International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 05-05-2025, Accepted: 06-06-2025, Published: 20-06-2025
Volume 10, Issue 1, 2025, Page No. 42-47

Updated drugs used in the treatment of pathogenic intestinal protozoa in the world

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Abstract
This study was conducted to identify the latest pharmacological agents available for the chemotherapy of pathogenic protozoa affecting the human intestine, specifically targeting Entamoeba histolytica and Cryptosporidium parvum. For the treatment of amoebiasis caused by E. histolytica, modern drugs include diloxanide furoate, iodoquinol (diiodohydroxyquin), and paromomycin, which are primarily used to eliminate intestinal cysts in the lumen. Metronidazole, tinidazole, and nitazoxanide are employed to eradicate tissue trophozoites of E. histolytica. For amebic liver abscesses or extraintestinal infections, the recommended drugs are paromomycin, metronidazole, emetine, and chloroquine. In pregnant women with amoebiasis, treatment should involve a tissue amebicide such as metronidazole, followed by a luminal agent like paromomycin after the first trimester, or second-line agents such as diloxanide furoate or iodoquinol.
The current treatment options for G. lamblia include a range of anti-giardial drugs such as 5-nitroimidazole compounds, including tinidazole, secnidazole, and metronidazole. Benzimidazole derivatives like mebendazole and albendazole, as well as acridine derivatives, nitrothiazolide, quinacrine, nitrofuran derivatives, nitazoxanide, furazolidone, and paromomycin, are also utilized, particularly during pregnancy. For C. parvum, updated treatment options include paromomycin and nitazoxanide, along with protease inhibitors. The aim of this study is to identify and assess the newly developed drugs available for the chemotherapy of intestinal protozoan parasites, enhancing treatment strategies against these infections.

Keywords: Intestinal protozoa metronidazole paromomycin nitazoxanide entamoeba histolytica

Introduction

Intestinal protozoa are parasitic organisms that inhabit the host's intestine, deriving nutrition from the host and resulting in pathological symptoms [1, 2]. Most protozoa are non-pathogenic, known as commensals, causing only mild disease. However, pathogenic forms such as Giardia lamblia, Entamoeba histolytica, and Cryptosporidium parvum are responsible for severe diseases or infections in the human intestinal tract [4]. These infections are highly prevalent in impoverished and socioeconomically disadvantaged communities in tropical and subtropical regions, posing significant global health challenges, particularly among children in developing countries [3, 4].
Transmission of G. lamblia, E. histolytica, and C. parvum typically occurs via the fecal-oral route [3], with contaminated water and food being the most common vectors [4]. The life cycle of these microbes begins with the ingestion of cysts or viable forms in the case of E. histolytica and G. lamblia, and through the infectious oocyst phase for C. parvum [5].
Motile trophozoites and sporozoites are released from cysts and oocytes, respectively, in the small intestine. Giardia lamblia and Cryptosporidium spp. typically remain confined to the bowel without disseminating hematogenously. In most patients, they persist as benign parasites in the large intestine [6]. However, in some cases, Entamoeba histolytica has the capacity to invade the intestinal mucosa, resulting in symptomatic colitis, or to penetrate the bloodstream, leading to the formation of distant abscesses in organs such as the liver, brain, or lungs [5, 6].
Following encystation, oocytes and infectious cysts are excreted in the stool and can remain viable for several weeks in moist environments [6]. The predominant mode of infection is characterized by asymptomatic cyst passage, while symptomatic colitis typically develops within 1 to 6 weeks post-ingestion. [5, 6]. Initial symptoms include mild diarrhea and lower abdominal pain, progressing to weight loss, discomfort, and diffuse lower abdominal pain [4, 6].
Clinical symptoms typically appear 2-3 weeks post-infection, including foul-smelling watery diarrhea, nausea, anorexia, flatulence, fat-soluble vitamin deficiency, and abdominal cramps. The parasite's mechanical interference with absorption, coating the intestinal mucosa, results in malabsorption of fat, known as steatorrhea, common in chronic G. lamblia cases [5].
Antigen detection by ELISA, stool culture, and PCR are highly sensitive and accurate methods for investigating E. histolytica infection [7]. Modern nucleic acid amplification tests (NAATs) are commonly used for diagnosing giardiasis and cryptosporidiosis [6].

1. Treatment of Asymptomatic Amoebiasis patients

All individuals who test positive for Entamoeba histolytica but remain asymptomatic should undergo targeted treatment to mitigate the risk of transmitting the infection to others and the wider community [10]. Luminal agents are primarily indicated for the elimination of cysts in patients suffering from colitis or hepatic abscesses, as well as for treating asymptomatic carriers. These agents are successful in clearing cysts in approximately 80–90% of treated cases [6,

[11]. The most effective luminal agents include diloxanide furoate—administered at 500 mg orally three times a day with meals for 10 days; iodoquinol—given at 650 mg orally three times a day for 21 days; and paromomycin—at a dosage of 30 mg/kg of base orally (up to a maximum of 3 g), divided into three doses taken after meals daily for 7 days [9].

Paromomycin sulfate, an aminoglycoside antibiotic, exhibits minimal systemic absorption owing to its high solubility as inorganic acid salts and is predominantly excreted unchanged via glomerular filtration [10]. However, in cases of renal insufficiency, accumulation may occur, potentially leading to nephrotoxicity [11]. Comparative studies indicate that paromomycin demonstrates similar efficacy to other luminal agents but with a more favorable toxicity profile; notably, one study identified its superior efficacy over diloxanide furoate in clearing asymptomatic infections [10, 11]. Due to its availability and safety profile, paromomycin is considered the preferred luminal anti-amebic agent [9, 10]. Its precise mechanism of action remains incompletely elucidated; reported adverse effects include gastrointestinal discomfort and diarrhea [10].

Iodoquinol, a halogenated hydroxyquinoline, predominantly remains within the intestinal lumen—approximately 90%—and is excreted in feces, with the residual entering systemic circulation, where it has a half-life of 11–14 hours and is eliminated via urinary glucuronidation [8, 10]. Historically, over five decades ago, diiodohydroxyquinoline was characterized as an iron chelator, sequestering iron from trophozoites and thereby inhibiting their proliferation [12]. Adverse effects are infrequent but may include diarrhea, anorexia, nausea, vomiting, abdominal pain, headache, rash, and pruritus [8]. To mitigate gastrointestinal toxicity, iodoquinol should be administered concomitantly with meals [10]. Prolonged use of halogenated hydroxyquinolines carries a risk of neurotoxicity, including optic neuropathy; therefore, caution is advised in patients with pre-existing optic nerve pathology, renal or thyroid disease, or non-amebic hepatic disease [8, 15].

The mechanism of action of diloxanide remains incompletely understood [15]. Discontinuation of therapy is recommended if persistent diarrhea or signs of iodine toxicity—such as dermatitis, urticaria, pruritus, or fever—develop [13]. It is contraindicated in individuals with iodine intolerance [10]. Diloxanide furoate is administered orally, hydrolyzed in the gastrointestinal tract to produce diloxanide, which is the active metabolite detected systemically [13, 10]. It is primarily excreted in urine as glucuronide conjugates [13]. Serious adverse effects are rare; common side effects include flatulence, while nausea, abdominal cramps, and rashes are less frequently observed [9, 10].

2. Treatments of Symptomatic Amoebiasis patients

Treatment of amebiasis involves two main pharmacological classes: tissue amebicides and intraluminal amebicides. Patients presenting with mild-to-moderate intestinal symptoms, severe intestinal involvement, or extraintestinal disease should initially receive a tissue amebicide, followed by a course of intraluminal therapy to eradicate residual cysts [16]. Symptomatic amebic colitis mandates combined therapy with both a tissue amebicide and an intraluminal agent [9].

Tissue amebicides include tinidazole—administered at 2 g orally once daily for 3–5 days; metronidazole—750 mg orally three times daily for 10 days; and nitazoxanide—1–2 g orally [9, 17]. Nitroimidazoles with extended half-lives, such as tinidazole, secnidazole, and ornidazole, allow for once-daily dosing, are generally better tolerated, and often lead to more rapid clinical improvement with fewer adverse effects compared to metronidazole. Despite these advantages, metronidazole remains the cornerstone of amebiasis treatment due to its well-established efficacy and cost-effectiveness [9, 18, 19].

Both metronidazole and tinidazole are efficiently absorbed following oral administration and exhibit extensive tissue distribution through passive diffusion [10]. Tinidazole undergoes hepatic metabolism to produce two primary metabolites, with the hydroxy metabolite having a half-life of approximately 12 hours and exhibiting roughly 50% of the antitrichomonal activity of metronidazole. The reduced metabolites are generated by gut flora, and some patients may notice a reddish-brown discoloration of urine, attributed to unidentified pigments derived from the drug [10, 20].

Metronidazole functions as a prodrug that requires reductive activation of its nitro group within susceptible organisms [10]. Anaerobic and microaerophilic pathogens—including Trichomonas vaginalis, Entamoeba histolytica, and Giardia lamblia—possess electron transport components with sufficiently negative redox potentials to facilitate this reduction [13].

Further reduction leads to the formation of reactive oxygen species (ROS), such as hydrogen peroxide and hydroxyl radicals, which inflict oxidative damage on critical cellular components—including DNA, proteins, and membranes—culminating in parasite death [13, 20].

The metabolism of metronidazole is modulated by hepatic cytochrome P450 enzymes; inducers like phenobarbital accelerate its clearance, whereas inhibitors such as cimetidine prolong its plasma half-life [26]. Common adverse effects include a disulfiram-like reaction characterized by nausea and vomiting when co-administered with alcohol, along with nausea, dry mouth, headache, dizziness, vertigo, paresthesia, and, rarely, neurotoxicity manifesting as encephalopathy or seizures—necessitating discontinuation [13, 20, 26].

Nitazoxanide (NTZ), a nitrothiazolyl-salicylamide derivative, exhibits broad-spectrum antiparasitic and antimicrobial activity, effective against protozoa, helminths, and anaerobic bacteria [22]. Following oral administration, NTZ is rapidly hydrolyzed to its active metabolite, tizoxanide (TIZ), which undergoes conjugation to form tizoxanide glucuronide [14]. It demonstrates excellent bioavailability, with excretion via urine, bile, and feces [21]. As a prodrug, NTZ is metabolized into TIZ, which undergoes a four-electron reduction of the 5-nitro group, generating short-lived intermediates, including hydroxylamine derivatives—suggesting a mechanism similar to metronidazole, though not identical [14, 21, 22]. NTZ is believed to inhibit pyruvate ferredoxin oxidoreductase, disrupting parasite bioenergetics [8, 22]. Unlike metronidazole and tinidazole, NTZ and TIZ do not fragment DNA and are considered non-mutagenic [14, 22].

Adverse effects of nitazoxanide are infrequent; a notable side effect includes a benign greenish discoloration of urine. While parasitic cysts persist in the intestine in

approximately 40–60% of patients treated with nitroimidazoles, subsequent therapy with paromomycin or second-line agents such as diloxanide furoate is necessary to achieve luminal cure [21, 23]. In cases of fulminant amebic colitis, broad-spectrum antibiotics may be employed to address secondary bacterial infections, and surgical intervention may be warranted in instances of acute abdomen, gastrointestinal hemorrhage, or toxic megacolon [23].

3. Treatment of Extraintestinal Amoebiasis Infections

Extraintestinal manifestations of amebiasis are infrequent, occurring in less than 1% of cases, with hepatic abscesses being the predominant form. The right hepatic lobe is primarily affected due to the portal circulation from the colon [9]. The standard treatment for an amebic liver abscess involves administering metronidazole for 5 to 10 days, followed by a luminal agent such as paromomycin to eliminate residual intestinal cysts [25]. If the response to metronidazole or tinidazole is inadequate, alternative agents like chloroquine, emetine, or dehydroemetine should be considered [9].

Chloroquine is utilized in treating amebic liver abscesses due to its ability to eradicate trophozoites within hepatic lesions. It is rapidly absorbed from the gastrointestinal tract, leading to a large volume of distribution and significant tissue accumulation, including in erythrocytes, liver, spleen, kidneys, lungs, melanin-containing tissues, and leukocytes [26]. Higher doses may cause adverse effects such as gastrointestinal disturbances, pruritus, headaches, and visual disturbances like blurred vision. Importantly, chloroquine can prolong the QT interval, so concurrent use with other QT-prolonging agents should be avoided when possible [26].

Emetine, an alkaloid from ipecac, and its synthetic analog, dehydroemetine, effectively target tissue trophozoites of E. histolytica. Dehydroemetine is generally preferred due to its relatively favorable toxicity profile [10, 30]. These agents should be administered for the shortest duration necessary to alleviate severe symptoms, typically 3 to 5 days, via subcutaneous or intramuscular injection under strict medical supervision [10]. They act as protoplasmic poisons, inhibiting protein synthesis in both protozoal and mammalian cells by disrupting protein elongation [2, 10]. While primarily used for symptomatic relief in intestinal amebiasis, with a cure rate of only 10–15%, they are most effective when combined with other antiamoebic agents to enhance overall efficacy [27].

4. Treatment of Amoebiasis During Pregnancy

Nitroimidazoles, including metronidazole and tinidazole, are contraindicated during the first trimester of pregnancy due to potential risks [24, 25]. Metronidazole readily crosses the placental barrier, and its effects on fetal development remain inadequately characterized, necessitating caution [24]. In pregnant women, the preferred treatment for amebiasis is paromomycin, administered at a dose of 25 to 35 mg/kg/day, divided into three doses over 5 to 10 days [25]. As an aminoglycoside, paromomycin exhibits poor systemic absorption from the gastrointestinal tract and has an excellent safety profile, making it suitable for use during pregnancy [24].

5. Resistance of Drugs in Amoebiasis

To date, clinical isolates of Entamoeba histolytica have not demonstrated resistance to metronidazole, and no cases of drug-resistant amoebiasis have been reported in *vivo*. However, resistance to metronidazole has been documented in *vitro* (25). Clinical evidence suggests that combination therapy involving nitroimidazoles and luminal amoebicides results in a lower rate of parasitological failure compared to metronidazole monotherapy (28). A comprehensive overview of all available treatment regimens for amoebiasis is provided in Table 1.

Table 1: Treatments of all types of Amoebiasis According to_____ protocol(reference).

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic Intestinal Infection	Luminal agents include diloxanide furoate, administered at 250 mg orally three times daily for 10 days; iodoquinol, at 650 mg orally three times daily for 21 days; or paromomycin, at 10 mg/kg orally three times daily for 7 days.	
Mild to Moderate Intestinal Infection	Metronidazole is administered at 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days. Alternatively, tinidazole can be given at 2 g orally daily for 3 days, in conjunction with a luminal agent (as previously described).	A luminal agent (as previously mentioned) can be combined with either tetracycline, administered at 250 mg orally three times daily for 10 days, or erythromycin, at 500 mg orally four times daily for 10 days.
Severe Intestinal Infection	Metronidazole is administered at 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days. Alternatively, tinidazole can be given at 2 g orally daily for 5 days, in conjunction with a luminal agent (as previously described).	A luminal agent (as previously mentioned) may be combined with either tetracycline, administered at 250 mg orally three times daily for 10 days, or dehydroemetine or emetine, at 1 mg/kg subcutaneously or intramuscularly for 3–5 days.
Hepatic or Abscess, Amoeboma, and Other Extraintestinal Disease	Metronidazole is administered at 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days. Alternatively, tinidazole can be given at 2 g orally daily for 5 days, in conjunction with a luminal agent (as previously described).	Dehydroemetine or emetine is administered at 1 mg/kg subcutaneously or intramuscularly for 8–10 days, followed by chloroquine at 500 mg orally twice daily for 2 days, then 500 mg daily for 21 days, in conjunction with a luminal agent (as previously described).

Treatment of Cryptosporidiosis patients

The management of *cryptosporidiosis* poses a notable clinical challenge, as no pharmacological agent has shown definitive efficacy. However, some studies indicate modest therapeutic benefits [32]. In immunocompetent individuals,

Cryptosporidium infections are typically self-limiting, with symptomatic treatment using antidiarrheal agents often being adequate [33]. Nevertheless, factors such as co-infections, physiological stress, advanced age, and malnutrition can temporarily weaken immune function, extending the duration of symptoms [32, 33]. Additionally, the infectious dose and virulence of the specific *Cryptosporidium* strain can affect both the severity and persistence of the disease. Therefore, in cases of persistent or severe infection, targeted anti-*Cryptosporidium* therapy becomes essential [32].

Current literature identifies several pharmacological options, including *paromomycin* and *nitazoxanide*. The latter, approved by the U.S. Food and Drug Administration (FDA) for this indication, is administered in doses ranging from 500 mg to 1 g orally twice daily for three days in immunocompetent patients, and for extended periods of 2 to 8 weeks in immunocompromised individuals, particularly those with advanced AIDS [32]. *Paromomycin*, a non-absorbable aminoglycoside, is typically prescribed at doses of 25–35 mg/kg orally for 14 days [32].

Proteases play a crucial role in various stages of the *Cryptosporidium* life cycle, and protease inhibitors (PIs) have shown inhibitory effects against the parasite. Several small-scale, open-label studies have demonstrated that immune reconstitution in AIDS patients with chronic *Cryptosporidium*-induced diarrhea often leads to rapid symptomatic improvement and eventual cessation of fecal parasite shedding [38]. A large-scale, multicenter study involving nearly 7,000 patients across Europe and Australia reported a 96% reduction in cryptosporidiosis incidence following the integration of protease inhibitors into combined antiretroviral therapy [39].

Pharmacokinetic considerations indicate that high-fat meals can significantly reduce the bioavailability of certain PIs, such as *indinavir*, while others remain largely unaffected. Protease inhibitors are extensively bound to plasma proteins, undergo significant hepatic metabolism, and are minimally excreted unchanged in the urine. Common adverse effects include gastrointestinal disturbances—such as nausea, vomiting, and diarrhea—and metabolic complications like impaired glucose regulation, diabetes mellitus, hypertriglyceridemia, and hypercholesterolemia [26, 39]. Chronic administration is also associated with lipodystrophic syndromes characterized by peripheral fat loss, central adiposity (notably abdominal and dorsocervical "buffalo hump" fat accumulation), and gynecomastia [26].

1. Treatment in immunocompromised patients

The effectiveness of *nitazoxanide* in treating *cryptosporidiosis* among HIV-infected individuals remains uncertain. A significant study revealed that an intensified regimen of *nitazoxanide*—500 mg administered twice daily for seven days—achieved parasitological clearance or reduced oocyst shedding by more than 95% in over 50% of AIDS patients [32, 34]. In a subsequent pediatric cohort with AIDS and cryptosporidiosis, the same dosing regimen was employed, but outcomes were suboptimal in malnourished children, with no significant clinical improvement. Retreatment with an additional three days of open-label *nitazoxanide* resulted in symptomatic relief in approximately 77% of these children, with parasitological clearance observed in 25% of those who initially failed therapy [35].

Higher doses and prolonged treatment durations have demonstrated greater efficacy in patients with higher CD4+ T-lymphocyte counts, suggesting potential synergism with concurrent antiretroviral therapy. Nonetheless, antiparasitic therapy alone remains insufficient for patients with advanced AIDS. In a clinical trial involving adult HIV-positive individuals with cryptosporidiosis, *nitazoxanide* administered at 500 mg to 1 g twice daily for two weeks showed superior outcomes in patients with CD4+ T-cell counts exceeding 50 cells/mm0³, whereas no benefit was observed in patients with lower counts [36].

Several case reports have highlighted successful alleviation of symptoms and elimination of parasites following extended oral combination therapy with *azithromycin* and *paromomycin*. These medications were administered at doses ranging from 25 to 35 mg/kg/day, divided into two to four doses, in patients with AIDS and those who have undergone bone marrow transplants. These dosing strategies result in drug concentrations in the intestinal lumen that slightly exceed the in *vitro* inhibitory levels for *Cryptosporidium* [34, 37]. Therefore, intensive supportive care with agents that reduce bowel motility is crucial when using *paromomycin*, with suggested doses between 500 and 900 mg/day over three weeks [37]. A prospective, open-label pilot study showed that combination therapy with *azithromycin* and *paromomycin* notably decreased oocyst shedding and stool frequency in AIDS patients, although complete eradication of the parasite was only achieved in a few cases [37, 40].

The Other uses of intestinal drugs

The drugs of pathogenic intestinal protozoa can be used in treatment of many other diseases as follow:

1. **Nitroimidazoles**

- Metronidazole is a widely utilized topical antibacterial agent in the management of rosacea. Its therapeutic efficacy is primarily attributed to its anti-inflammatory and immunosuppressive properties, which modulate the underlying inflammatory processes associated with the condition [29].
- Metronidazole has been recommended as the first-line treatment for pseudomembranous colitis induced by Clostridioides difficile, demonstrating its effectiveness in managing severe bacterial infections of the gastrointestinal tract [29, 30].
- Its also employed in the treatment of bacterial vaginosis and vulvovaginal candidiasis, highlighting its broad-spectrum antimicrobial activity in various gynecological infections [30].

2. **Antimalarial agents as chloroquine, hydroxychloroquine and quinacrine**

- In dermatology, these agents are used to manage various skin conditions, such as cutaneous lupus erythematosus, cutaneous dermatomyositis, polymorphous light eruption, porphyria cutanea tarda, and sarcoidosis. Among these, only *hydroxychloroquine* is currently FDA-approved for treating lupus erythematosus [9, 11].
- Chloroquine and hydroxychloroquine also effective a rheumatoid arthritis and Covid 19 infection [11].

3. Albendazole drug of choice in treatment of some helminthic infections such as ascariasis, trichuriasis, hydatid disease and neurocysticercosis [31].

4. Protease inhibitors approved for treatment of HIV infection [20].
5. Paromomycin is aminoglycoside antibiotic useful in treating hepatic encephalopathy [34].
6. Nitazoxanide also effective against Ascaris lumbricoides, and Enterobius vermicularis [20].
7. Ipecac syrup contain Emetin to induce emesis in cases of oral toxicity [20].

Conclusion

Protozoa that invade the human gastrointestinal system and lead to illness include Entamoeba histolytica, Giardia lamblia, and Cryptosporidium parvum. The broad-spectrum antiparasitic drug nitazoxanide has recently gained approval for the treatment of cryptosporidiosis and giardiasis in pediatric patients, marking C. parvum as the first protozoan pathogen effectively targeted by this medication. Metronidazole remains the standard and most potent therapy for invasive infections caused by E. histolytica and G. lamblia. Achieving full eradication of E. histolytica often necessitates supplementary treatment with paromomycin after using metronidazole. Conversely, instances of giardiasis that do not respond to metronidazole have been managed with alternatives like nitazoxanide, higher doses of metronidazole, or combined therapy with quinacrine. Addressing intestinal protozoan infections in immunocompromised individuals, such as those with AIDS, poses substantial challenges, as the efficacy of newer treatments like nitazoxanide remains uncertain in these groups. In settings with limited resources, the persistent health problems and mortality associated with these infections underscore the inadequacies of current therapies. Thus, comprehensive research is urgently required to elucidate parasite biology and host immune responses, which will be essential in creating more effective therapeutic and preventive solutions.

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