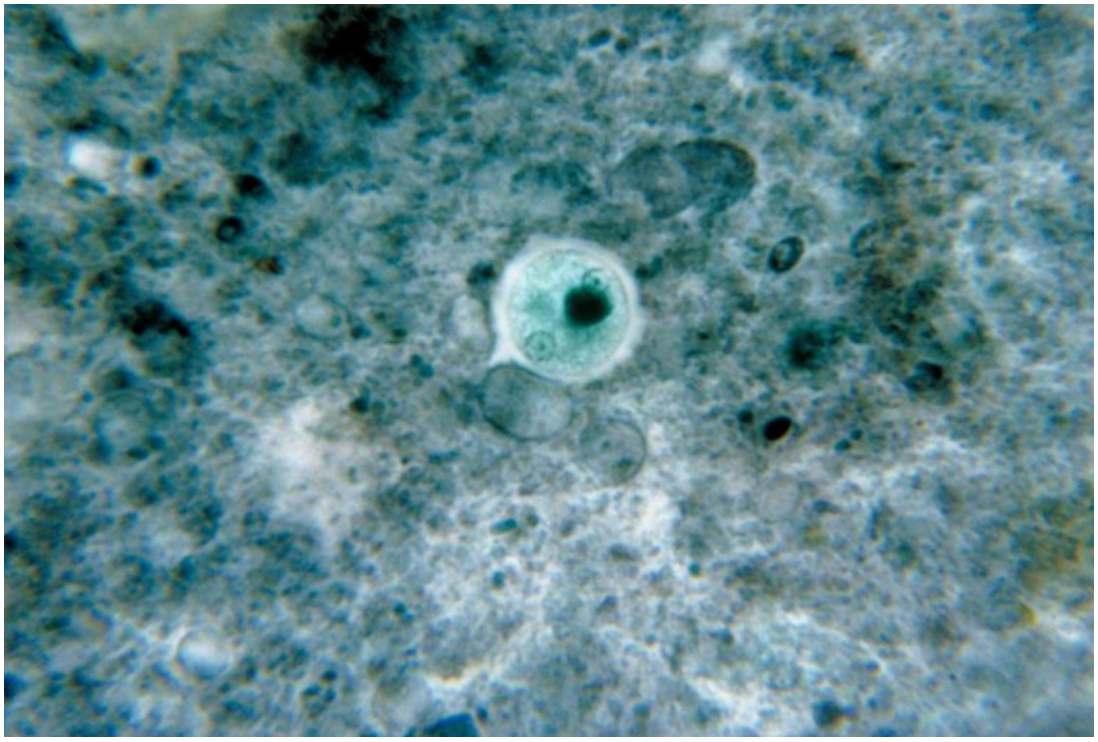
Amebicidal Drugs

See online here

Amebiasis is an infection of the colon caused by *Entamoeba histolytica*. Infection occurs through ingestion of water and food contaminated with feces (containing cysts of *E. histolytica*). In this article, we examine the various amebicides, their mechanisms of action, adverse effects/toxicity, contraindications, drug interactions, and the drugs of choice. Other important therapeutic aspects of individual drugs will also be studied.



Overview of Amebiasis

Amebiasis is an infection of the intestine caused by *Entamoeba histolytica,* a protozoan parasite. Humans and other non-human primates are the main hosts. Infection occurs through ingestion of water and food contaminated with feces. The contaminated food/water contains cysts of *E. histolytica*. It can cause extraintestinal invasive infections.

1. *E. dispar* and *E. histolytica* are the only pathogenic amoebas known to humans. The protozoan enters the digestive tract and multiplies in the terminal ileum or colon to the trophozoite stage. Trophozoite of *E. histolytica* is a motile form.

Inside the intestine, the parasite causes necrosis and perforation of the intestinal wall. It can also penetrate the intestinal wall and reach the liver via the portal vein, where it may cause a fatal liver abscess.

Cysts are excreted into the feces. The life cycle of *E. histolytica* is completed at this

stage. It can survive in the environment for weeks to months. Factors that increase the chances of amebiasis include travel to an endemic area, consumption of contaminated food/water, and anal intercourse. The infection can cause asymptomatic disease, mild to moderate intestinal cases (ulcers, dysentery), or severe or chronic cases.

Amebiasis is highly prevalent in developing countries where general sanitation standards may not be high.

The classic symptoms of amebiasis are bloody or watery diarrhea, fever (10%–30% of patients), anorexia, and weight loss. Rectal bleeding can occur without diarrhea in children. Amebiasis remains asymptomatic in most individuals and resolves on its own. Invasive infections result when *E. histolytica* reaches organs such as the liver via the systemic circulation. If the infection is limited to the intestine, it is called a non-invasive infection.

Treatment is directed at disinfecting luminal trophozoites (non-invasive infection), as well as those in the tissue (invasive infection) if the infection has spread that far. Not all drugs can disinfect the cysts of *E. histolytica*. Drugs are usually active either in the tissues or the intestinal lumen, thereby necessitating a combination therapy for symptomatic amebiasis. Patients should be educated to avoid contaminated food/water or undercooked food.

Functional and Chemical Classification of Amebicides

Tissue amebicides

- Nitro-imidazoles: metronidazole, tinidazole, etc.
- Alkaloid derivatives: emetine and dehydroemetine

Luminal amebicides

- Amide: diloxanide furoate, nitazoxanide
- 8-hydroxyquinolines: iodoquinol
- Antibiotics: tetracycline and erythromycin

Amebicidal Drugs

Tissue amebicides

Metronidazole

- A nitro-imidazole
- Selectively toxic to anaerobic microorganisms
- Half-life is 7.5 hours

Mechanism of action	The nitro-group of nitro-imidazoles undergoes bioactivation by ferredoxin (which is present only in anaerobic microorganisms) to form reactive toxic metabolites (nitro-radicals) that inhibit nucleic acid synthesis. This occurs by nitro-radicals competing with the energy metabolism pathway of anaerobic microorganisms.

Clinical uses	• **Amebiasis**: drug of choice. It kills the tissue and intestinal trophozoites; however, it is not effective against cysts of *E. histolytica*. • Also indicated for **an invasive type of amebiasis** • **Giardiasis**: drug of choice • **Trichomoniasis**: drug of choice (a single dose of 2 g) • **Pseudomembranous colitis** (caused by ***Clostridium difficile***): drug of choice • Effective against ***Helicobacter pylori***. However, this should only be used in combination with another antibiotic (e.g., amoxicillin) and a proton pump inhibitor (e.g., omeprazole). • Effective as treatment or prophylaxis of **peri- and post-operative anaerobic infections** (usually in combination with cephalosporins for a broad-spectrum coverage). • **Acute necrotizing ulcerative gingivitis** (ANUG): drug of choice (in combination with amoxycillin, tetracycline, or erythromycin)
Adverse effect/toxicity	• Nausea, vomiting, abdominal cramps, metallic taste, oral moniliasis, headache, dark urine • Rare: neurotoxicity; if it occurs, the drug should be discontinued. • Rare: opportunistic infections may occur • Resistance to nitro-imidazoles develops when the microorganisms become deficient in the pathway that generates nitro-radicals.
Drug interactions	• Alcohol should not be used during metronidazole therapy because a disulfiram-like reaction can occur. • Cimetidine can reduce metronidazole metabolism. If administered together, dose adjustment is required. • Metronidazole reduces warfarin metabolism. • Metronidazole decreases renal excretion of lithium.
Contraindications	• Blood dyscrasias • Neurological disease • Chronic alcoholism • Not contraindicated in pregnancy, but should be used with caution.

Tinidazole

Tinidazole is a 2nd-generation nitro-imidazole. Its efficacy equals that of metronidazole, but it has a shorter course of treatment (3 days vs. 10 days for metronidazole), a longer half-life (12–14 hours), and is more expensive.

Mechanism of action	Similar to metronidazole
Clinical uses	• **Amebiasis**: drug of choice along with metronidazole. However, it must be used with a luminal agent. • **Giardiasis**: drug of choice along with metronidazole • **Trichomoniasis**: can be used either as the first-line drug or in cases of metronidazole resistance • Effective against ***Helicobacter pylori***. However, this should only be used in combination (see metronidazole for details). • **ANUG**: drug of choice (in combination with amoxicillin, tetracycline, or erythromycin)
Adverse effect/toxicity	Similar to metronidazole
Drug interactions	Similar to metronidazole
Contraindications	Similar to metronidazole

Other nitro-imidazoles

- Secnidazole, ornidazole, and satranidazole
- Similar to metronidazole/tinidazole but with a longer half-life
- Satranidazole has much better tolerability (fewer side effects).

Nitazoxanide

Nitazoxanide is a new nitrothiazole antiparasitic drug and prodrug, which is converted to tizoxanide. It is effective against numerous intestinal protozoa and helminths.

Mechanism of action	Inhibits pyruvate ferredoxin oxidoreductase enzyme (PFOR), which is essential for electron transport energy metabolism in anaerobic organisms.
Clinical uses	• **Amebic dysentery** • Approved by U.S. Food and Drug Administration only for diarrhea caused by ***Cryptosporidium*** and ***Giardia intestinalis***. • Shown to be effective against many other organisms such as ***Ascaris***, ***Trichomonas vaginalis***, **tapeworms**, **several helminthic infections**, etc.
Adverse effect/toxicity	• Usually extremely well tolerated. • Gastrointestinal (GI) symptoms such as abdominal pain, nausea, vomiting, and diarrhea (dose-dependent)
Drug interactions	None documented. However, the active metabolite tizoxanide is highly protein-bound. Therefore, its use with other highly protein-bound drugs must be avoided or done with caution.

Emetine and Dehydroemetine

These drugs are rarely used because of toxicity concerns; for example, severe amebiasis when metronidazole cannot be used. They act only against trophozoites, not against the cysts. In cases of severe amebiasis, these drugs should be administered subcutaneously

or intramuscularly (and not intravenously) for at least 3–5 days.

Mechanism of action	Block ribosomal movement along mRNA
Adverse effect/toxicity	• Dose/time-dependent • GI symptoms: nausea, vomiting, diarrhea • Pain and tenderness at the injection site; muscle weakness; minor ECG changes • Severe effects involve cardiotoxicity, e.g., arrhythmias. • Dehydroemetine is somewhat better tolerated than emetine.
Contraindications	• Absolute: **cardiac disease** and **renal disease** • Relative: younger children and pregnant women

Luminal amebicides

Diloxanide furoate

- Amide
- Directly kills luminal trophozoites
- Does not kill the tissue trophozoites
- No antibacterial action
- Prodrug (releases free diloxanide as the active metabolite)

Mechanism of action	Unknown
Clinical uses	• **Asymptomatic intestinal infection** (alone) • **Amebic colitis** (in conjunction with a nitro-imidazole; can be used alone in very mild cases) • Less effective in invasive dysentery because of poor tissue amebicidal action • Although 1 course is usually sufficient, some chronic cases may require repeat courses for eradication. • Diloxanide furoate is not available in the United States.
Adverse effect/toxicity	• Usually well tolerated • Flatulence, nausea, itching • Rare: urticaria
Drug interactions	No known interactions

Iodoquinol

Iodoquinol directly kills amebic trophozoites, thereby inhibiting cyst production. It is ineffective as a tissue amebicide.

Mechanism of action	Unknown
Clinical uses	• Asymptomatic intestinal infection (alone) • Amebic colitis (in conjunction with a nitro-imidazole; can be used alone in very mild cases) • Giardiasis • Local treatment of monilial and trichomonas vaginitis
Adverse effect/toxicity	• Usually well tolerated • Nausea, transient greenish discoloration of stool, pruritus • Thyroid enlargement, possible neurotoxic effects (related to iodine after considerable systemic absorption, e.g., due to high doses)
Contraindications	• Pregnancy • Hepatic insufficiency • Hypersensitivity to iodine

Paromomycin

- Aminoglycoside
- May be superior to diloxanide in asymptomatic infection
- It is only active as a luminal amebicide.

Mechanism of action	Protein synthesis inhibitor by interacting with the 30S ribosomal subunit
Clinical uses	• **Asymptomatic intestinal infection** (alone) • **Amebic colitis** (in conjunction with a nitro-imidazole; can be used alone in very mild cases) • **Cryptosporidiosis** in AIDS patients • **Visceral leishmaniasis**
Adverse effect/toxicity	Headaches, dizziness, rashes, arthralgia (due to considerable systemic absorption, e.g., in a patient with renal insufficiency)
Contraindications	• Known hypersensitivity • Intestinal obstruction

Other antibiotics

Some antibiotics can be used in the treatment of intestinal amebiasis. Examples include erythromycin and tetracycline.

Summary of Antiamebicidal Drug Treatment

Form of amebiasis	Treatment
Asymptomatic intestinal infection	• Luminal agent (i.e., diloxanide furoate*, 500 mg 3 times daily × 10 days or • Iodoquinol, 650 mg 3 times daily × 21 days or • Paromomycin, 10 mg/kg 3 times daily × 7 days)
Amebic colitis (mild to moderate)	• Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) × 10 days or • Tinidazole, 2 g daily × 3 days plus • Luminal agent
Amebic colitis (severe)	• Metronidazole (same as above) or • Tinidazole, 2 g daily × 3 days plus • Luminal agent
Extraintestinal amebiasis	• Metronidazole (same as above) or • Tinidazole, 2 g daily × 5 days plus • Luminal agent

*Diloxanide furoate is not available in the United States.

References

Faust, D. M., & Guillen, N. (2012). Virulence and virulence factors in Entamoeba histolytica, the agent of human amoebiasis. *Microbes and Infection*, *14*(15), 1428–1441. http://doi.org/10.1016/j.micinf.2012.05.013

Fox, L. M., & Saravolatz, L. D. (2005). Nitazoxanide: A New Thiazolide Antiparasitic Agent. *Clinical Infectious Diseases*, *40*(8), 1173–1180. http://doi.org/10.1086/428839

Goessling, W., & Chung, R. T. (2002). Amebic liver abscess. *Current Treatment Options in Gastroenterology*, *5*(6), 443–449. http://doi.org/10.1007/s11938-002-0032-z

Gupta, Y. K., Gupta, M., Aneja, S., & Kohli, K. (2004). Current drug therapy of protozoal diarrhoea. *The Indian Journal of Pediatrics*, *71*(1), 55–58. http://doi.org/10.1007/bf02725657

Whalen, K. (2014). *Lippincott's Illustrated Reviews: Pharmacology* (6th ed.). Philadelphia: Lippincott Williams & Wilkins.

Katzung, B. G., & Trevor, A. J. (2014). *Basic & clinical pharmacology* (13th ed.). New York: McGraw-Hill Education.

Mcauley, J. B., & Juranek, D. D. (1992). Paromomycin in the Treatment of Mild-to-Moderate Intestinal Amebiasis. *Clinical Infectious Diseases*, *15*(3), 551–552. http://doi.org/10.1093/clind/15.3.551

Dhawan, V. K. (2017, December 6). Amebiasis. Retrieved March 14, 2018, from https://emedicine.medscape.com/article/212029-overview#showall

Stanley, S. L. (2003). Amoebiasis. *The Lancet*, *361*(9362), 1025–1034. http://doi.org/10.1016/s0140-6736(03)12830-9

Trevor, A. J., Katzung, B. G., & Masters, S. B. (2010). *Pharmacology examination & board review*(9th ed.). New York: McGraw-Hill Medical.

Tripathi, K. D. (2013). *Essentials of medical pharmacology* (7th ed.). New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.

Notes