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Review Article

Recent Advances In Clinical Evaluation Of Antiulcer Drug

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ABSTRACT

Ulcers, particularly peptic ulcers, have long been a significant medical concern, with potential complications ranging from discomfort to life-threatening hemorrhage. Over the years, numerous antiulcer agents have been developed and introduced into clinical practice, aiming to alleviate symptoms, promote healing, and prevent recurrence. This review delves into the recent advancements in the clinical evaluation of these agents, highlighting the methodologies employed, the efficacy observed, and the safety profiles established. Recent studies have emphasized the importance of a multifaceted approach to the clinical evaluation of antiulcer agents. Beyond merely assessing symptomatic relief, researchers now focus on mechanisms of action, pharmacokinetics, and pharmacodynamics to provide a comprehensive understanding of drug efficacy. Advanced imaging techniques, such as endoscopy and capsule endoscopy, have enabled real-time visualization of ulcer healing, facilitating a more precise assessment of therapeutic outcomes. Safety remains paramount in the evaluation of antiulcer agents, with recent research focusing on the identification and mitigation of adverse effects, drug interactions, and long-term complications. The integration of patient-reported outcomes and quality-of-life assessments has further enriched our understanding of the overall impact of antiulcer therapy on patient well-being.

INTRODUCTION

Peptic ulcer disease (PUD) still carries a large financial burden and has a high rate of morbidity and death, despite a recent decline in prevalence [1]. Ulcers are open sores of the skin or mucous membrane that are characterized by sloughing of inflammatory dead tissue. [2] Ulcers are superficial lesions on the skin's surface or mucous membranes that are characterized by a loss of tissue. Ulcers are most commonly found on the skin of the lower limbs and in the gastrointestinal tract, though they can appear almost anywhere. Mouth, esophageal, peptic, and vaginal ulcers are only a few of the several kinds of ulcers. Of these, many people experience peptic ulcers The erosion of the stomach lining, or duodenum, is the cause

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of peptic ulcers.[3] The true causes of peptic ulcers have been found to be bacterial infections (Helicobacter pylori) or reactions to medications, especially nonsteroidal anti-inflammatory medicines (NSAIDS). Although they have been shown to be exacerbating factors alone, spicy food and stress were once thought to be the main causes of peptic ulcers. [4] Anxiety, dyspepsia, and, in extreme circumstances, death are among the symptoms of gastrointestinal (GIT) disease, a disorder that is of extreme concern to humans. Peptic ulcers are one of the disorders of the GIT.[5] An imbalance between the stomach's mucosal defensive and aggressive features is thought to be the primary cause of peptic ulcers.[6] Bloody stools, severe stomach pain, cramps, and blood in the vomit are all indications of peptic ulcers that can occasionally be fatal.[7] Sloughing of inflammatory, dead tissue is a characteristic of ulcers, which are mucous membranes. A gastric ulcer would produce epigastric pain during a meal because it increases the production of gastric acid as food enters the stomach. The symptoms of duodenal ulcers are initially relieved by eating because the pyloric sphincter tightens to concentrate the stomach contents, preventing acid from reaching the duodenum.[8] Peptic ulcers have been treated with a variety of traditional pharmaceutical drugs, such as anticholinergics, proton pump inhibitors, antacids, and histamine H2receptor antagonists; however, these drugs have a number of unfavorable side effects. since they are believed to have less adverse effects and to be more easily accessible, affordable, and plantibased, alternative medicines have gained popularity in recent years [9]

Classification:

1. Reduction of gastric acid secretion
2. a. H2 antihistamines

eg.Cimetidine, Ranitidine, Famotidine

b. Proton pump inhibitors

eg .Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rubberize, Dexrabeprazole

c. Anticholinergic drugs

eg.Pirenzepine, Propantheline

d. Prostaglandin analogue:

eg.Misoprostol

3. Neutralization of gastric acid (Antacids)

a. Systemic:

eg.Sodium bicarbonate, Sodium Citrate

b. Non systemic:

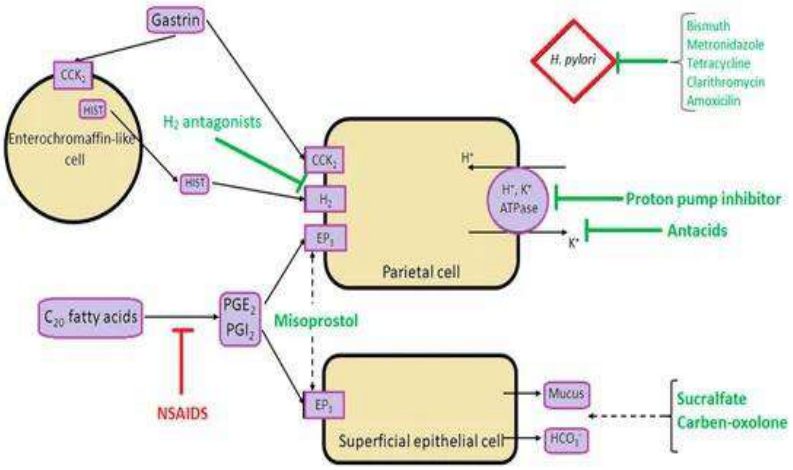
eg. Magnesium hydroxide, Mag, trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

4. Ulcer protectives (drugs that protect the mucosa):

eg. Colloidal bismuth subcitrate (CBS)

5. Anti-H. pylori drugs :

eg. Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline



Target therapy:

1. H. pyroli

For many years prior to the discovery of H.pylori, ulcer patients were often treated with acid-suppressive drugs because ulcers were known to recur. Ever since the proverb "no acid, no ulcer" was first introduced, medical treatments for post-puberty ulcer disease have centred on the release of stomach acid and mucosal defensive mechanisms.[10] After H. pylori has been detected, the typical first-line treatment is a proton pump inhibitor (PPI) plus two antibiotics, such as metronidazole and clarithromycin, administered for seven to fourteen days (triple therapy) or with bismuth/tetracycline (quadruple therapy)[11,12,13].Therapy was nearly never effective for patients with H. pylori infections who were resistant to clarithromycin. [15, 14] The main reason for H. pylori elimination failure is antibiotic resistance, yet certain conditions including acidic pH and production of biofilm greatly diminish the effectiveness of many antimicrobial drug treatments. There are well-established mechanisms associated with antimicrobial resistance, and these mechanisms also apply to H. pylori. The only medications that work against Helicobacter pylori are clarithromycin, tetracycline, rifabutin, levofloxacin, norfloxacin, amoxicillin, and metronidazole. The fact that metronidazole and clarithromycin resistance is rising is concerning. It is now known that two or more antimicrobials must be taken for a duration of 14 days in order to treat H. pylori effectively. Additionally, an antisecretory medication to decrease gastric secretion must be used. Drug susceptibility testing helps determine the best course of treatment for antibiotics by identifying susceptible patients. [16, 17, 18,] It's unclear exactly how H. pylori causes various disorders in the mucosa of the stomach. To determine the type of peptic ulcer, one can use the H. pylori infection, which can cause either hyperchlorhydria or hypochlorhydria. The principal mediators of Helicobacter pylori infection are cytokines that block parietal cell secretion; however, H. pylori can also directly impact the H+/K+ ATPase subunit, activate sensory neurons linked to somatostatin and calcitonin gene-related peptide (CGRP), or prevent the production of gastrin [19].

2. NSAIDs Induced Mucosal Damage

Abuse of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, aspirin, and indomethacin, has been related to gastric ulcers. Models of NSAID-induced stomach ulcers in rats have been created utilizing this phenomenon. The model's correlation with gastric acid secretion and mucosal prostaglandin formation in the underlying pathophysiology makes it important to investigate potential advantages of anti-secretory and cytoprotective medications. This ulcer model is the most commonly used in antiulcer research The second most common cause of peptic ulcers, after those brought on by Helicobacter pylori, is NSAID-induced peptic ulcers. This could be the reason they are prescribed so often.[20] One of the medications that is most frequently administered worldwide, NSAIDs, significantly raises the risk of upper gastrointestinal problems.[21] The mechanism of damage to the gastroduodenal mucosa caused by NSAIDs is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is involved in prostaglandin synthesis and is linked to decreased mucosal blood flow, low mucus and bicarbonate secretion, and inhibition of cell proliferation. The enzyme is reversibly and concentration-dependently inhibited by NSAIDs. Exogenous prostaglandins and cyclooxygenase-2 (COX-2) selective NSAIDs might be used together to lessen mucosal injury.[22] By binding permanently to the gastric parietal cells' hydrogen/potassium ATPase enzyme, The method of action lowers the formation of acid in the stomach. A PPI combined with an NSAID that is specific for COX-2

provides the best protection against complications resulting from peptic ulcers.[23] It is widely recognized that by blocking prostaglandin synthase, NSAIDs cause ulcers, an enzyme involved in the cyclooxygenase cycle.[24]A non-selective JAK inhibitor was recently granted a European license for the treatment of adult patients with moderate to severe active UC who either lost responsiveness to biologic medicines or conventional therapy, or who were intolerant of them. [25].

3. LT02

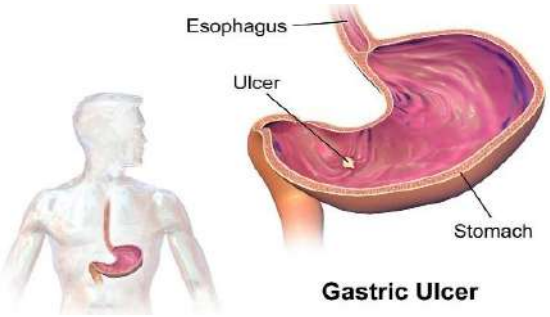
The distal ileum's release of phospholipids was pH-dependent. The major outcomes, clinical remission and clinical response, were significantly improved when compared to placebo, in addition to the marked improvement of endoscopic and histological testing. MH was never formally examined, though. The study examined mucosal barrier augmentation in ulcerative colitis (UC) using LT-02, a new modified-release phosphatidylcholine drug. [26] Treating moderate-to-severe ulcerative colitis with inhibitors of the JAK-STAT pathway is an intriguing and promising therapeutic approach. The primary benefit of oral JAK inhibitors is their ability to suppress various cytokines and decrease immunogenicity. When the medicine is given orally, injection-related side effects such as bleeding, hematomas, or infections are avoided, and the pain of injections is also avoided.[27]

4. Pylorus-Ligation method (Shay's Method)

Ulcers arise from ligation of the pylorus, and this model can be used to evaluate the extent to which medications affect stomach secretions. The pyloric end of the stomach produces an accumulation of gastric acid in the stomach, which causes ulcers to become clogged. The gastric mucosal barrier is weakened by the autodigestion of the stomach mucosa, which results in these ulcers. Put another way, increased acid-pepsin accumulation caused on by pylorus constriction may cause mucosal digesting. The model can be used to evaluate the effects of anti-secretory drugs, which reduce the stomach's known to be aggressive secretions of pepsin and acid. Additionally, the model can be used to assess the cytoprotective benefits of drugs that encourage release of mucus. The animals undergo a 36–72 hour starvation period prior to having their stomachs bound.[28] One of the review's goals was to showcase some medicinal plants that have been demonstrated to have strong antibacterial and antioxidant properties against H. pylori and peptic ulcer illness. However, as resistant strains of H. pylori multiply, some plants become less effective against them. Therefore, it is advised to separate various components from the plant extracts with the highest level of activity. [29] After centrifugation, the stomach content's volume was determined, Both Toppfer's reagent and phenolphthalein were used as indicators while titrating with 0.01 N NaOH to measure the acidity of the solution.[30]. Estimates were also made of the percentage inhibition (PI) of ulcer formation.[31]

$$PI = \frac{\text{UI of the control group} - \text{UI of the treatment group}}{\text{UI of the control group}} \times 100.$$

Signs and symptoms



Gastric Ulcer

- Strong correlations between mealtimes and abdominal pain, which is traditionally epigastric.
- bloating and a full stomach; in the event of a duodenal ulcer, the pain usually manifests three hours after eating and causes the sufferer to awaken;

- waterbrash, a surge of saliva that occurs during a regurgitation episode and is more commonly linked to gastric reflux illness;
- intense vomiting and nausea;
- Anorexia and weight loss due to stomach ulcers
- weight increase when eating to relieve discomfort from a duodenal ulcer;
- Hematemesis, or blood vomiting, which can result from severe or persistent vomiting-related oesophageal injury or direct bleeding from a stomach ulcer.
- A stomach or duodenal perforation can occasionally result from an ulcer and cause rapid peritonitis and excruciating, stabbing pain.
- Melena is a condition marked by tarry; foul-smelling stools caused by oxidized iron from hemoglobin.33]
- Suspicion for peptic ulcers may increase with a a history of medication use and heartburn or gastroesophageal reflux disease (GERD). Most glucocorticoids, such as prednisolone and dexamethasone, are used as treatments for peptic ulcers. and NSAIDs (non-steroidal anti-inflammatory medications) that block cyclooxygenase. (Reference needed)

Complication (medicine) :

Age, health, immunological system condition, and degree of susceptibility are some of the variables that affect the development of problems. Preventive measures and treatment planning are made possible by being aware of the most frequent and serious side effects of an illness, surgery, or treatment. Seizures, or aftereffects that follow the acute (first, most severe) event, should not be confused with complications [33].

List of withdrawn drugs :

1. The medication Alatrofloxacin major hepatotoxicity that requires a liver transplant or results in death.[34]

2. Due to a rare but severe case of hepatotoxicity, Alidem (Ananxyl) was taken off the market in 1995. (35)

3. PROWESS-SHOCK trial indicates that dotrecogin alfa (Xigris) is ineffective [36].
4. Risk of suicide and severe depression after using Rimonabant (Acomplia) [37]

5. Zantac (ranitidine) has been shown to spontaneously decompose into the carcinogen N-nitroso dimethylamine [38].

6. Amezolidine Peril of hypersensitive reaction, hepatotoxicity, and Guillain-Barré syndrome [39]

Commonly used antiulcer drugs :

Clinical trials phases :

In order to gather enough data for a therapy to be recognized as an effective medical treatment, scientists test it utilizing health interventions during the clinical research phases After the drug's safety has been shown in a limited number of human patients—possibly tens of thousands—it will be possible to assess the efficacy of the treatment a large number of study volunteers are eventually included in the clinical phases of drug development. Clinical research focuses on novel medical devices, therapeutic candidates, immunization candidates, and diagnostic instruments. Clinical investigations examining potential medicinal goods are frequently categorized using phases. It usually takes several years to finish the four steps in the drug development process. Where it is specifically mentioned, such as in "Phase I" clinical studies research, the phase of the study is capitalized in both the name and the Roman numeral. A drug that successfully completes Phases I, II, and III is often authorized for use in the general public by the national regulatory organization. Phase IV clinical studies monitor a drug's safety over a period of years by "surveillance" or "post-marketing" investigations.[40]

Preclinical studies :

A potential medication, immunization, apparatus, or diagnostic test is first investigated in-depth in preclinical investigations before moving forward with clinical trials. Several dosages of the study drug are used in vivo (animal model) as well as in vitro (test tube or cell culture) settings in these investigations to get preliminary data on the pharmacokinetics, toxicity, and efficacy of the agent. These tests allow the inventor to assess if a promising medicine has enough support from science to advance its development as an experimental innovative drug.[40]

Clinical study phases

- Phase 0
- Phase I
- Phase II
- Phase III

1. **Phase 0**

Federal Drug Administration (FDA) of the United States published recommendations in 2006 for optional exploratory investigations that are conducted in accordance with the criteria; these studies may now be referred to as phase0.[41] In order to determine as quickly as feasible whether a medication or imaging agent behaves in human volunteers in a manner consistent with preclinical investigations, human microdosing studies also known as Phase 0 trials aim to accelerate the development of therapeutic compounds or prescription medications that show promise. Phase 0 investigations involve administering a single subtherapeutic dose of the study medicine to a limited number of participants (10 to 15) in order to collect preliminary data on the pharmacokinetics of the agent (i.e., how the body processes the medications) [42]. Since a Phase 0 study's dose is by definition too low to produce any therapeutic effect, it cannot provide information on safety or efficacy. In order to move forward with further development, drug research companies conduct phase 0 studies to identify new drug candidates and determine which have the best pharmacokinetic properties in people. They make it possible to make decisions about whether or not to move forward based on pertinent human models rather than erratic animal data [.43]

1. **Phase I**

In the field, phase I trials were referred to by the gender-neutral phrase "first-in-humans" prior up to the 1990s, as opposed to "first-in-man studies"[44]. These studies constitute the initial phase of experimentation on humans.45] Its goal is to assess the drug's safety, efficacy, suitable dosage, and preparation method. [46] Phase I studies may have selection bias because they are not randomised.[47] Generally, 20–100 fits individuals will be selected as a small sample. [48] Many times, these trials take place at an institute for clinical trials where full-time professionals can keep an eye on the participants. These Clinics for clinical trials are frequently managed by contract research organizations, for the benefit of pharmaceutical companies or other investigators. (citation Needed) The patient taking the medicine is frequently seen after several pharmacological half-lives. The evaluation of a drug's pharmacovigilance, safety, tolerability, pharmacokinetics, and pharmacodynamics is the goal of this step. Phase I studies usually incorporate dosage varying, sometimes termed investigations of dosage escalation , to identify the optimal and optimum dosage for safety as well as the occasion at which a medication is too hazardous to use [.49] Most of the time, The range of dosages under investigation is a portion [measure]of the dosage that resulted in injury to the test animals. Generally, phase I trials involve healthy people. In certain circumstances, however, such as when a patient has HIV or is nearing the end of their cancer therapy and the medication could make healthy people ill, clinical patients are used. Typically, these investigations are carried out in tight-knit establishments dubbed Central Pharmacological Units, where patients receive round-the-clock medical care in addition to oversight Another subset of the sick population previously described is "patients who have typically already tried and failed to improve on the existing standard therapies" [50]. may additionally participate in Phase I investigations. In return in exchange for their time at the community service facility, contributors receive a variable disturbance charge. Before initiating a Phase I study the organizer is required to give in to the FDA an Investigational New medication application describing the initial information about the medicine collected via investigations on animals and biological prototypes.(Reference required)

Phase II

Once a dose or spectrum of dosages has been determined the medication's potential for

Biomedical Function or effect is analyzed Phase II research is carried out. on bigger populations (between 50 and 300 people) with the aim of evaluating The effectiveness of the medication and extending Phase I security evaluations in a more extensive cohort of patients and volunteers. Testing for genes is often done, especially when there is verification of an a physiological difference.[50] If a novel medicine fails its Phase II trials due to toxic side effects or unpredictable side effects, the drug's development process is usually abandoned. (citation needed).

There are occasions when Phase II investigations are separated into Phase IIa and Phase IIb. These two subcategories lack a specific definition, yet generally speaking:

- Studies classified as "dose finding" in Phase IIa are often pilot projects aimed at determining the ideal dosage and evaluating safety.[51]
- Phase IIb research, sometimes known as "evidence of the idea," trials, evaluate the drug's effectiveness in humans by measuring its dosage-dependent pharmacokinetics.[51]

Phase III

The evaluation phase is designed to determine the new intervention's performance and, consequently, its efficacy in the field of medicine. Phase III investigations are large patient groups (300–3,000 or more, dependant on the disease/medical issue examined) randomization supervised worldwide trials designed to be the final determination of the effectiveness of a medication relative to the "gold standard" medication presently in use. Phase III clinical studies are extremely time-consuming, expensive, and complex to plan and conduct due to their scale and very long duration, particularly in treatments for long-term medical disorders. In comparison to the length of time that the therapy would be utilized in practice, phase III trials for chronic illnesses or diseases sometimes feature a short follow-up interval for completion.[50This stage is additionally referred to as the "prior to marketing phase" since it gauges how the medication is received by consumers.[citation needed] Some Phase III studies are typically carried out even though the governing filing is being processed by the relevant regulatory body. This permits people to get possibly curative drugs until they can buy the medication. Additional motivations at this stage for carrying out experiments, such as those funded by sponsors attempts at "label expansion" (demonstrating that the medication works for people with conditions other than the ones For that reason, it had been originally allowed for distribution), gathering further security information, or bolstering medication marketing declares. Some companies undertake inquiry into this phase that they classify as "Phase IIIB studies."[52] While not always necessary, it is generally expected that a medicine will require the completion of at least two successful Phase III studies to prove its safety and effectiveness and receive clearance from the relevant regulatory bodies, such as the European Medicines Agency (EMA) or the US Food and medicine Administration (FDA).A medicine's Phase III trial results are typically integrated into a lengthy A record that contains specifics about the manufacturing procedures, composition details, duration of storage, and the methods and results of investigations on humans and animals, once the drug has proven satisfactory. The "regulatory submission" that is forwarded to the appropriate authorities for assessment is composed of this compilation of data [53]. across various nations. Once the submission has been reviewed, they will grant the sponsor permission to market the medication. With the right advice and guidance and a completed New Drug Application (NDA) that includes every information pertaining to production, preliminary testing, and clinical the majority of medications undertaking Clinical

studies in phase III can be commercialized according to the FDA regulations. The medications need to be taken off the market right away if any negative effects are being documented anywhere. A large number of medications are in Phase III clinical trials within the industry., however most pharmaceutical corporations avoid doing this.[54]

FUTURE PERSPECTIVE :

A futures perspective in the clinical evaluation of anti-ulcer drugs involves considering potential developments and challenges in the field. This includes anticipating advancements in drug discovery, exploring innovative treatment modalities, and addressing emerging issues such as drug resistance or long-term efficacy. Additionally, incorporating patient-centric approaches and personalized medicine concepts may play a crucial role in shaping the future of anti-ulcer drug evaluation, tailoring treatments to individual needs for improved outcomes. The future of anti-ulcer drugs holds promise with ongoing advancements. Researchers are exploring novel therapeutic targets, such as mucosal protection mechanisms and microbiome modulation, aiming to enhance drug efficacy and reduce side effects. Additionally, personalized medicine approaches may evolve, considering individual genetic factors and unique patient profiles for optimized treatment outcomes. The integration of innovative drug delivery systems, like nanotechnology, could also revolutionize how anti-ulcer drugs are administered, improving bioavailability and patient compliance. Overall, a futuristic outlook involves a multifaceted approach, combining scientific breakthroughs, personalized care, and advanced drug delivery for more effective ulcer management. The future of clinical trials is poised for transformation with several key trends. Decentralized clinical trials, leveraging digital technologies and remote monitoring, are likely to become more prevalent, enhancing patient participation and reducing logistical challenges. Advances in biomarkers and personalized medicine may enable more targeted and efficient trial designs, leading to better treatment outcomes. Incorporating real-world evidence and artificial intelligence into trial methodologies could streamline processes and accelerate drug development. Ethical considerations and participant engagement may also gain increased emphasis, ensuring trials are not only scientifically rigorous but also ethically sound and patient-centric. Overall, the future of clinical trials involves embracing technology, tailoring approaches, and fostering collaboration for more effective and inclusive research. The future perspective of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) involves ongoing research and development aimed at improving efficacy and minimizing side effects. Scientists are exploring selective NSAIDs that target specific inflammatory pathways, potentially reducing detrimental impacts on the digestive system. Nanotechnology and medicines delivery innovations may lead to more controlled and targeted release, enhancing the therapeutic benefits while minimizing systemic impact. Moreover, future NSAID development might focus on personalized medicine approaches, considering individual patient factors to tailor treatment regimens. Researchers are also investigating the potential of combining NSAIDs with other agents, such as antioxidants or gastroprotective agents, to enhance overall safety and effectiveness. As the field advances, a more nuanced understanding of NSAID pharmacology and its impact on various tissues is likely to shape the the creation of the following century anti-inflammatory medicines

CONCLUSION:

The recent advancements in the clinical evaluation of antiulcer drugs signify a transformative phase in the management of gastrointestinal disorders.

Through rigorous research methodologies, including advanced imaging techniques and comprehensive outcome assessments, our understanding of these drugs' efficacy, safety profiles, and therapeutic potentials has been significantly enriched. The introduction of novel therapeutic targets and formulations underscores the dynamic landscape of antiulcer therapy, offering clinicians a broader spectrum of treatment options tailored to individual patient needs. Comparative studies have further elucidated the relative merits and limitations of traditional versus newer agents, facilitating evidence-based decision-making in clinical practice. Looking ahead, ongoing research initiatives and collaborative efforts among clinicians, researchers, and pharmaceutical stakeholders hold the promise of continued innovation in antiulcer drug development and evaluation. By addressing existing gaps in knowledge and embracing emerging technologies, the field is poised to redefine standards of care, optimize therapeutic outcomes, and ultimately enhance the quality of life for individuals affected by peptic and other gastrointestinal ulcers.

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