omeprazole. It is use as I.V for bleeding peptic ulcer, and for prophylaxis of acute stress ulcers. Also used foe peptic ulcer, stress ulcer, Zollinger- Ellison syndrome.

C. Esomeprazole: It is S-enantiomer of Omeprazole. Have higher bioavailability and better control of intra-gastric pH than omeprazole in GERD patients because of slower elimination and longer t1/2. It is provide

healing effects in erosive gastritis and symptomatic relief in GERD. Side effects and drug interactions are similar to of omeprazole.

D. **Lansoprazole:** It has similar action like omeprazole. More potent than omeprazole. Reversible inhibition of H+K+ ATPase. It has higher oral bioavailability. Fastest onset of action and slightly longer t1/2 than omeprazole. Dose should be reduced in case of liver disease. Side effects are similar but less drug interactions, diazepam and phenytoin metabolism may be reduced.

E. **Rabeprazole:** It is the fastest acid suppressant drug. Due to its higher pKa, it is more rapidly converted into active species. Potency and efficacy are exactly similar to omeprazole. No drug interaction has been observed.

F. **Dexrabeprazole:** It is active dextro-isomer of rabeprazole, produces similar acid suppression at half the dose.

G. **Ilaprazole:** Ulcer healing efficacy and tolerability is similar to omeprazole. It is excreted in urine both as unchanged drug and as sulphone metabolite.

2.2.3. Anticholinergics:

A. **Pirenzepine:** It is M1 selective antagonist, is used in the treatment of peptic ulcer, as it reduces gastric acid secretion and reduces muscle spasm.

B. **Propantheline:** It is used with other medicine to treat ulcer. It works by slowing the movement of food through the stomach and intestines and decreasing the amount of acid made by the stomach. It has a direct effect on smooth muscles. About 70% drug is excreted in the urine mostly as metabolites.

2.2.4. Prostaglandin analogue:

A. **Misoprostol:** PGE2 and PGI2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretions and inhibits gastrin release, increase mucosal blood flow and have cyto-protective action. Misoprostol is PGE1 analogue.

- **Pharmacokinetics:** Misoprostol is a longer acting synthetic PGE1 derivative which inhibits acid output. Shorter duration of action having very short t1/2. Ulcer healing rates comparable to cimetidine have been obtained in 4-8 weeks, but misoprostol is poorer in relieving ulcer pain.
- **Side effects:** Diarrhea abdominal cramps, uterine bleeding, abortion.
- **Uses:** Prevention and treatment of NSAID associated gastrointestinal injury and blood loss.

2.2.5. Antacids:

Antacids are basic substances which neutralize gastric acid and raise pH of gastric contents. Peptic acidity is reduced if pH rises above.

A. **Systemic antacids:**

a. **Sodium bicarbonate:** It is a potent neutralizer pH may rise above 7. Duration of action is short.

- **Side effects:** large dose induces alkalosis, ulcer perforation, CHF, edema, acid rebound occurs (due to higher pH more acid is secreted in patients with hyperacidity and duodenal ulcers cause acid rebound).
- **Uses:** Heartburn, to treat acidosis.

b. **Sodium citrate:** Similar properties to sodium bicarbonate.

B. **Non-systemic Antacids:** These are insoluble poorly absorbed basic compounds.

a. **Magnesium hydroxide:** It reacts with HCL promptly and is an efficacious antacid. It has lower water solubility.

b. **Magnesium trisilicate:** It has low solubility and reactivity. About 5% of Mg is absorbed systemically. All Mg salts have laxative property.

c. **Aluminium hydroxide gel:** It is weak and slowly acting antacid. Its 5ml suspension neutralize only 1mEq HCL. The Al3+ ions relax smooth muscle, it delays gastric emptying. It frequently causes constipation due to its smooth muscle relaxant property.

d. **Calcium carbonate:** It is potent and rapidly acting acid neutralizer. Ca ions are partly absorbed. It may cause acid rebound. Milk alkali syndrome is a major side effect. Large quantity of milk was prescribed with CaCO3 for peptic ulcer, such regimen may cause syndrome like headache, anorexia, weakness abdominal discomfort.

C. **Antacid combination:** A combination of two or more antacids is frequently used:

- Fast (Mag. hydroxide) and slow (Alum. hydroxide) acting components yield sustained effect.
- Mag. salts are laxative, while Alum. Salts are constipating, combinations may annul each other's effect and bowel movement may be least affected.
- Gastric emptying is least effected, while alum slats tend to delay it, mag/cal. salts tend to hasten it.
- Drug interactions of antacids: By raising gastric pH antacids may reduce the absorption of many drugs, Ketconazole, indomethacin, H2blockers, diazepam, fluoroquinolones, isoniazid and ethambutanol.
- **Uses:** Healing peptic ulcer, GERD, dyspepsia.

2.2.6. Ulcer protective:

A. **Sucralfate:** It is basic aluminum salt of sulfated sucrose. It is strongly adhering to the ulcer base, remain there for 6hrs especially in duodenal ulcer. Surface proteins present at ulcer base starts precipitated together with which it acts as a physical barrier, it prevents acid, pepsin and bile coming in contact with ulcer base.

- **Pharmacokinetics:** Absorbed orally. Healing efficacy is exactly similar to cimetidine.
- **Side effects:** Constipation is recorded in 2%patients. Dry mouth and nausea are infrequent.
- **Interactions:** It interferes with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin.
- **Uses:** Bile reflex, gastritis, prophylaxis of stress ulcers.

B. **Colloidal bismuth Subcitrate (CBS)**: It is a colloidal bismuth compound, water soluble. It heals 60% of ulcers at 4weeks and 80-90% at 8 weeks. It is also use for gastritis and non-ulcer dyspepsia associated with H. pylori.

2.2.7. Anti *H. pylori* drugs: *H. pylori* is gram negative bacteria survive in hostile environment of stomach.

A. **Clarithromycin:** The bacteriostatic activity of this antibiotic depends on its capacity to inhibit the protein synthesis by binding to 50s ribosomal subunit.

B. **Metronidazole**: Bactericidal activity of metronidazole depends on the reduction of its nitro-groups in anionic radicals, nitroso-derivatives and hydroxylamines which are able to damage DNA-helical structure.

C. **Levofloxacin**: The use of levofloxacin for *H. pylori* eradication is increasing worldwide after its major role in 'rescue therapy' regimens. This drug exerts a dose dependent bactericide effect by binding the subunit A of DNA gyrase an essential enzyme for the maintenance of DNA helical structure. In susceptible strains, levofloxacin stops DNA and at a high doses, even RNA synthesis. When the dose is increased, levofloxacin becomes bacteriostatic agents.

D. **Amoxicillin**: Amoxicillin is beta lactam antibiotic. It acts by interfering with the peptidoglycan synthesis, especially by blocking transporters named as penicillin binding proteins (PBP).

E. **Tetracycline**: It acts as a bacteriostatic against gram positive and gram-negative species by inhibiting codon-anticodon link at level of 30S ribosomal subunit and blocking the attachment of aminoacyl-tRNA to the receptor site. It is used in 'quadruple therapy'.

"Rescue therapy" regimen: Combination of "Omeprazole+ Amoxicillin+ Levofloxacin"

"Quadruple therapy" regimen: Combination of "Omeprazole+ Tetracycline+ Metronidazole" [31]

2.3.Treatment

A. Proton Pump Inhibitors: Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole, they are administered as an inactive prodrug. This blocked the stomach acid secretion from parietal cells by inhibiting the proton pump. Sen Gupta P.R. [32].

B. H2 Anti-Histamines: Cimetidine, Ranitidine and Nizatidine. These drugs block the histamine receptors on the parietal cell because they inhibit acid secretion. They are less effective than proton pump inhibitors. Rang et al. [33].

C. Prostaglandin Analogue Misoprostol: This drug inhibits acid secretion and promotes mucus in the mucosal membrane as well as increase the bicarbonate secretion. This reduced the incidence of NSAIDs induced ulcers. Richard at all [34].

D. Mucosal Protective Agents: Sucralfate, it stimulates the mucosal prostaglandin and bicarbonate secretion [35].

E. *Helicobacter pylori* Eradication: Even though the complete eradication of H. pylori is essential for curing related peptic ulcers and preventing relapses, this has become a global issue due to the rising incidence of antibiotic resistance. The first successful treatment was introduced in the 1980s and consisted of a two-week course of bismuth, tetracycline, and metronidazole [36]. A proton pump inhibitor (PPI) and two antibiotics, such as clarithromycin plus amoxicillin or metronidazole, are administered for seven to fourteen days as the conventional first-line treatment [37].The success of triple therapy has, however, significantly decreased over the past 10-15 years due to a growing prevalence of antibiotic resistance, particularly for clarithromycin. Antimicrobial susceptibility tests should be the foundation for the elimination of H. pylori. The selection of first-line treatments should be based on the local prevalence of antibiotic resistance, and clarithromycin-based regimens should be abandoned in areas where the local clarithromycin resistance rate is greater than 15% because susceptibility testing is frequently unavailable in clinical practice [38]. By using high-dose PPI and prolonging the course to 14 days, the rate of elimination can be accelerated [39].

The standard first-line treatment is either a 14-day concomitant therapy for patients who are intolerant to bismuth (PPI, clarithromycin, amoxicillin, and metronidazole) or a bismuth-containing quadruple therapy (PPI, a bismuth salt, tetracycline, and metronidazole). Both regimens have eradication rates of more than 90% [40].

If a first-line regimen doesn't work, second-line therapy is recommended, but it shouldn't contain clarithromycin or metronidazole [41]. With eradication rates between 74 to 81%, levofloxacin triple therapy (PPI, amoxicillin, and levofloxacin) for 14 days appears to be an effective treatment [42].

A bismuth quadruple therapy with eradication rates of 77-93% or a high-dose dual-therapy regimen with amoxicillin and a PPI, as H. pylori seldom develops amoxicillin resistance, are recommended treatment

options for patients who underwent first-line treatment with a clarithromycin-based regimen [43]. Despite comprehensive guidelines for selecting the best treatment plans, 5–10% of individuals still have chronic infections. Susceptibility testing is particularly advised in cases where H. pylori is resistant to one or more medications because these are the two most frequent causes of treatment failure after two courses of therapy. One of the frequently advised salvage regimens is rifabutin-based triple therapy (PPI, rifabutin, and amoxicillin) for 10 days, with eradication rates of 66-70% [44]. However, rifabutin's side effects, such as myelotoxicity and red secretions, should be taken into consideration [45].

F. NSAID-Associated Ulcer Disease and the Use of PPIs: There are many methods for preventing NSAID and aspirin-related gastro-duodenal ulcers and their side effects. These include using COX-2-selective NSAIDs, co-therapy with a PPI, an H2 receptor antagonist, or misoprostol, or their combination with a gastro-protective agent. The most well-liked and reliable preventative medications are PPIs [46]. The hydrogen/potassium ATPase enzyme on gastric parietal cells is irreversibly bound by the substance, which reduces the amount of stomach acid produced. The best defense against peptic ulcer complications is provided by a combination of PPIs and COX-2-selective NSAIDs [47]. H2 receptor antagonists cannot lower the risk of stomach ulcers at standard doses [48].

Although misoprostol effectively prevents peptic ulcer complications, it is limited in its use for stomach protection due to gastrointestinal disturbance and its abortifacient effects. If the offending agent is stopped, more than 85% of instances of ulcers resolve with six to eight weeks of PPI medication. To determine whether the stomach ulcers have healed, a second endoscopy is necessary. Drug compliance needs to be examined if ulcers don't heal. Although the evidence is limited, it is frequently advised that patients with refractory ulcers double their PPI dosage for a further six to eight weeks. After ruling out false-negative H. pylori status, it is important to investigate atypical causes of peptic ulcers, including cancer, infections, Crohn's disease, vasculitis, upper abdominal radiation, cocaine usage, and Zollinger-Ellison syndrome.

PPIs are among the most widely prescribed and frequently used drugs in the world [49]. The PPIs' modest and usually treatable side effects include headaches, diarrhea, constipation, and abdominal discomfort. However, recent research has revealed a link between PPI use and a number of serious ill effects, which has caused both patients and doctors great anxiety. Due to PPIs' reduction of gastric acid secretion, ingested microorganisms that would have been wiped out by stomach acid are now able to colonies the upper gastrointestinal tract and cause infections. According to reports, PPI use may raise the incidence of community-acquired pneumonia [50], Clostridium difficile infections [51], and spontaneous bacterial peritonitis [52], as well as gastrointestinal infections including Salmonella and Campylobacter.

When gastric acid is suppressed, endocrine D cells are not stimulated to make somatostatin, which prevents G cells from inhibiting the release of gastrin and causes hyper-gastrinemia. Gastrin is a growth factor that can boost colon and Barrett metaplasia proliferative activity [53]. However, PPI-induced hyper-gastrinemia in humans is typically modest, and unless a patient has a hereditary mutation, carcinoid tumors rarely develop in humans [54]. Additionally, since PPIs treat reflux esophagitis, which reduces the risk of developing cancer by reducing chronic esophageal inflammation, using them may help prevent cancer in Barrett's ,esophagus.

PPIs can inhibit gastric acid production, which can impact how well some vitamins, minerals, and medications are absorbed. PPI users have reportedly experienced iron and vitamin B12 deficiencies as well as anemia [55].

PPIs may also make it more likely for people to develop osteoporosis and suffer from bone fractures by preventing the ionization and solubilization of the calcium salts, which are necessary for their absorption [56]. It is yet unclear what causes hypomagnesaemia to occur. Digoxin absorption is facilitated by PPI-induced stomach acid reduction, which also reduces the absorption of ketoconazole [57]. PPIs can also impact how other medications that are metabolized by the cytochrome (CYP) P450 system work, for example, they can slow down how quickly warfarin, diazepam, and phenytoin leave the body. Since both clopidogrel and PPIs are metabolized by the CYP2C19 enzyme, there has been a lot of focus on the possibility that PPIs could lessen the antiplatelet activity of clopidogrel [58]. The Food and Drug Administration (FDA) has issued cautions to avoid using omeprazole or esomeprazole with clopidogrel even though the clinical significance of the interaction is still debatable.

Over the past few years, there has been a sharp rise in reports of various, unforeseen side effects of PPIs, including myocardial infarction, stroke, acute and chronic renal disease, and eosinophilic esophagitis. Although there is a chance that PPIs may have cardiovascular effects that are independent of their effects on the activation of clopidogrel, perhaps by the decreased production of nitric oxide and altered vascular homeostasis, the increased frequency of cardiovascular events in patients taking clopidogrel who also use PPIs may be caused by the drugs competing for metabolism by CYP2C19 [59]. PPIs' effects on peptic digestion have been theorized to play a role in the emergence of eosinophilic esophagitis [60]. Inhibiting acid production causes the gastric pH to rise, pepsin to become inactive, which prevents the digestion and breakdown of peptides and results in allergic reactions in the small intestine.

G. Potassium-Competitive Acid Blockers: Since up to 13% of patients treated with lansoprazole still experience ulcer recurrence, the search for alternative treatment is ongoing. Vonoprazan is a potassium-competitive acid blocker that inhibits H^+, K^+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway [61]. Vonoprazan's mode of action differs from PPIs' in that it inhibits the enzyme in a K+-competitive and reversible way without the need for an acidic environment to activate it. Vonoprazan also exhibits a quick beginning of action and long-lasting reduction of intra-gastric acidity [62]. With good tolerance, a comparable safety profile, and no new safety concerns, vonoprazan at doses of 10 mg and 20 mg was non-inferior to lansoprazole for the prevention of peptic ulcer recurrence in Japanese patients receiving NSAID therapy [63] or those who needed aspirin therapy for cardiovascular or cerebrovascular protection [64]. Additionally, compared to PPIs, vonoprazan administration for five weeks dramatically reduced post-endoscopic submucosal dissection bleeding [65]. Additionally, it has been demonstrated to be more effective than rabeprazole and esomeprazole for scarring fake ulcers, which may contribute to the safety of an endoscopic submucosal dissection.

H. Future Research Questions: Along with the global decline of peptic ulcer disease and in the prevalence of *H. pylori*, there is a rising problem of growing antimicrobial resistance, which reduces the efficiency of eradication therapy, and the overuse of PPIs, resulting in unexpected new side effects [68]. Additionally, there is a need to define the best care for the idiopathic condition because idiopathic ulcer prevalence is rising and is associated with significant mortality [69]. The optimal way to treat patients who have both concerns remains unclear because it is still unclear how H. pylori infection and NSAID or aspirin interact. There is still much to learn about the aetiology of stomach lesions brought on by H. pylori. The precise interaction between H.

pylori factors and the host genetic profile is yet unknown, but it is thought that it is driven by a mix of virulent H. pylori factors and the host immune response. Why some patients are more susceptible than others to the gastric toxicity of NSAIDs and aspirin, and which genetic polymorphisms are associated with *H. pylori*-induced peptic ulcer also remain unclear.

Antibiotic resistance is a significant problem in the lack of any potentially effective new antimicrobial agents for H. pylori, and new treatments are actually old treatments. The development of an antiulcer medication has focused emphasis on H. pylori urease. Although they have limited selectivity, several effective in vitro inhibitors have been discovered. Due to the large dosage needed, increased cost of treatment, and greater risk of bleeding, they typically never reach the clinical environment. Promising options for the pathogen's persistence in the host, like adherence, have been identified as a result of recent developments in the molecular description of H. pylori pathogenesis. A high binding affinity and genetic variety in the receptor-binding site of H. pylori make it difficult to develop effective inhibitors, despite the fact that several anti-virulence drugs can target the pathogen's adherence specifically [70].

The question of how these inhibitors can help treat H. pylori remains unanswered since the genetic variability of the virulence proteome in H. pylori directs future anti-virulence developments towards its more conserved assembly and secretion pathways.

Comorbidities are now the predominant cause of death in these patients, and gastrointestinal bleeding, a consequence of peptic ulcer disease, continues to be life-threatening. To determine the best patient care approach, prospective data and randomized controlled trials are urgently required. To sustain effective peptic ulcer treatment in the interim, accurate diagnostics, adherence to current recommendations, and avoidance of subpar H. pylori treatment regimens will be required.

2.4.Alternative Therapy for Peptic Ulcer

As old as humans, the practice of using medicinal plants to treat various illnesses is known as phyto-therapy. Additionally, there has been an increase in interest in herbal goods, particularly those made from medicinal plants, over the past few years [71]. Additionally, medicinal plants are regarded as the main source of potentially new medications due to the emergence of diverse adverse effects from the use of traditional drugs for a variety of disorders. The most important sources of novel medications are plant extracts and their compounds, which have also been demonstrated to have promising outcomes in the treatment of stomach ulcers [72]. Proton pump inhibitors, anticholinergics, antacids, antimicrobials, H2-receptor antagonists, sucralfate, and bismuth are just a few examples of medications that aren't completely effective and can have a variety of negative side effects, including impotence, arrhythmia, hematopoietic changes, hypersensitivity, and gynecomastia [73]. As a result, research into novel pharmacologically active compounds through the screening of various plant extracts resulted in the identification of efficient and secure medications with gastro-protective function. For the treatment of ulcer disease, plants with antioxidant capacity as the primary mechanism are used in particular [74].

The therapeutic capabilities of medicinal plants are a result of their ability to create a wide range of secondary metabolites, or phytochemical ingredients, which are renewable and diverse. These phytochemicals have thus been utilised by many plants as a defence strategy against diseases [75].

The emergence of resistant bacteria, on the other hand, has greatly influenced pharmaceutical corporations to alter their approach to the creation of traditional antibiotics and create novel antimicrobial medications derived from medicinal plants [76]. However, when it comes to antimicrobial medications, synthetic antibiotics continue to rule.

In fact, the prevalence of infectious diseases has increased over the past three decades, involving both old and new infections, and it has been determined that about 60% of these diseases are zoonotic in nature (transmitted between humans and animals). One of the most prominent members of that group, H. pylori, has been linked to stomach cancer, peptic ulcer disease, and chronic gastritis [77]. To highlight several medicinal plants with notable antibacterial and antioxidant action against H. pylori and peptic ulcer disease was one of the goals of this review. However, due to the rise of resistant strains, several plants lose their effectiveness against H. pylori. Consequently, the isolation of various constituents from the most active plant extracts is encouraged [78].

It is crucial to stress that herbal products may contain a variety of bioactive components with both harmful and advantageous effects. Therefore, legislation to control the quality of herbal products is needed, as well as increased training for doctors and patients about herbal therapy. This is especially true for future randomized studies to ascertain the efficacy and safety of many products in treating digestive and other disorders [79].

Finally, the combination of contemporary medicine with Ayurvedic expertise could result in more effective antiulcer medications made from therapeutic herbs that have fewer side effects [80].

2.4.1. Herbal treatment:

You can use these natural remedies for stomach ulcers. The remedies mentioned below can help you take care of your stomach and manage the symptoms of stomach ulcers.

- **Turmeric:** The powerful anti-inflammatory and antioxidant properties of turmeric make it a valuable therapeutic herb. India as a whole is home to it. It might lessen ulceration due to its antioxidant properties. Additionally, it might lessen stomach lining swelling and inflammation. You may add turmeric to dishes and foods. Adding turmeric powder to a glass of warm water is another option. Your stomach ulcers will improve if you drink this water.
- **Tea:** One of the most widely used nonalcoholic beverages globally is tea, or Camellia sinensis. Due to its abundant antioxidant effects, it may be beneficial in treating stomach ulcers. Tea's antioxidant properties may be helpful for treating ulcers. It might help enhance mucin production and lessen stomach swelling. The protective layer of the stomach wall is created by mucin. Black tea may be made at home, giving you access to all of its antioxidant advantages.
- **Ginger:** In many cultures around the world, ginger is a popular medicinal herb. Many stomach conditions including indigestion and gas may respond well to ginger treatment. It helps to ease gastrointestinal discomfort. Due to its antioxidant properties, it might potentially be useful for treating stomach ulcers. Ginger can be added to foods and recipes as an ingredient. Ginger can be used in salads, soups, and other side dishes.
- **Liquorice:** The root of the plant, Glycyrrhiza glabra, is commonly referred to as liquorice. In Europe, it is frequently applied to the treatment of stomach ulcers. By aiding ulcer healing, boosting stomach mucus production, and boosting the health of the cells lining the stomach, liquorice may be of assistance. Tea made

from liquorice root is a possibility. In a kettle or saucepan, bring some water to a boil. For flavor, you can add a little honey and powdered licorice root to the boiling water. Set a moderate burner to simmer the tea. Enjoy it after straining it into a cup.

- **Indian Gooseberry:** Amla, often known as the Indian gooseberry, is a popular fruit and culinary item. The Ayurvedic and Siddha systems of medicine frequently use this fruit as a therapeutic component. It has anti-inflammatory and antioxidant qualities that may help in treating ulcers. Consuming amla as fruit or juice may help you treat stomach ulcers.
- **Kutki:** The therapeutic plant kutki, or Picrorhiza kurroa, is grown across the nation's tropical regions. This plant is renowned for its anti-oxidant properties, which may make it an efficient stomach protector. Kutki powder can be consumed with a glass of warm water. For flavour, you can also add some honey.
- **Myrobalan:** The plant Harad is also referred to as Myrobalan in English. It has numerous health advantages. Additionally, it might be helpful for a variety of gastrointestinal conditions like gastritis and stomach ulcers. It might aid in creating a barrier of defence for the stomach lining and halt the growth of ulcers. You can warm some water and some harad powder. Consuming this mixture may aid in the relief of stomach ulcers.
- **Aloe Vera:** Numerous medical diseases are treated using aloe vera as an herbal remedy. Aloe vera, for instance, has the ability to heal wounds and is anti-inflammatory, making it a potential beneficial treatment for stomach ulcers. Regularly consuming pure aloe vera gel may aid in reducing stomach lining edema and accelerating ulcer healing. To reap the benefits, you can also try aloe vera juice.
- **Honey:** One of the most often used pharmaceutical components in the Ayurvedic medical system is honey. It is beneficial for a variety of stomach disorders like gastritis and peptic ulcers. It is mostly advised for treating stomach ulcers. Honey has therapeutic properties that could help in treating stomach ulcers. A tablespoon of honey can be consumed right away. To treat stomach ulcers, you can also consume honey with a glass of warm water. [107]

3. ADVERSE DRUG REACTION

According to the definition of an adverse drug reaction (ADR), it is "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, adverse effects typically predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the drug." [81]. It is a "reaction to a drug which is toxic and unintended and which occurs at doses normally used in man for disease prevention, diagnosis, or treatment, or for the modification of physiologic function." Keep in mind that a drug and a negative drug reaction have a causal relationship. In conclusion, an adverse drug reaction is harm that is directly brought on by the medicine when used normally and at normal levels. Keep in mind that a drug and a negative drug reaction have a causal relationship. In conclusion, an adverse drug reaction is harm that is directly brought on by the medicine when used normally and at normal levels. Unplanned inpatients account for a sizeable share of adverse drug reactions (ADRs), unplanned, undesirable events that are linked to the use of medications. ADRs also happen during these admissions.

3.1.Risk factors

Several characteristics have been suggested as risk factors for the development of ADRs which have been discussed in below:

3.1.1. Age: There is debate on the association between age and ADR. According to certain studies, those who are extremely young or very old are more likely to experience negative effects. This reflects variations in body composition and metabolic pathway activity brought on by ageing. In the extremely young and the very old, the liver's capacity to metabolize some medications may be decreased. The amount of a medicine that is distributed to infants, child, adult, and elderly patients varies significantly [82]. A number of risk factors. The severity and specificity of ADRs in children may be explained by a variety of factors, such as changes in drug metabolism, which can result in higher vulnerability to specific medications. Some organs may be extremely sensitive to negative effects in this situation. Additionally, certain substances may affect a child's development, and a number of medications used to treat pediatric disorders can result in particular adverse drug reactions (ADRs) [83]. ADR in children has been linked to age younger than 12 months [84]. However, according to certain research, adults are more likely than children to experience ADRs [85, 86]. Advanced age has been identified by several writers as a risk factor for the emergence of ADRs [87, 88]. Drug interactions are more likely to occur in the elderly since they are more likely to be taking many medications. Furthermore, as we age, renal function tends to decline. Drug interactions are more likely to occur in the elderly since they are more likely to be taking many medications. Furthermore, as we age, renal function tends to decline.

3.1.2. Gender: Because of the hormonal environment, it is thought that women are more likely than men to experience ADRs [87, 89]. Such a tendency could be brought on by gender-related variations in medication exposure, amount of drugs prescribed, drug pharmacology, and perhaps even variations in how the bad reaction is perceived. Although the overall mortality rate is not significantly different between the sexes, the incidence pattern differs, in part because estrogens protect against heart disease before menopause. ADRs were generally more frequently reported in females for specific pharmacological types (such as Genito-urinary, sex hormone, antineoplastic, antiparasitic, and respiratory medicines) [89].

3.1.3. Multiple drug therapy: Because the likelihood of adverse drug reactions (ADRs) from medication interactions rises rapidly with the number of drugs used, poly-pharmacy has been identified as a risk factor [90].

3.1.4. Current illness: Patients with compromised metabolism, such as renal or liver impairment, may handle drugs differently. Even though they are not significant major risk factors, allergies and atopy have been mentioned as ADR predisposing factors. ADRs are also more probable to develop in diseases that require numerous medication therapies.

3.1.5. Current illness: Patients with compromised metabolism, such as renal or liver impairment, may handle drugs differently. Even though they are not significant major risk factors, allergies and atopy have been mentioned as ADR predisposing factors. ADRs are also more probable to develop in diseases that require numerous medication therapies.

3.1.6. Ethnic and genetic variations: Variations in diet or genetics may enhance the incidence of ADRs. Examples include the interaction between nutrition and a lack of glucose 6-phosphate dehydrogenase and iron overload brought on by giving iron supplements to sickle cell patients who don't require them. Genetic polymorphisms are a source of variance in how the human body reacts to drugs.

3.1.7. Pharmaceutical Factors: Examples include variations in pharmacokinetics (processes by which a drug is absorbed, distributed, metabolized, and eliminated by the body) brought on by various delivery systems, as well as reactions to drug excipients (such as binding agents, solvents, and antibacterial agents) [91].

3.1.8. Other: Several factors have been proposed as additional intrinsic risk factors for the development of ADRs, including a history of prior ADRs, length of hospital stay, concurrent infection such as HIV [93], dose and route of drug administration and duration of therapy, personality and habits such as alcoholism, smoking, diet, drug addiction, nicotine, and compliance. On the other hand, various risk factors associated with medications, therapy, and patients (including age, gender, co-occurring diseases, and prior reactions to related medications) have been recognized as playing a significant role in pharmacological hypersensitivities [94].

3.2.Importance of reporting

Reporting ADRs is necessary and should be regarded as equally crucial to patient care as treatment [95]. Patients, chemists, other healthcare providers, and the organisation can all gain from a consistent ADR moni toring and reporting programme. These advantages include the following:

1. Providing an indirect measure of the quality of pharmaceutical care through identification of preventable ADRs and anticipatory surveillance for high-risk drugs or patients.
2. Complementing organizational risk-management activities and efforts to minimize liability.
3. Assessing the safety of drug therapies, especially recently approved drugs.
4. Measuring ADR incidence.
5. Educating health care professionals and patients about drug effects and increasing their level of awareness regarding ADRs.
6. Providing quality-assurance screening findings for use in drug-use evaluation programs.
7. Measuring the economic impact of ADR prevention as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability [96].

3.3.Reports' methods

Health care professionals who oversee patients' medication regimens should be provided instructions on what ADRs need to be reported. The institution's ADR monitoring system should be notified of any reactions that meet the clinician's working definition.

Following the thalidomide catastrophe in the early 1960s, an international reporting system for ADRs was started [97]. Although the FDA had already been created in the United States for a number of years, this catastrophe served as the impetus for the start of a systematic data collection on ADRs, particularly through the Hospital Reporting Program. The WHO Pilot Research Project for International Drug Monitoring was established in 1968 as a result of a decision made by ten nations with national reporting systems to work together under WHO supervision [98].

Pharmaceutical makers are required by law to disclose all ADRs, according to the FDA. ADRs must be reported to the FDA within 15 days in cases of fatalities, unanticipated events, or significant reactions. The FDA started the Med Watch program (a voluntary reporting of ADRs that allows practitioners to utilize a single telephone number to report reactions) (www.fda.gov/medwatch) in order to consolidate and streamline the ADR reporting process [99].

One nation can learn whether similar reports are being produced in other nations by participating in the WHO initiative (the European Union also has its own system).

The Uppsala Monitoring Centre processes, assesses, and enters the reports that member nations provide there into the WHO International Database. This procedure may result in the detection of a signal—an alarm about a potential hazard shared with member countries—when there are numerous reports of adverse medication responses. This only occurs following thorough analysis and professional examination.

In order to identify and report any suspected ADR to their national pharmacovigilance center or to the manufacturer, healthcare professionals (and in certain countries, consumers) are relied upon as the primary data-generating method for international pharmacovigilance. Almost typically, spontaneous reports are provided voluntarily. In the majority of nations, manufacturers are mandated to submit information to the national authorities that they receive from healthcare providers.

This reporting system is the cornerstone of post-marketing drug safety surveillance, as demonstrated by the yellow card system in the United Kingdom [100]. The Committee on Safety of Medicines (CSM) has now received over 400,000 notifications under the yellow card program, which was first implemented for reporting suspected ADRs in 1964.

The following four essential details must be mentioned on the yellow card:

- Suspected drug(s) – brand name of drug(s) (or name and manufacturer for herbal drugs), batch number if known, mode of administration, dose, dates of administration, and indication.
- Suspected reaction(s): a description of the reaction(s), any treatments that were administered, the dates the reaction began and ended, and whether the response was deemed serious.
- Patient information: The most important information is the patient's sex, age, and weight (if available). The patient's initials and a local identification number are useful in case it becomes essential to refer back to the patient, but information that would allow for the patient's identification should not be utilized (for reasons of confidentiality). Although it should be discussed with the patient, getting the patient's permission is not required in order to report an ADR.
- Reporter information includes the reporter's name and complete business address so that the report can be recognized and contacted for more information, as needed. Other medications used, results of diagnostic tests, and known allergies are examples of additional information that may be provided [101].

3.4.Types of adverse drug reaction

Drug reactions may be classified as:

- **Type A: Dose-related reactions** (adverse effects at either normal dose or overdose), e.g., serotonin syndrome or anticholinergic effects of tricyclics
- **Type B: Non-dose-related reactions** (i.e., any exposure is enough to trigger such a reaction), e.g., allergic or anaphylaxis reactions
- **Type C: Dose and time-related reactions,** e.g., due to dose accumulation, or with prolonged use (e.g., adrenal suppression with corticosteroids)
- **Type D: Time related reactions,** i.e., due to prolonged use in a drug which doesn't tend to accumulate (e.g., tardive dyskinesia from antipsychotics)

- **Type E: Withdrawal reactions,** i.e., the undesired effects of ceasing the drug (for example, opiate withdrawal)
- **Type F: Unexpected failure of therapy,** where a drug undesirably increases or decreases in efficacy- for example, the decreased clearance of a drug by dialysis, or the decreased effect of antibiotics due to resistance [102, 103]

3.5.Identifying & evaluation of adverse drug reaction

3.5.1. Pre-Marketing Studies: It involves two types: Pre-clinical studies and Clinical studies. In pre-clinical studies the safety of new medicines is tested in animal models. Specific animal tests for acute toxicity, carcinogenicity, teratogenicity and mutagenicity are also available. However, animals can only serve as approximately models for humans. In clinical studies, the clinical trials are carried out in different phases prior to the submission of a marketing authorization application, with a stepwise increase in the number of individuals being exposed.

3.5.2. Post marketing surveillance: Post marketing drug surveillance refers to the monitoring of drugs once they reach the market after clinical trials. It evaluates drugs taken by individuals under a wide range of circumstances over an extended period of time. It can be done by different methods.

3.5.3. Anecdotal reporting: First reports of ADR come through anecdotal reports from individual doctors when a patient has suffered some peculiar effect need to be verified.

3.5.4. Intensive monitoring studies: Provide systemic and detailed collection of data from inpatients. Done by specially trained health care professionals. Statistical screening for drug-event association may lead to special studies. [104]

3.5.5. Cohort studies: Patient taking a particular drug are identified and events are then recorded.

3.5.6. Case control studies: Patient with symptoms or an illness that could be due to an adverse drug reaction are screened. The prevalence of drug taking group is then compared with the reference with the reference population who do not have the symptoms or illness. Suitable for determining whether the drug causes a given adverse event once there is some initial indication. Method for detecting completing new adverse reactions.

3.5.7. Case cohort studies: Hybrid of perspective and retrospective case control study.

3.5.8. Record linkage: Bring together a variety of patient like general practice records of illness events and general records of prescriptions. Possible to match illness events with drugs prescribed: less expensive and time consuming than other surveillance methods. [104]

3.5.9. Meta-analysis: It is quantitative analysis of two or more independent studies for the purpose of determining an overall effect and of describing reasons for variation in study result, it another potential tool for identifying ADRs and assessing drug safety.[105]

3.6.Causality assessment between drug and suspected reaction

It is determined to what extent a medicine and a rumored reaction are related. It might be challenging to determine whether a negative clinical event is an ADR or the result of the fundamental diseases getting worse. Additionally, if it is an ADR, what medication caused it should be known because many people take several new medications when ill, especially if they are admitted to the hospital.

These are various approaches:

- WHO-UMC
- HARTWIG Scale
- NARANJO'S Causality assessment

3.6.1. WHO- UMC

- Certain: a clinical occurrence, including a lab test anomaly that occurs in a reasonable time frame after drug delivery and cannot be accounted for by an underlying condition or by the use of additional medications or substances. The reaction to drug withdrawal (DE challenge) should be clinically conceivable. The event must be conclusive in terms of pharmacology or phenomenology, with the use of a successful challenge process if necessary.
- Probable/likely: a clinical event, including a lab test abnormality, that takes place within a reasonable amount of time after the drug is administered, is unlikely to be brought on by an underlying illness or by the use of other drugs or substances, and occurs after a clinically acceptable withdrawal response (DE challenge). It is not necessary to have knowledge of challenges to satisfy this requirement.
- Possible: a clinical occurrence, such as a lab test anomaly, that occurs within a reasonable time frame after the medicine is administered but that may also be explained by an underlying illness or by the use of other medications or chemicals. Drug withdrawal information may be few or ambiguous.
- Unlikely: a clinical occurrence, such as a lab test anomaly that is related to drug administration in a temporal manner that renders a causal connection unlikely, but for which other medications, chemicals, or underlying diseases offer plausible explanations.
- Conditional/unclassified: a clinical occurrence, including a lab test abnormalities, that is reported as an unpleasant response and about which additional information is either being examined or more information is required for a proper assessment.
- Un-assessable/unclassifiable: a report indicating an unfavorable reaction that cannot be evaluated because the available data is insufficient or inconsistent and cannot be backed up or validated.

3.6.2. HARTWIG SCALE

Table 1: HARTWIG scale

Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed.
Level 4	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

3.6.3. NARANJO'S CASUALITY ASSESSMENT

Table 2: **NARANJO'S causality assessment**

SCORE	INTERPRETATION OF SCORES
Total Score ≥9	Definite.
Total Score 5 to 8	Probable.
Total Score 1 to 4	Possible.
Total Score ≤0	Doubtful.

It is important to consider and document severity of the allergies/adverse reactions in the field provided in CPRS template. The pull-down menu lists "mild", "moderate" or "severe" These may be thought of as follows:

- **MILD**- Requires minimal therapeutic intervention such as discontinuation of drugs.
- **MODERATE**- Requires active treatment of adverse reaction, or further testing or evaluation to assess extent of non-serious outcome (see below for definition of serious).
- **SEVERE**- Includes any serious outcome, resulting in life- or organ-threatening situation or death, significant or permanent disability, requiring intervention to prevent permanent impairment or damage, or requiring/prolonging hospitalization.[106]

3.7.Prevention of ADR

While some ADRs are unpredictable – such as anaphylaxis in a patient after one previous uneventful exposure to a penicillin-containing antibiotic – many are preventable with adequate foresight and monitoring. Preventability (or avoid ability) usually refers to when the drug treatment plan is inconsistent with current evidence-based practice or is unrealistic when taking known circumstances into account. Epidemiological studies tend to find that between a third and a half of ADRs are (at least potentially) preventable although preventability is much easier to diagnose in hindsight. However, interventions that reduce the probability of an ADR occurring can be an important way to reduce the risk of patient harm.

There are two basic steps that can be followed to prevent an ADR occurring:

1. Identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly.
2. Ensure the treatment plan mitigates any possible adverse effects.

Also done as:

- Anticipation by patient monitoring.
- Anticipation of dosage reduction.
- Monitoring of drug serum level.
- Monitoring of pharmacological activity.
- Minimizing of non-predictable like idiosyncratic and hypersensitivity reaction.

3.8.Management of ADR

Altering a dosage regimen or withdrawing a medicine suspected of causing an ADR are common methods of managing ADRs in practice. However, the course taken to manage an ADR is likely to vary from clinician to clinician. Under EU legislation, the approval of all new medicines onto the market must now be accompanied by a robust risk management plan from the marketing authorization holder, which may involve the development of specific treatments for managing specific ADRs, as well as ongoing safety trials. Such has been the case with antidotes for direct oral anticoagulant-induced bleeding. This and other notable examples of approaches for the management of specific ADRs.

- Conformation of ADR.
- ADR disappears after discontinuation of drug.
- Recovery on withdrawal of respected drug if no other drug is withdrawn and no therapy given.

3.9.Reporting serious ADR to pharmacovigilance center /ADR regulating authorities.

- Various adverse drug reaction.
- U.S food and drug administration FDA.
- Canadian adverse drug reaction monitoring program
- The UK medicine and healthcare products regulating agencies. (Yellow card)
- Australia's voluntary reporting system for adverse drug reaction. (Blue card)

3.10. Reporting form

- It should be simple and user friendly and certain.
- Patient info- medical record, age, sex, weight, height.
- ADR- outcome, description, diagnostic, medical history.
- Drug/product- name, dose, frequency, route administration, use, expiration date.
- Treatment given
- Reporter information.

3.11. Need for detection of ADR

- Major clinical problems in terms of human sufferings and increased healthcare costs.
- Adversely affect patient's quality of life.
- ADRs are one of the leading causes of morbidity and mortality
- Gives the idea about the increased frequency of a given reaction is suspected.
- Gives the information if the drug is overdose or mediational error.

3.12. Adverse drug reaction and adverse events

Adverse drug reaction is a response which is noxious and unintended and which occurs at doses

Normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this medicinal product.

An adverse drug reaction, is distinguished from the adverse event by, the former has a suspicion of a causal relationship between the medicinal product and the reaction, i.e. judged as being at least possibly related to the reaction by the reporting or the reviewing health professional, while the adverse event does not necessarily have such causal relationship.

3.13. Role of pharmacist in ADR monitoring

- Monitor the patients who are at greater risk of developing ADRs
  - Compromised ability to handle drugs
  - Previous documentation of allergy or ADR
  - Geriatric or pediatric patients.
- Monitoring the patients who are prescribed with drugs highly susceptible to cause ADR
  - High incidence of adverse effects
  - Low therapeutic index
  - Potential for multiple interactions.
- Assess and document the patient's previous allergic status
- Assess the patient's drug therapy for its appropriateness
- Create awareness about ADRs amongst patients, HCP and public.
- Assist HCP in detection and assessment of ADRs
- Educate and encourage the HCPs and patients in reporting of an ADR
- Document the reported ADR in the patient's medical record.
- Communicate the reported ADRs to appropriate concerned.
- Present the reports in meetings and conferences
- Conduct workshops or seminars on ADRs for HCPs
- Disseminate the signals generated through publication of reports in bulletins/ journals [31].

4. CONCLUSION

A. Graph showing relation between gender and number of patients

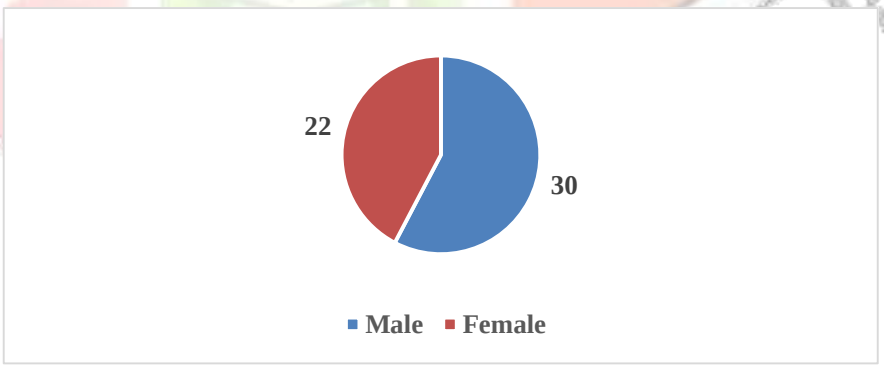

Fig 5: Graph showing relation between gender and number of patients

B. Graph showing relation between ADR reported and number of patients

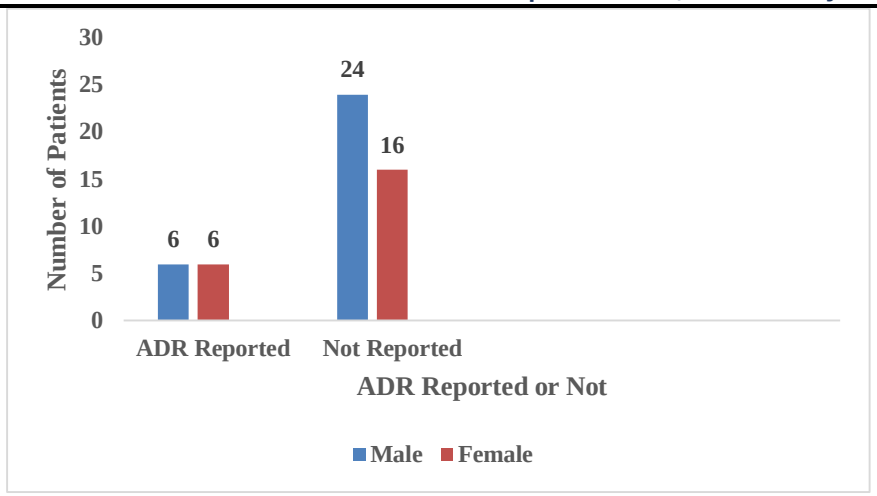

Fig 6: Graph showing relation between ADR reported and number of patients

C. Graph showing relation between drug used and number of patients

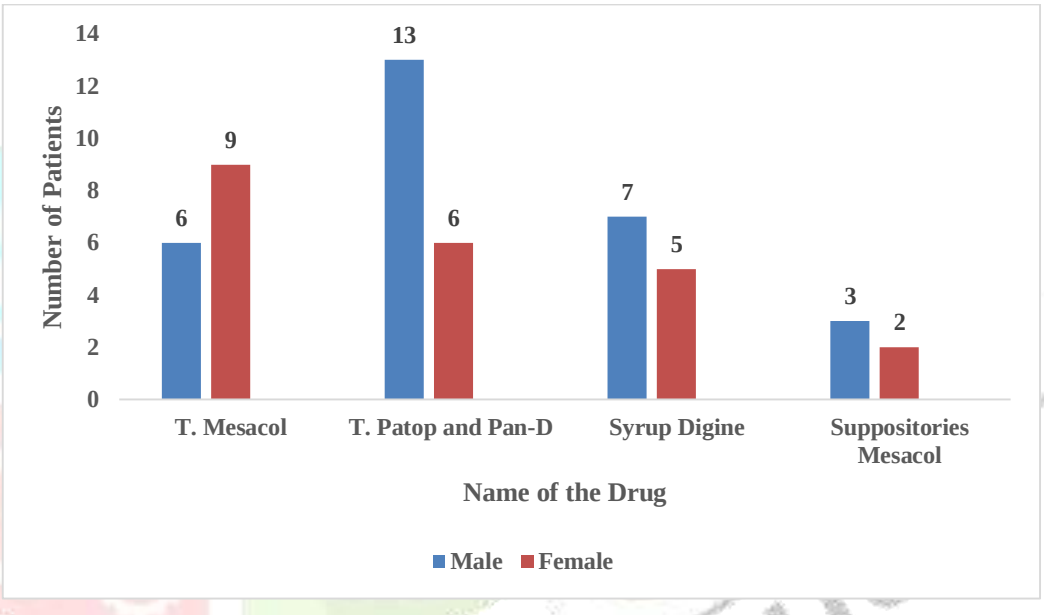

Fig 7: Graph showing relation between drug used and number of patients

D. Graph showing relation between age group and number of patients

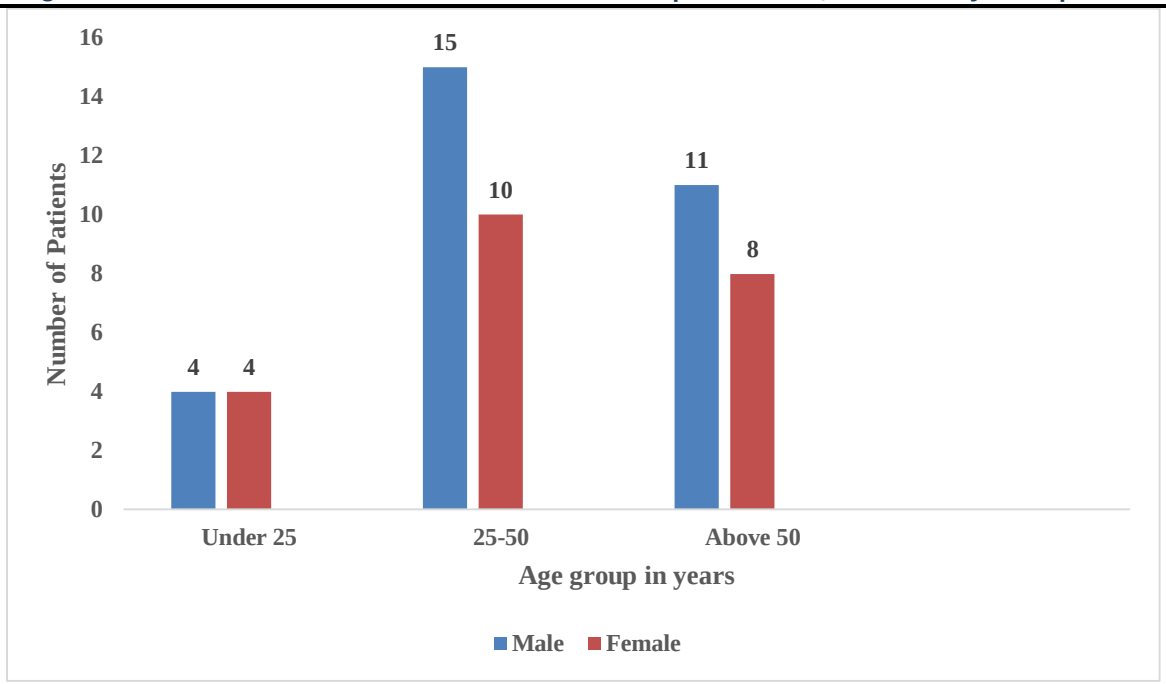

Fig 8: Graph showing relation between age group and number of patients

E. Graph showing relation between type of ulcer and number of patients

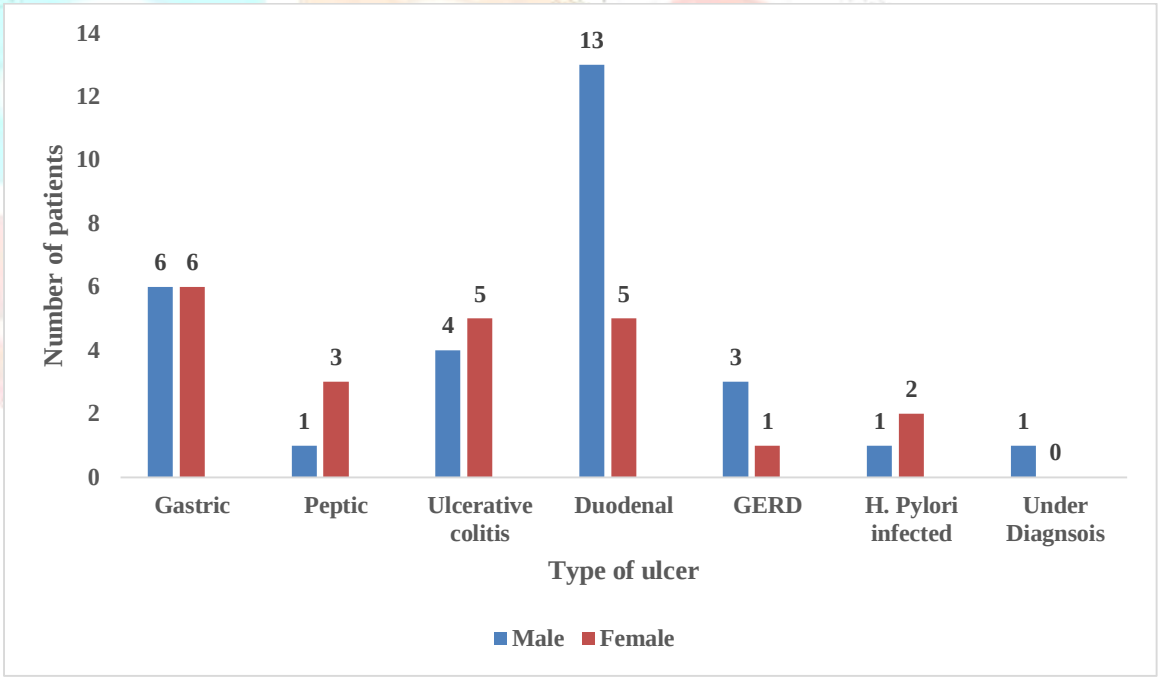

Fig 9: Graph showing relation between type of ulcer and number of patients

From the whole survey and epidemiological studies the group concludes the data as shown in above plotted pie and column graphs. The data is interpreted based on the survey done between the month of February and April, collecting it from the hospitals in Delhi NCR. We found that males are affected more by peptic ulcer and other gastric ulcers because of their lifestyle. Among various types of GI ulcers duodenal ulcer is most common. Patients prescribed with suppositories were complaining about the rectal irritation. Most of the common symptoms for diagnostic purpose are bloody stool, gastric irritation, vomiting and gastric pain. About 90% of the patients are satisfied with their treatment. Many of the counseled patients were also following alternative therapy specially the older generation relied more on the herbal approach. On an average more than 60 % patients complained about some inconvenience like reflux gastric irritation, vomiting, nausea, GIT

pain, flatulence and others. As per the conclusion group made there is no ADR reported by the 52 counseled patients though we founds that reflux gastric pain, flatulence and nausea-vomiting are possible adverse events.

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