ClinicalEvidence

Amoebic dysentery

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ABSTRACT

INTRODUCTION: Amoebic dysentery is caused by the protozoan parasite Entamoeba histolytica. It is transmitted in areas where poor sanitation allows contamination of drinking water and food with faeces. In these areas, up to 40% of people with diarrhoea may have amoebic dysentery. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of drug treatments for amoebic dysentery in endemic areas? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 6 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: diiodohydroxyquinoline (iodoquinol), diloxanide, emetine, metronidazole, nitazoxanide, ornidazole, paromomycin, secnidazole, and tinidazole.

QUESTIONS

What are the effects of drug treatments for amoebic dysentery in endemic areas?. 3

INTERVENTIONS

DRUG TREATMENTS

Likely to be beneficial

Metronidazole* 3

Secnidazole* 7

Ornidazole 8

Tinidazole* 10

Nitazoxanide 11

Unknown effectiveness

Emetine 13

Unlikely to be beneficial

Paromomycin* 13

Diloxanide* 13

Diiodohydroxyquinoline* 14

Footnote

* Categorisation based on consensus.

Key points

- Invasive infection with the parasite *Entamoeba histolytica* can be asymptomatic, or can cause diarrhoea with blood and mucus, abdominal pains, and fever.
- Amoebic dysentery is transmitted in areas where poor sanitation allows contamination of drinking water and food with faeces. In these areas, up to 40% of people with diarrhoea may have amoebic dysentery.
- Fulminant amoebic dysentery is often fatal. Other complications include perforation of the colon, colonic ulcers, amoeboma, or chronic carriage.
- Metronidazole may be less effective than tinidazole at reducing clinical symptoms, but may be as effective at clearing parasites. Metronidazole may be more likely than tinidazole to cause adverse effects such as nausea.
- Ornidazole may be effective at curing amoebic dysentery compared with placebo, but can cause nausea and vomiting.
- Secnidazole, tinidazole, and metronidazole may be as effective as ornidazole at curing amoebic dysentery.
- Nitazoxanide is likely to be more effective than placebo at reducing clinical failure. Nitazoxanide may not be more effective than placebo at preventing parasitological failure.
- We don't know whether emetine, paromomycin, diloxanide, or diiodohydroxyquinoline are effective in treating amoebic dysentery as we found no trials. However, paromomycin, diloxanide, and diiodohydroxyquinoline are luminal amoebicides and there is consensus that they have insufficient tissue penetration to be effective against invasive intestinal disease.

Clinical context

GENERAL BACKGROUND

Amoebiasis is caused by the parasite *Entamoeba histolytica*. Prevalence rates of amoebiasis are highest in developing countries in Asia, particularly the Indian subcontinent and Indonesia, sub-Saharan and tropical regions of Africa, and areas of Central and South America, although prevalence estimates are limited by a lack of studies. *E histolytica* infection can cause a spectrum of clinical symptoms, ranging from mild diarrhoea and abdominal pain to fulminant dysentery. It is estimated that only 10% to 20% of infected individuals develop symptoms. Fulminant amoebic

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dysentery is often fatal. Metronidazole is the established drug of choice for the treatment of amoebic dysentery in adults and children. Metronidazole is generally effective in treatment but has associated adverse effects and may be insufficient to fully eradicate infection.

FOCUS OF THE REVIEW

This review highlights the clinical evidence for the use of anti-amoebic therapeutic agents in the treatment of amoebic dysentery. We compare the efficacy and safety of amoebicides that penetrate the epithelium (e.g., metronidazole, tinidazole, ornidazole, secnidazole) and luminal amoebicides (e.g., paromomycin, diloxanide, diiodohydroxyquinoline) for treatment of amoebic dysentery.

COMMENTS ON EVIDENCE

The evidence for management of amoebic dysentery is generally limited by the poor methodological quality of trials, in particular in regards to randomisation and appropriate diagnostics. Randomised trials with accurate diagnostics for inclusion and standardised outcomes for clinical and parasitological failure are needed to completely compare the efficacy and safety of drug regimens for amoebic dysentery.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, April 2010, to June 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved five studies. After deduplication and removal of conference abstracts, four records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of three studies and the further review of one full publication. Of the one full article evaluated, no systematic reviews nor RCTs were included at this update.

ADDITIONAL INFORMATION

Other amoebicides that penetrate the epithelium (tinidazole, ornidazole, secnidazole) may have similar efficacy as metronidazole at reducing parasitological or clinical failure, and have fewer reported adverse effects. Luminal amoebicides (paromomycin, diloxanide, diiodohydroxyquinoline) are not recommended for treatment of symptomatic amoebic infection. There is some evidence that treatment with luminal amoebicides after treatment with a tissue amoebicide, such as metronidazole, improves eradication of surviving parasites in the colon. Therefore, luminal amoebicides may have a role in reducing parasitological failure, preventing relapse, and interrupting transmission of parasite cysts.

DEFINITION

Amoebic dysentery is caused by the protozoan parasite *Entamoeba histolytica*. Invasive intestinal parasitic infection can result in symptoms of fulminant dysentery, such as fever, chills, bloody or mucous diarrhoea, and abdominal discomfort. The dysentery can alternate with periods of constipation or remission. This review focuses on amoebic dysentery only, and includes populations with both suspected and documented disease in endemic areas where levels of infection do not exhibit wide fluctuations through time. [1] The term "amoebic dysentery" encompasses people described as having symptomatic intestinal amoebiasis, amoebic colitis, amoebic diarrhoea, or invasive intestinal amoebiasis. Extraintestinal amoebiasis (e.g., amoebic liver abscess) and asymptomatic amoebiasis are not covered.

INCIDENCE/ PREVALENCE

We found no accurate global prevalence data for *E histolytica* infection and amoebic dysentery. Estimates on the prevalence of *Entamoeba* infection range from 1% to 40% of the population in Central and South America, Africa, and Asia, and from 0.2% to 10.8% in endemic areas of developed countries such as the US. [2] [3] [4] [5] However, these estimates are difficult to interpret, mainly because infection can remain asymptomatic or go unreported, [6] and because many older reports do not distinguish *E histolytica* from the non-pathogenic, morphologically identical species *Entamoeba dispar*. Development and availability of more sophisticated methods (such as the enzyme-linked immunosorbent assay [ELISA]-based test) to differentiate the two species might give a more accurate estimate of its global prevalence. [7] Infection with *E histolytica* is a common cause of acute diarrhoea in developing countries. One survey conducted in Egypt found that 38% of people with acute diarrhoea in an outpatient clinic had amoebic dysentery. [8]

AETIOLOGY/ RISK FACTORS

Ingestion of cysts from food or water contaminated with faeces is the main route of *E histolytica* transmission. Low standards of hygiene and sanitation, particularly those related to crowding, tropical climate, contamination of food and water with faeces, and inadequate disposal of faeces, all account for the high rates of infection seen in developing countries. [9] [10] In developed countries, risk factors include communal living, oral and anal sex, compromised immune system, and migration or travel from endemic areas. [9] [11] [12]

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PROGNOSIS Amoebic dysentery may progress to amoeboma, fulminant colitis, toxic megacolon, and colonic ulcers, and may lead to perforation. [13] Amoeboma may be mistaken for colonic carcinoma or pyogenic abscess. Amoebic dysentery may also result in chronic carriage and the chronic passing of amoebic cysts. Fulminant amoebic dysentery is reported to have 55% to 88% mortality. [14] [15] It is estimated that more than 500 million people are infected with *E histolytica* worldwide. [10] Between 40,000 and 100,000 will die each year, placing this infection second to malaria in mortality caused by protozoan parasites. [16]

AIMS OF INTERVENTION To reduce the infectious period, length of illness, risks of dehydration, risks of transmission to others, and rates of severe illness; to prevent complications and death, with minimal adverse effects.

OUTCOMES **Mortality**; **complications** (i.e., amoeboma, extension to pleural cavity, chronic cyst carriage); **treatment effectiveness:** therapeutic cure (defined as absence of parasites in stools, disappearance of symptoms, and healing of ulcers); clinical failure (defined as persistence of symptoms), and parasitological failure (defined as persistence of parasites in stools or in other diagnostic tests); and **adverse effects** of treatment.

METHODS *Clinical Evidence* search and appraisal June 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2013, Embase 1980 to June 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search run by an information specialist were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including open studies, with no minimum number of participants. There was no minimum length of follow-up required for included studies, and no restriction applied based on number of withdrawals. We included systematic reviews of RCTs and RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 16). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug treatments for amoebic dysentery in endemic areas?**

OPTION **METRONIDAZOLE**

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- Metronidazole may be less effective than tinidazole at reducing clinical symptoms, but may be as effective at clearing parasites. Metronidazole may be more likely than tinidazole to cause adverse effects such as nausea.
- Metronidazole seems as effective as ornidazole at treating both clinical and parasitological signs. Both interventions exhibited similar rates of adverse effects.
- We found no direct information from RCTs about whether metronidazole is better than no active treatment. We found no clinically important results from RCTs about metronidazole compared with secnidazole, emetine, paromomycin, diloxanide, nitazoxanide, or diiodohydroxyquinoline in people with amoebic dysentery.

Benefits and harms

Metronidazole versus placebo:

We found no systematic review or RCTs.

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Metronidazole versus tinidazole:

We found one systematic review (search date 2008, 10 RCTs) comparing metronidazole versus tinidazole. [17]

Treatment effectiveness

Metronidazole compared with tinidazole Metronidazole may be less effective than tinidazole in decreasing clinical failure at 15 to 60 days after completion of treatment. However, we don't know how effective metronidazole and tinidazole are, compared with each other, at decreasing parasitological failure (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical failure					
[17] Systematic review	285 people 2 RCTs in this analysis	**Clinical failure , 1–14 days after completion of treatment** 6/132 (5%) with metronidazole 1/153 (1%) with tinidazole	RR 0.17 95% CI 0.02 to 1.30 P = 0.088	⟷	Not significant
[17] Systematic review	477 people 8 RCTs in this analysis	**Clinical failure , 15–60 days after completion of treatment** 48/229 (21%) with metronidazole 13/248 (5%) with tinidazole	RR 0.28 95% CI 0.15 to 0.51 P less than or equal to 0.001	●●○	tinidazole
Parasitological failure					
[17] Systematic review	285 people 2 RCTs in this analysis	**Parasitological failure , 1–14 days after completion of treatment** 63/132 (48%) with metronidazole 79/153 (52%) with tinidazole	RR 1.01 95% CI 0.58 to 1.74 P = 0.98	⟷	Not significant
[17] Systematic review	507 people 9 RCTs in this analysis	**Parasitological failure , 15–60 days after completion of treatment** 34/245 (14%) with metronidazole 26/262 (10%) with tinidazole	RR 0.64 95% CI 0.25 to 1.64 P = 0.35 Significant heterogeneity present in analysis (P = 0.007). Subgroup analysis revealed that analysis by clinical group reduced some of the observed heterogeneity (see further information on studies)	⟷	Not significant

Mortality

No data from the following reference on this outcome. [17]

Complications

No data from the following reference on this outcome. [17]

Adverse effects

Metronidazole compared with tinidazole Metronidazole may be more likely to be associated with adverse effects than tinidazole (low-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	477 people 8 RCTs in this analysis	**Proportion of people with adverse effects** 103/229 (45%) with metronidazole 72/248 (30%) with tinidazole Most common adverse effects included decreased appetite, vomiting, nausea, abdominal cramping, and metallic taste. Importantly, there were no reports of discontinuation of treatment due to adverse effects	RR 0.65 95% CI 0.46 to 0.92 P = 0.015	●○○	tinidazole

Metronidazole versus ornidazole:

We found one systematic review (search date 2008, 3 RCTs) comparing metronidazole versus ornidazole. [17]

Treatment effectiveness

Metronidazole compared with ornidazole We don't know how effective metronidazole and ornidazole are, compared with each other, in clearance of both clinical symptoms and parasitological signs (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical failure					
[17] Systematic review	40 people 2 RCTs in this analysis	**Clinical failure , 1–14 days after completion of treatment** 0/20 (0%) with metronidazole 0/20 (0%) with ornidazole	The review reported that the number of trials was too small to detect any difference		
[17] Systematic review	118 people 2 RCTs in this analysis	**Clinical failure , 15–60 days after completion of treatment** 0/59 (0%) with metronidazole 1/59 (2%) with ornidazole	RR 3.00 95% CI 0.13 to 71.89 P = 0.50 The review reported that the number of trials was too small to detect any difference	⟷	Not significant
Parasitological failure					
[17] Systematic review	40 people 2 RCTs in this analysis	**Parasitological failure , 1–14 days after completion of treatment** 0/20 (0%) with metronidazole 0/20 (0%) with ornidazole	The review reported that the number of trials was too small to detect any difference		
[17] Systematic review	135 people 2 RCTs in this analysis	**Parasitological failure , 15–60 days after completion of treatment** 6/69 (9%) with metronidazole 1/66 (2%) with ornidazole	RR 0.18 95% CI 0.02 to 1.41 P = 0.10 The review reported that the number of trials was too small to detect any difference	⟷	Not significant

Mortality

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No data from the following reference on this outcome. [17]

Complications

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	20 people Data from 1 RCT	**Proportion of people with adverse effects** 3/10 (30%) with metronidazole 2/10 (20%) with ornidazole Adverse effects included: severe nausea (1 person), nausea associated with hypersalivation, anorexia, dizziness (1 person), and slight dizziness (1 person) with metronidazole; dizziness (2 people) with ornidazole	RR 0.67 95% CI 0.14 to 3.17 P = 0.61	⟷	Not significant

Metronidazole versus secnidazole, emetine, paromomycin, diloxanide, nitazoxanide, or diiodohydroxyquinoline:

We found no systematic review or RCTs.

Further information on studies

[17] The quality of the RCTs included in the analysis was generally low, with a lack of standardised methods for inclusion, diagnosis, and outcome reporting. Many of the RCTs included in the meta-analysis were not blinded, while those studies that used blinding did so with diverse methods. Diagnosis of amoebic dysentery was predominately achieved by direct visualisation of either trophozoites or cysts in stool. Other diagnostic methods included ELISA detection from stool, concentration of sample for increased sensitivity for cyst detection, flotation techniques, and trophozoite fixation. While some trials reported on concomitant infection with other intestinal pathogens (parasite or bacteria), not all trials determined if *Entamoeba histolytica* was the single likely cause of dysentery. **Metronidazole versus tinidazole** The review reported that it was not clear whether two RCTs involved the same group of people or different groups sampled from the same population. [18] [19] The meta-analysis demonstrated that removal of a possible duplicate study ([18] [19]) along with exclusion of trials funded by pharmaceutical companies did not significantly change the overall results of tinidazole versus metronidazole. The fact that not all trials determined if *E histolytica* was the single likely cause of dysentery could impact on data interpretation and could account for some of the difference observed between tinidazole and metronidazole in clinical failures outcome, while no significant difference was observed in the parasitological failure outcome. The RCTs displayed significant heterogeneity, as reported in the meta-analysis. When analysed by subgroup, the meta-analysis found reduced heterogeneity in three groups: those who used WHO diagnostic criteria, "unspecified amoebic colitis", and "non-dysenteric amoebic colitis"; this could affect the interpretation of included RCTs as a whole.

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Comment: **Clinical guide:**
While tinidazole had reduced clinical failure rates when compared with metronidazole, tinidazole did not differ significantly from metronidazole in the parasitological failure outcome. Furthermore, metronidazole is the established drug of choice for treatment of amoebic dysentery. While we found no studies that show metronidazole efficacy compared with placebo, this is likely to be due to the ethical questions involved in treatment of a potentially fatal condition with placebo. Therefore, metronidazole is likely to be beneficial, as are tinidazole and ornidazole.

OPTION SECNIDAZOLE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- Secnidazole may have similar efficacy as ornidazole at reducing parasitological or clinical failure in treatment of amoebic dysentery.
- We found no direct information from RCTs about whether secnidazole is better than no active treatment. We found no clinically important results from RCTs about secnidazole compared with metronidazole, tinidazole, emetine, paromomycin, diloxanide, diiodohydroxyquinoline, or nitazoxanide in people with amoebic dysentery.

Benefits and harms

Secnidazole versus placebo:

We found no systematic review or RCTs.

Secnidazole versus ornidazole:

We found one systematic review (search date 2008), [17] which identified one unblinded RCT comparing secnidazole (30 mg/kg daily for 3 days) versus ornidazole (15 mg/kg daily for 10 days). [20]

Treatment effectiveness

Secnidazole compared with ornidazole We don't know how effective secnidazole and ornidazole are, compared with each other, at reducing clinical or parasitological failure (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical failure					
[20] RCT	102 children with amoebic dysentery In review [17]	**Persistence of diarrhoea and abdominal discomfort , 10 days after treatment ended** 3/60 (5%) with secnidazole 2/42 (5%) with ornidazole	Significance assessment not performed		
Parasitological failure					
[20] RCT	102 children with amoebic dysentery In review [17]	**Failure to clear parasites , 10 days after treatment ended** 19/60 (32%) with secnidazole 10/42 (24%) with ornidazole	Significance assessment not performed		

Mortality

No data from the following reference on this outcome. [20]

Complications

No data from the following reference on this outcome. [20]

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] RCT	102 children with amoebic dysentery In review [17]	**Adverse effects** with secnidazole with ornidazole No adverse effects reported with either secnidazole or ornidazole			

Secnidazole versus metronidazole, tinidazole, emetine, paromomycin, diloxanide, diiodohydroxyquinoline, or nitazoxanide:

We found no systematic review or RCTs.

Comment: None.

OPTION ORNIDAZOLE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- Ornidazole may be effective at curing amoebic dysentery compared with placebo, but can cause nausea and vomiting.
- Ornidazole may be as effective as tinidazole, metronidazole, and secnidazole at curing amoebic dysentery.
- We found no direct information from RCTs about ornidazole compared with emetine, paromomycin, diloxanide, diiodohydroxyquinoline, or nitazoxanide in people with amoebic dysentery.

Benefits and harms

Ornidazole versus placebo:

We found one RCT. [21]

Treatment effectiveness

Ornidazole compared with placebo Ornidazole may be more effective than placebo in clearing parasites at 8 to 10 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Parasitological failure					
[21] RCT Randomisa-tion unclear	55 people	**Failure to clear parasites , 8 to 10 days** 7/35 (20%) with ornidazole 20/20 (100%) with placebo	Significance assessment not performed		

Mortality

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No data from the following reference on this outcome. [21]

Complications

No data from the following reference on this outcome. [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT Randomisation unclear	55 people	**Proportion of people with adverse effects** 3/35 (8.6%) with ornidazole 0/20 (0%) with placebo Nausea and vomiting were more common with ornidazole than with placebo	Significance assessment not performed		

Ornidazole versus tinidazole:

We found one systematic review (search date 2008, 2 RCTs). [17]

Treatment effectiveness

Ornidazole compared with tinidazole We don't know how effective ornidazole and tinidazole are, compared with each other, in reducing both clinical and parasitological failure at 1 to 14 days after completion of treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical failure					
[17] Systematic review	66 children 2 RCTs in this analysis	**Clinical failure , 1–14 days after completion of treatment** 0/35 (0%) with ornidazole 3/31 (10%) with tinidazole	RR 0.23 95% CI 0.03 to 1.96 P = 0.18	⟷	Not significant
Parasitological failure					
[17] Systematic review	66 children 2 RCTs in this analysis	**Parasitological failure , 1–14 days after completion of treatment** 1/35 (3%) with ornidazole 0/31 (0%) with tinidazole	Significance assessment not performed		

Mortality

No data from the following reference on this outcome. [17]

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Complications

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] RCT	40 children In review [17]	**Adverse effects** with ornidazole with tinidazole Mild vomiting was reported in 1 person with ornidazole			

Ornidazole versus metronidazole:
See option on metronidazole, p 3 .

Ornidazole versus secnidazole:
See option on secnidazole, p 7 .

Ornidazole versus emetine, paromomycin, diloxanide, diiodohydroxyquinoline, or nitazoxanide:
We found no systematic review or RCTs.

Further information on studies

[17] **Ornidazole versus tinidazole:** The review reported that both RCTs had high withdrawal rates. Most of the children in one of the RCTs [22] also had helminthiasis (presence of *Ascaris*, *Trichuris*, or *Ancylostoma*: 17/20 [85%] in the tinidazole group *v* 18/20 [90%] in the ornidazole group).

Comment: None.

OPTION TINIDAZOLE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- Tinidazole may be more effective than metronidazole at reducing clinical symptoms, but may be as effective at clearing parasites. Tinidazole may be less likely to cause adverse effects than metronidazole.
- Tinidazole may be as effective as ornidazole at preventing clinical and parasitological failure.
- We found no clinically important results from RCTs about tinidazole compared with secnidazole, emetine, paromomycin, diloxanide, nitazoxanide, or diiodohydroxyquinoline in people with amoebic dysentery.

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Benefits and harms

Tinidazole versus placebo:

We found no systematic review or RCTs.

Tinidazole versus metronidazole:

See option on metronidazole, p 3 .

Tinidazole versus ornidazole:

See option on ornidazole, p 8 .

Tinidazole versus secnidazole, emetine, paromomycin, diloxanide, nitazoxanide, or diiodohydroxyquinoline:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION NITAZOXANIDE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- Nitazoxanide is likely to be more effective than placebo at reducing clinical failure. Nitazoxanide may be no more effective than placebo at preventing parasitological failure.
- We found no clinically important results from RCTs about nitazoxanide compared with metronidazole, secnidazole, ornidazole, tinidazole, emetine, paromomycin, diloxanide, or diiodohydroxyquinoline in people with amoebic dysentery.

Benefits and harms

Nitazoxanide versus placebo:

We found one systematic review (search date 2008, 2 RCTs). [17]

Treatment effectiveness

Nitazoxanide compared with placebo Nitazoxanide may be more effective than placebo at reducing clinical failure at 1 to 14 days after completion of treatment, but we don't know whether it is more effective at reducing parasitological failure (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinical failure					
[17] Systematic review	153 people 2 RCTs in this analysis	**Clinical failure , 1–14 days after completion of treatment** 9/80 (11%) with nitazoxanide 40/73 (55%) with placebo	RR 0.21 95% CI 0.06 to 0.81 P = 0.023	●●○	Nitazoxanide

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Parasitological failure					
[17] Systematic review	167 people 2 RCTs in this analysis	**Parasitological failure , 1–14 days after completion of treatment** 14/86 (16%) with nitazoxanide 46/81 (57%) with placebo	RR 0.25 95% CI 0.05 to 1.27 P = 0.095	⟷	Not significant

Mortality

No data from the following reference on this outcome. [17]

Complications

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	67 people Data from 1 RCT	**Proportion of people with adverse effects** 6/36 (17%) with nitazoxanide 4/31 (13%) with placebo	RR 1.29 95% CI 0.40 to 4.16	⟷	Not significant

Nitazoxanide versus metronidazole, secnidazole, ornidazole, tinidazole, emetine, paromomycin, diloxanide, or diiodohydroxyquinoline:

We found no systematic review or RCTs.

Further information on studies

[17] The review commented that the RCT participants had clinical symptoms of intestinal amoebiasis, without distinguishing between amoebic dysentery and non-dysenteric amoebic colitis.

Comment: More high-quality studies are needed to determine whether nitazoxanide is significantly more effective than placebo at reducing parasitological signs of amoebic dysentery. Furthermore, studies comparing nitazoxanide and other currently used interventions (metronidazole, tinidazole, ornidazole, and secnidazole) will be useful in demonstrating efficacy.

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OPTION EMETINE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- We don't know whether emetine is beneficial in treating amoebic dysentery.

Benefits and harms

Emetine:

We found no systematic review or RCTs comparing emetine versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, paromomycin, diloxanide, diiodohydroxyquinoline, or nitazoxanide.

Further information on studies

Comment: None.

OPTION PAROMOMYCIN

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- We don't know whether paromomycin is effective in treating amoebic dysentery as we found no studies.
- Paromomycin would not be expected to be beneficial in treating amoebic dysentery because it achieves therapeutic levels solely in the lumen of the gut (and not in the intestinal mucosa).

Benefits and harms

Paromomycin:

We found no systematic review or RCTs comparing paromomycin versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, emetine, diloxanide, diiodohydroxyquinoline, or nitazoxanide.

Comment: Paromomycin is a luminal amoebicide that is not recommended for treatment of symptomatic amoebic infection as it does not penetrate into the intestinal epithelium. [23] [24] There is some evidence that treatment with luminal amoebicides after treatment with a tissue amoebicide, such as metronidazole, improves eradication of surviving parasites in the colon. Therefore, luminal amoebicides may have a role in reducing parasitological failure, preventing relapse, and interrupting transmission of parasite cysts.

OPTION DILOXANIDE

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- We don't know whether diloxanide is effective in treating amoebic dysentery as we found no trials.
- Diloxanide would not be expected to be beneficial in treating amoebic dysentery because it achieves therapeutic levels solely in the lumen of the gut (and not in the intestinal mucosa).

Benefits and harms

Diloxanide:

We found no systematic review or RCTs comparing diloxanide versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, emetine, paromomycin, diiodohydroxyquinoline, or nitazoxanide.

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Further information on studies

Comment: Diloxanide is a luminal amoebicide that is not recommended for treatment of symptomatic amoebic infection as it does not penetrate into the intestinal epithelium. [23] [25] [26] There is some evidence that treatment with luminal amoebicides after treatment with a tissue amoebicide, such as metronidazole, improves eradication of surviving parasites in the colon. Therefore, luminal amoebicides may have a role in reducing parasitological failure, preventing relapse, and interrupting transmission of parasite cysts.

OPTION DIIODOHYDROXYQUINOLINE (IODOQUINOL)

- For GRADE evaluation of interventions for Amoebic dysentery, see table, p 16 .
- We don't know whether diiodohydroxyquinoline is effective in treating amoebic dysentery as we found no trials.
- Diiodohydroxyquinoline would not be expected to be beneficial in treating amoebic dysentery because it achieves therapeutic levels solely in the lumen of the gut (and not in the intestinal mucosa).

Benefits and harms

Diiodohydroxyquinoline:

We found no systematic review or RCTs comparing diiodohydroxyquinoline versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, emetine, paromomycin, diloxanide, or nitazoxanide.

Further information on studies

Comment: Diiodohydroxyquinoline is a luminal amoebicide that is not recommended for treatment of symptomatic amoebic infection as it does not penetrate into the intestinal epithelium. [23] There is some evidence that treatment with luminal amoebicides after treatment with a tissue amoebicide, such as metronidazole, improves eradication of surviving parasites in the colon. Therefore, luminal amoebicides may have a role in reducing parasitological failure, preventing relapse, and interrupting transmission of parasite cysts.

GLOSSARY

Amoeboma A granulomatous lesion of the caecum or ascending colon caused by localised chronic *Entamoeba histolytica* infection.

Enzyme linked immunosorbent assay (ELISA) A testing method using immune responses to detect substances such as hormones, bacterial antigens, and antibodies.

Helminthiasis The presence in the human gastrointestinal tract of nematode worms (i.e. roundworms) such as *Ancylostoma duodenale*, *Ascaris lumbricoides*, and *Trichuris trichiura*.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

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GRADE **Evaluation of interventions for Amoebic dysentery.**

Important outcomes	Adverse effects, Complications, Mortality, Treatment effectiveness								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for amoebic dysentery in endemic areas?									
9 (at least 711 people) [17]	Treatment effectiveness	Metronidazole versus tinidazole	4	–2	0	–1	0	Very low	Quality points deducted for methodological flaws (lack of blinding of RCTs and possible inclusion of duplicate study in analysis). Directness point deducted for uncertainty about diagnosis of amoebic dysentery
8 (477) [17]	Adverse effects	Metronidazole versus tinidazole	4	–2	0	0	0	Low	Quality points deducted for methodological flaws (lack of blinding of RCTs and possible inclusion of duplicate study in analysis)
3 (128) [17]	Treatment effectiveness	Metronidazole versus ornidazole	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and methodological weaknesses in included RCTs. Directness point deducted for uncertainty about diagnosis of amoebic dysentery
1 (102) [20]	Treatment effectiveness	Secnidazole versus ornidazole	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no blinding, and no statistical assessment performed
1 (55) [21]	Treatment effectiveness	Ornidazole versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, uncertainty about randomisation, and no statistical assessment performed
2 (66) [17]	Treatment effectiveness	Ornidazole versus tinidazole	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and no statistical assessment performed. Directness point deducted for uncertainty about diagnosis of amoebic dysentery
2 (167) [17]	Treatment effectiveness	Nitazoxanide versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about diagnosis of amoebic dysentery

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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