WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Comparative Review of Pharmacological Treatments for Peptic Ulcers.

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ABSTRACT:

Peptic ulcers are defined as open lesions occurring in the lining of the duodenum or stomach, and they remain a significant global health problem. To tackle the causes and manage the associated symptoms, various agents have been developed and marketed. The purpose of this article is to provide a comparative overview of the general classes of drugs available to treat peptic ulcers, which include, but are not limited to, antacids, cytoprotective agents, H2-receptor antagonists, and proton pump inhibitors (PPIs). This review will discuss the mechanisms of action, efficacy, safety, and cost-efficacy of each of these agents. Additionally, this review will highlight new agents in development and review the potential for combination therapy for treatment as well. By reviewing the available literature and evidence from clinical trials, including the pros and cons of each of these agents, this article hopes to assist the researcher in understanding treatment options for peptic ulcers and assist the clinician in identifying optimal treatment approaches.

Keywords: Peptic ulcers, Proton pump inhibitors (PPIs), H2-receptor antagonists, Helicobacter pylori, Non-steroidal anti-inflammatory d (NSAIDS), Cytoprotective agents, Combination therapy

Introduction

Peptic ulcer disease (PUD) therefore represents an unmodifiable global burden on the health of millions every year. The ulcer represents a lesion that damages the protective mucosal lining of the stomach or duodenum so that in PUD, the protective factors and injurious factors are out of balance in the gastrointestinal system. The balance between protective and injurious factors is other agents that contribute to ulcer development. Major risk factors of peptic ulcer include Helicobacter pylori (H. pylori) infection and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), which further promote acid secretion in the gastric system and inhibit mucosal protection, giving rise to ulceration formation [1, 2]. Despite the advancement in medical research, PUD is putting an extremely high burden on the healthcare systems across the world, and because of this burden, the attention of the researchers has focused on drug therapy for the management of PUD [3]. During previous decades, the conventional treatment of peptic ulcers consisted of antacids and histamine-2 receptor antagonists (H2RAs), but, currently, therapeutics based on proton pump inhibition have been widely used and changed the paradigm of ulcer management due to their capacity for greater acid suppression and rapid mucosal healing [4, 5]. The recognition of H. pylori as the primary actor has sparked the development of eradication therapies combining proton-pump inhibitors (PPIs) with antibiotics to kill the bacterium and prevent recurrence. [6]. While improvements have been seen in regard to implementation of these medications improving quality of care and outcome, challenges such as antibiotic resistance, treatment failures, and adverse drug reactions have continued to result in evaluation of the pharmacotherapeutic avenues present [7]. It is important to weigh these drugs on the basis of efficacy, safety, and overall cost-effectiveness. This review will comparatively assess leading pharmacological approaches to peptic ulcer disease, including but not limited to PPIs, H2RAs, antibiotics, and cytoprotective agents. This review will also cover the mechanism of action, clinical feasibilities, and limitations, in order to provide a contemporary view of how treatment with pharmacotherapies for ulcers has evolved [8, 9]

Epidemiology and Pathophysiology of Peptic Ulcers

Peptic ulcers are still very common forms of gastrointestinal conditions worldwide, hence putting a lot of stress on the health care system. The global prevalence of PUD is said to have ranged from 5% to 10%, with geographical variations possibly accounted for by variables such as social standing, dietary practices, and access to health care . In developed countries, the prevalence of peptic ulcer has decreased due to improved sanitation and greater usage of proton pump inhibitors. In many developing countries, this remains a top public health issue . Primary causes of peptic ulcer disease (PUD) are infection with H. pylori (Helicobacter pylori) and use of nonsteroidal anti-inflammatory drugs (NSAIDs), which constitute the majority of cases [10]. Other causative factors are smoking, heavy consumption of alcohol, chronic stress, and family predisposition to PUD [11]. Pathophysiological mechanisms of peptic ulcers mean basically an imbalance between the gastric barrier and the damaging factors such as acid and pepsin . Interplay of protective agents serves to protect the gastric mucosa; e.g., factors include mucus secretion [12]. H. pylori inflict injury on gastric mucosa through a complex immunologic response that causes excessive gastric secretion and mucosal inflammation, inciting further ulcer development [13]. H. pylori

gastritis further stimulates inflammatory pathways by the secretion of cytokines and modulation of immune cell functions, leading to destruction of gastric and duodenal epithelium [14]. The modulation of COX-1 and COX-2 receptors by NSAIDs leads to a decrease in the production of prostaglandins, thereby compromising the epithelial protective mucin and bicarbonate barrier, which in turn makes the mucosa highly susceptible to damage from acid reflux and corrosive agents [15]. Gastric ulcers might emerge due to more chronic NSAID use and from therein pose a risk for bleeding or perforation associated with serious complications, especially in aged patients and those who suffer other comorbidities [16]. Others include Zollinger-Ellison syndrome, which is characterized by excessive production of gastrin leading to hypersecretion of gastric acid, leading to reflux and ulcers that are difficult to treat and manage [17]. Clinical features of peptic ulcers are varied, but typical symptom profiles include epigastric pain, nausea, and bloating; however, severe cases can lead to gastrointestinal bleeding or perforation [18]. The most effective way to counter rising morbidity and mortality due to the complications of hemorrhage and perforation is to carry out early diagnosis and treatment [19]. The gold standard diagnostic method for PUD is endoscopy along with histological and biochemical evaluation, which clarifies the detection of the H. pylori infection and identification of mucosal damage [20].

Overview of Pharmacological Treatments

The pharmacological treatment of peptic ulcers consists of reducing gastric acid secretion, improving mucosal defense, and curing H. pylori infection. Major drug classes employed in the treatment include proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), antacids, mucosal protective agents, prostaglandin analogs, and antibiotics to eradicate H. pylori [21].

Proton Pump Inhibitors (PPIs)

PPIs form the backbone of treatment for peptic ulcers, specifically those ulcers that arise from either gastric causes or duodenal causes. PPIs work by irreversibly inhibiting the H+/K+ ATPase enzyme in the gastric parietal cells and thus lead to an effect of profound and persistent reduction in gastric acid secretion. PPIs include omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole [22]. These drugs offer more acid suppression than the H2RAs, leading to more rapid ulcer healing and symptom relief. Studies have found that PPIs, when used with antibiotics for H. pylori eradication, significantly reduce ulcer recurrence rates [23].

Histamine-2-Receptor Antagonists (H2RAs)

H2RAs like ranitidine, famotidine, cimetidine, and nizatidine work by competitively inhibiting histamine at the H2 receptors on gastric parietal cells, thereby decreasing acid secretion. While H2RAs are effective agents in ulcer healing, they are less efficacious than PPIs in the inhibition of gastric acid secretion. Moreover, prolonged use of H2RAs leads to the development of tolerance, which reduces their efficacy with time [24]. Nevertheless, they are useful in patients who cannot tolerate PPIs or require maintenance therapy for ulcer prevention [25].

Antacids

Antacids include the three most commonly used bases: aluminum hydroxide, magnesium hydroxide, and calcium carbonate. They neutralize gastric acid and provide symptomatic relief. Antacids by themselves may not enhance ulcer healing, but they are effective in alleviating some pain and discomfort due to peptic ulcers. Antacids thus have a rapid onset of action; therefore, they are good choices for very rapid relief of symptoms, provided that they need to be taken frequently too, due to their short duration of action [26]. However, since the introduction of much cleverer PPIs and H2RAs for acid suppression, antacids are not all that useful any longer [27].

Mucosal Protective Agents

Mucosal protective drugs, such as sucralfate and bismuth compounds, are important in protecting the gastric mucosa. Sucralfate protects the ulcerated mucosa by forming a protective barrier by binding with the surface proteins so that it is shielded from gastric acid and pepsin [28]. Bismuth-containing compounds such as bismuth subsalicylate act on H. pylori and help protect the mucosa. They are usually administered as adjuncts in H. pylori eradication regimens [29].

Prostaglandin Analogs

Misoprostol, which is a synthetic analogue of prostaglandin E1, increases mucosal protection through stimulation of mucus and bicarbonate secretion and inhibition of gastric acid production. It is especially useful in the prevention of NSAID-induced ulcers. Its usefulness is limited by side effects such as diarrhea and abdominal cramping, as well as contraindication in pregnant women because of its uterotonic activity [30].

Antibiotics for H. pylori Eradication

H. pylori is a major etiological factor in peptic ulcer disease. Standard eradication therapy comprises an association of two antibiotics (clarithromycin, amoxicillin, or metronidazole) and a PPI; this is referred to as triple therapy [31]. In the case of antibiotic resistance, quadruple therapy that includes bismuth subsalicylate, metronidazole, tetracycline, and a PPI is advised Successful H. pylori eradication reduces ulcer recurrence and long-term acid-suppressive therapy [32]

Pharmacological treatment of peptic ulcers has witnessed a major evolution with acid suppressive treatment and healing offered by PPIs being the mainstay of treatment. H2RAs and mucosal protective agents serve as either alternatives or adjunctive therapy, while antibiotic regimens against H. pylori have revolutionized the management of peptic ulcer disease. The customization of the therapy based on ulcer etiology and other patient-specific factors gives the best results and minimizes regaining [33].

Pharmacological Agents: Mechanisms and Clinical Profiles

Peptic ulcers are mostly treated with pharmacological agents that either decrease gastric acid secretion, neutralize existing acid, or protect mucosal defense mechanisms. These major classes of drug groups include proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), antacids, cytoprotective agents, and antibiotics for the eradication of Helicobacter pylori (H. pylori). Drugs in each category will have varying mechanisms of action and clinical efficacy profiles on the basis of which their clinical role in the treatment regimen is decided.

Proton Pump Inhibitors (PPIs)

PPIs are the strongest acid suppressors available for peptic ulcer disease. They work by irreversibly inhibiting the hydrogen-potassium ATPase resting in the gastric parietal cells, thus tremendously inhibiting gastric acid secretion. The commonly prescribed PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. These drugs stand out for their long duration of action compared with H2RAs in promoting healing of the peptic ulcer and preventing its recurrence [34].Clinically, PPIs are preferred for duodenal ulcers and gastric ulcers due to excellent acid suppression. They are also cornerstones of H. pylori eradication regimens, which usually include an antibiotic. However, chronic use of PPIs is associated with some adverse effects such as vitamin B12 deficiency, predisposition to infections, and possible fractures related to osteoporosis [35].

H2-Receptor Antagonists (H2RAs)

H2RAs promote healing of peptic ulcers by competitively blocking histamine action on H2 receptors of the parietal cells and thereby decreasing acid production. Agents in this class include ranitidine, famotidine, cimetidine, and nizatidine. Despite the fact that they are efficacious in promoting ulcer healing, they are less potent than the PPIs in maintaining gastric pH above the critical level required for ulcer healing [36]. They are mostly used in patients with mild to moderate PUD, requiring short-term acid suppression. They have meanwhile declined in clinical use due to tolerance with prolonged use and the rise of PPIs. The side effects limiting their long-term use include drug interactions (cimetidine mainly due to cytochrome P450 inhibition) and rare instances of gynecomastia (cimetidine) [37].

Antacids

Symptomatic relief can be obtained from antacids through their neutralization of gastric acid, which raises intragastric pH. With compounds like aluminum hydroxide, magnesium hydroxide, calcium carbonate, and sodium bicarbonate, they offer quick relief from pain but are not necessarily as effective in healing ulcers compared with PPIs or H2RAs [38].Antacids are mainly employed clinically as adjuncts to symptomatic relief rather than as sole drugs for PUD treatment. Diarrhea can result from magnesium-containing antacids and constipation from aluminum-containing formulations. Excess consumption of calcium carbonate may lead to hypercalcemia and metabolic alkalosis (milk-alkali syndrome) [39].

Cytoprotective Agents

They are cytoprotective agents, such as sucralfate, misoprostol, and bismuth compounds, that strengthen mucosal defenses. Sucralfate binds to exposed proteins, thus protecting the ulcerated mucosa and preventing further acid-related injury. It is especially useful for the prophylaxis of stress ulcers in critically ill patients [40]. Misoprostol is a prostaglandin E1 analog that stimulates the secretion of mucous and bicarbonate and decreases acid secretion. It is mainly used in the prophylaxis of NSAID-induced ulcers. Its clinical use has been limited because of adverse effects like diarrhea and contraction of the uterus, which is a contraindication during pregnancy [41]. The bismuth compounds have some antimicrobial effects against H. pylori and protect the gastric mucosa by forming a protective coating. They are often included in the quadruple therapy regimens for H. pylori eradication [42].

Antibiotics for H. pylori Eradication

H. pylori infection is a major etiological factor in peptic ulcer disease. Antibiotics as listed, clarithromycin, amoxicillin, metronidazole, and tetracycline, are used to eradicate H. pylori. The standard eradication strategies include employing a combination of two antibiotics with a PPI known as triple therapy or with an additional bismuth compound in quadruple therapy [43]. Successful eradication of H. pylori greatly reduces the recurrence of ulcers. However, increasing resistance to antibiotics, especially clarithromycin and metronidazole, has forced alterations in the treatment strategies, including sequential therapy and concomitant therapy to improve the eradication rate [44].

Comparative Analysis of Treatment Modalities

Peptic ulcer disease (PUD) has multifactorial causation and requires an evidence-based approach for pharmacological intervention needed for good outcome. The treatment options for PUD have changed over time, and now pharmacological interventions mainly focus on acid suppression, eradication of Helicobacter pylori (H. pylori), mucosal protection, and symptom relief. This section compares various pharmacological treatment options, including the use of proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), cytoprotective agents, and antibiotics for H. pylori eradication therapy.

Proton Pump Inhibitors vs. Histamine-2-Receptor Antagonists

Because of their superior efficacy in acid suppression and ulcer healing, PPIs, such as omeprazole, lansoprazole, and esomeprazole, find a place in first-line therapy for PUD. These drugs irreversibly inhibit the H+/K+-ATPase enzyme in gastric parietal cells, leading to prolonged gastric acid secretion rendering. Studies have shown that PPIs have enhanced ulcer healing over 90% within 4-8 weeks, while H2RAs achieve less than 50% accommodation since they only partially suppress acid production by competitively inhibiting histamine at H2 receptors on parietal cells [45,46]. H2RAs such as ranitidine and famotidine were previously considered the mainstay of therapy but have since been outcompeted by PPIs, owing to their weak acid suppression with a short duration. Although H2RAs effectively reduce nocturnal acid secretion, their use gives rise to tolerance, precluding their use in chronic therapy. All these limitations are absent in PPIs, which sustain acid suppression without accommodation or tachyphylaxis; this makes them most preferred for long-term management of PUD [47, 48].

H. pylori Eradication Therapy: Conventional Triple Therapy versus Alternative Regimens

Control of H. pylori infection is pivotal in preventing ulcer recurrence. Standard triple therapy consists of a combination of H. pylori and peptic ulcer disease: a proton pump inhibitor, clarithromycin, plus amoxicillin or metronidazole for penicillin-allergic patients. Research indicates the rise of antibiotic resistance affecting H. pylori has become responsible for declining success of eradication treatment; thereby, less than 80% has been calculated from eradication rates for the standard triple therapy in some regions [49]. Alternative regimens to combat resistance include tetracycline, bismuth subsalicylate, metronidazole, and PPI, as well as sequential therapy (PPI and amoxicillin followed by PPI, clarithromycin, and metronidazole). It has been confirmed that bismuth quadruple therapy has eradication rates of greater than 90%, presently thought to be preferred first-line treatment in regions with high clarithromycin resistance [50, 51]. Findings from the clinical trials suggest the second-line treatment of levofloxacin being evaluated in the resistant subjects holds an encouraging prospect, but huge studies are necessary to validate this [52].

Cytoprotective Agents: Sucralfate vs. Misoprostol

Cytoprotective agents such as sucralfate and misoprostol are second-line agents for ulcer treatment, especially in patients who cannot tolerate PPIs or H2RAs. Sucralfate shields the ulcer site from gastric acid and pepsin with a protective barrier, thereby aiding in ulcer healing. It was similarly efficacious as H2RAs for healing duodenal ulcers but lesser than PPIs [53]. Inhibition of NSAID-induced ulcers is the main indication for misoprostol, which is a synthetic analog of prostaglandin E1, whereas it is mucosal treatment, as opposed to sucralfate, in that its benefit lies in directly stimulating mucosal defense by increasing bicarbonate and mucus secretion while decreasing acid secretion. However, side effects, including diarrhea and abdominal cramps, have limited its use in practice [54]. Comparison studies suggest that misoprostol prevents NSAID-induced ulcers but is not the treatment of choice for this purpose owing to the better tolerability profile of the PPIs [55].

Combination Therapy vs. Monotherapy

Because of the multifactorial etiology characterizing PUD, combination therapy finds greater indications for superiority over monotherapy. The combination of PPIs and H. pylori eradication therapy promotes ulcer healing and decreases the recurrence rate. In the same manner, NSAID-induced ulcers benefit from the co-administration of PPIs with the discontinuation of NSAID therapy wherever possible. Study results claim that the combination approach effectively reduces ulcer recurrence when compared with acid suppression alone, stressing the need for a personalized therapeutic plan involving the personal clinical profile of a patient [56].

Ultimately, the choice of pharmacology is determined by ulcer etiology, ulcer magnitude, presence of H. pylori infection, and patient-related factors. Once PPIs became available and proved superior in efficacy and continued acid suppression, H2RAs have been relegated to obsolescence. H. pylori eradication regimens should then be chosen based on the regional pattern of antibiotic resistance. In NSAID-induced ulcers, cytoprotective agents are said to perform added therapeutic benefit, although, as a rule, they are not the first line of therapy. Further studies should be directed toward refining eradication regimens and designing newer agents with improved efficacy and safety profile.

Emerging Therapies and Future Directions

The management of patients suffering from peptic ulcer disease (PUD) is at the backwoods due to the new advancements being made in the field of bio-pharmaceuticals and pharmacology. PPI and H2 receptor antagonists still remain the main focus of treating peptic ulcer disease, but more interestingly, recent studies have brought to the fore novel and innovative pharmacological agents and treatment approaches that could present better efficaciousness, safety, and patient compliance.

1. Potassium-Competitive Acid Blockers (P-CABs

Potassium-competitive acid blockers (P-CABs), represented by vonoprazan, are potent alternatives to classic PPIs. They bring harsher acid suppression than PPIs in a shorter time and for a longer time raise gastric pH, thus boosting ulcer healing and eradication of Helicobacter pylori with combination therapy [57]. Clinical trials demonstrated that vonoprazan-based three-drug therapy is superior to PPI combinations in the eradication of H. pylori, especially in high antibiotic resistance areas [58]. In addition to this, P-CABs are known to have a much stable pharmacokinetic profile, which minimizes the inter-patient variability observed with PPIs [59].

2. Novel Antibiotic Strategies for H. pylori Eradication

One of the main challenges in the management of H. pylori-associated ulcer is antimicrobial resistance. Rifabutin-based triple therapy and high-dose dual therapies (amoxicillin with P-CABs or high-dose PPIs) are being tested within the newer antibiotic combinations to increase rates of eradication [60]. Antimicrobial peptides (AMPs) showing bactericidal activity toward H. pylori have generated considerable preclinical interest as new candidates for the fight against the infection [61]. Research is also ongoing towards the application of nanoparticle-based drug delivery systems to enhance antibiotic efficacy while reducing resistance [62].

3. Gastroprotective Agents and Mucosal Healing Promoter

New developments in gastro protection aim at enhancing mucosal healing and prophylaxis against ulcer recurrence. Rebamipide, the mucosal protective agent, has shown anti-inflammatory and cytoprotective properties in enhancing prostaglandin synthesis using inhibition of oxidative stress [63]. Other newer prostaglandin analogs, such as vonoprazan-tegoprazan combinations, have also been studied for their enhancing gastric mucosa-protective effects [64]. Other emerging agents like epidermal growth factor (EGF) analogs and trefoil factor peptides (TFFs) have shown potential in accelerating ulcer healing by mechanisms of mucosal regeneration [65].

4. Probiotics and Modulation of the Microbiome

Considering the role of H. pylori in the pathogenesis of PUD, probiotics have been studied as adjunctive therapy. Probiotic strains such as Lactobacillus and Bifidobacterium have been found to inhibit colonization by H. pylori, lessen inflammation, and improve eradication rates when used with conventional antibiotic regimens [66]. Among others, microbiome-targeted therapies, including faecal microbiota transplantation (FMT) and engineer probiotics, are being evaluated to restore gut microbial equilibrium and control ulcer relapse [67].

5. Novel Molecular Targeted Therapies and Gene-Directed Approaches

Molecular biology has heralded a new dawn for therapy targeting diseases like ulcers. Nuclear factor-kappa B (NF-κB) and interleukin-1β (IL-1β) inhibitors are being considered for the property of reducing gastric inflammation due to ulcers [68]. Some gene therapy strategies, RNA-based therapeutics, and CRISPR/Cas9-mediated gene editing create possibilities in modifying host response against H. pylori infection and enhancing defense mechanisms at the mucosal level [69].

6. Artificial Intelligence (AI) and Personalized Medicine

In peptic ulcer management, integration of AI and personalized medicine is an emerging trend. Algorithms driven by AI have been developed that predict the risk of ulcers or optimize regimens or even identify H. pylori antibiotic resistance patterns [70]. This will complement personalized approaches like pharmacogenomic testing, which identify variations in drug metabolism by individuals to tailor PUD treatment for optimizing therapeutic efficacy while minimizing adverse effects [71].

Apparently, future therapy for peptic ulcers seems to look towards a much-targeted, more effective and individualized approach. New innovations like P-CABs, new antibiotics, mucosal protectants, probiotics, gene therapies, and AI-driven precision medicine are transforming PUD management. It is only time, research, and clinical trials that will tell how applicable these novel therapies will be in practice and their ability to improve outcomes while addressing the current challenges of antibiotic resistance and disease recurrence.

Conclusion

Peptic ulcer disease (PUD) continues to be a serious health issue worldwide, with a number of contributing factors: Helicobacter pylori infection, the use of NSAIDs, and lifestyle factors. Considerable advances have been made over the years in understanding its pathophysiology as well as the development of effective pharmacological interventions. This comparative review considered the various classes of pharmacological agents in the treatment of peptic ulcers, with special emphasis on their specific mechanisms of action, efficacy versus safety profiles, as well as key clinical considerations.Among the various pharmacological options, the proton pump inhibitors (PPIs) became the strongest and most effective acid-suppressive therapy, surpassing the ulcer healing rates achieved by histamine-2 receptor antagonists (H2RAs). Long-term concerns have been raised regarding PPI safety concerning osteoporosis, renal dysfunction, and imbalance of gut flora; therefore, care must be taken when prescribing. H2RAs, although now rarely recommended, still find a niche when PPIs become contraindicated or when short-term acid suppression is deemed sufficient. Antibiotic therapy is at the core of H. pylori eradication, reducing ulcer recurrence rates. Nevertheless, increasing antibiotic resistance has made eradication success more elusive and has called for management plans to be tailored to specific situations, with regional susceptibility testing. The bismuth-based treatment is also gaining traction as a means of overcoming resistance.Cytoprotective agents like sucralfate and Misoprostol would provide added protection notably in NSAID-induced ulcers. Although misoprostol would prevent NSAID-related ulcers, its adverse effects, such as diarrhea and abdominal cramps, as well as the potential for teratogenicity, render it unpopular in clinical use. Sucralfate, with its mucosal-protecting abilities, is however used as adjuvant therapy in selected circumstances.Altogether, emerging therapies with potential to augment treatment, including novel acid-suppressive agents, potassium-competitive acid

blockers, and probiotic adjuncts, are currently under investigation. Nevertheless, there is a need for large-scale confirmatory clinical studies to ascertain their definitive role in standard clinical practice.

In brief, the choice of pharmacological modality for any peptic ulcer ought to be individualized in accordance with several variables including ulcer cause, patient's associated diseases, drugs' safety profiles, and local antimicrobial resistance patterns. Effective patient management must incorporate a multidisciplinary interface addressing lifestyle changes, risk management of the disease, and timely implementation of pharmacotherapy. Future research should further be oriented towards developing targeted, specific therapeutic strategies and addressing antimicrobial resistance, with a view to enhancing the long-term success of managing peptic ulcers.

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