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Comparative efficacy of drugs for treating giardiasis: a systematic update of the literature and network meta-analysis of randomized clinical trials

José M. Ordóñez-Mena[1]*, Noel D. McCarthy[2,3] and Thomas R. Fanshawe[1,2]

[1]*Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, UK;* [2]*NIHR Health Protection Research Unit in Gastrointestinal Infections, University of Oxford, Oxford, UK;* [3]*Warwick Medical School, University of Warwick, Coventry, UK*

*Corresponding author. Tel: +44 1865 689307; E-mail: jose.ordonezmena@phc.ox.ac.uk

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Background: Giardiasis is the commonest intestinal protozoal infection worldwide. The current first-choice therapy is metronidazole. Recently, other drugs with potentially higher efficacy or with fewer and milder side effects have increased in popularity, but evidence is limited by a scarcity of randomized controlled trials (RCTs) comparing the many treatment options available. Network meta-analysis (NMA) is a useful tool to compare multiple treatments when there is limited or no direct evidence available.

Objectives: To compare the efficacy and side effects of all available drugs for the treatment of giardiasis.

Methods: We selected all RCTs included in systematic reviews and expert reviews of all treatments for giardiasis published until 2014, extended the systematic literature search until 2016, and identified new studies by scanning reference lists for relevant studies. We then conducted an NMA of all available treatments for giardiasis by comparing parasitological cure (efficacy) and side effects.

Results: We identified 60 RCTs from 58 reports (46 from published systematic reviews, 8 from reference lists and 4 from the updated systematic search). Data from 6714 patients, 18 treatments and 42 treatment comparisons were available. Tinidazole was associated with higher parasitological cure than metronidazole [relative risk (RR) 1.23, 95% CI 1.12–1.35] and albendazole (RR 1.35, 95% CI 1.21–1.50). Taking into consideration clinical efficacy, side effects and amount of the evidence, tinidazole was found to be the most effective drug.

Conclusions: We provide additional evidence that single-dose tinidazole is the best available treatment for giardiasis in symptomatic and asymptomatic children and adults.

Introduction

Giardiasis is an infectious disease caused by the parasite *Giardia lamblia* (also known as *Giardia duodenalis*)[1] that is highly associated with poor hygiene, low water quality and poor sanitation.[2] Giardiasis is the commonest gastrointestinal protozoal pathogen worldwide[3] and has been identified as a neglected tropical disease.[4] Incidence is highest in children, but adults are also affected, especially travellers to endemic countries.[5] Every year an average of 280 million people are infected with this parasite, but this may be an underestimate considering the difficulties of diagnosis in endemic countries.[6] Giardiasis often presents with symptoms such as diarrhoea, abdominal pain, nausea, dehydration and weight loss.[7] Although giardiasis is rarely fatal, WHO disease burden estimates are of 170000 disability-adjusted life years (DALYs) annually.[8] The substantial burden in childhood, with associated weight loss and potentially chronic nature if untreated, contributes to this and highlights the importance of effective treatment. Although not well quantified, treatment is also likely to be important in the control of infection given the importance of the human reservoir for this infection and person-to-person transmission.

Metronidazole (MTZ), a drug of the 5-nitroimidazole (5-NI) class, is the first-choice giardiasis treatment. It is the only giardiasis treatment included as such in the 2015 WHO Essential Medicines List[9] or advised by PHE.[10] Tinidazole (TNZ) is now also acknowledged by other UK and USA health authorities.[11–13] Alternative treatments include nitazoxanide (NTZ), paromomycin (PRM), mepacrine or quinacrine (QC), furazolidone (FZD), albendazole (ABZ) and mebendazole (MBZ).[11] These drugs may be useful in cases where metronidazole has failed, as they belong to different chemical families and target different pathways.[14]

Systematic reviews of randomized controlled trials (RCTs), including two Cochrane reviews, have shown evidence of higher efficacy of metronidazole compared with other drugs,[15–18] and to

Table 1. Summary of characteristics for all included RCTs, for those including children only, and for those including symptomatic patients only

	Overall		Children only		Symptomatic only	
Characteristic	*N*	%	*N*	%	*N*	%
Total trials (*N*)	60	100	38	100	37	100
Publication year						
≤1979	6	10	3	8	5	14
1980–89	9	15	2	5	6	16
1990–99	18	30	16	42	9	24
2000–09	17	28	13	34	11	30
≥2010	10	17	4	11	6	16
Participants (*n*)						
<100	30	50	17	45	18	49
≥100	30	50	21	55	19	51
Age						
children	38	63	38	100	23	62
children and adults	13	22	0	0	8	22
adults	8	13	0	0	5	14
unclear	1	2	0	0	1	3
Setting						
outpatient	38	63	27	71	26	70
hospital	12	20	7	18	7	19
mixed	1	2	0	0	0	0
unclear	9	15	4	11	4	11
Patient characteristics						
symptomatic	37	62	23	61	37	100
asymptomatic	5	8	3	8	0	0
mixed	12	20	8	21	0	0
unclear	6	10	4	11	0	0
WHO region[a]						
Americas	26	43	19	50	15	41
South-East Asia	12	20	8	21	4	11
Eastern Mediterranean	10	17	6	16	9	24
European	11	18	4	11	9	24
African	1	2	1	3	0	0
Western Pacific	0	0	0	0	0	0
Follow-up (days)						
<14	22	37	13	34	15	41
≥14	35	58	23	61	19	51
unclear	3	5	2	5	3	8
Giardiasis treatment						
albendazole	17	28	14	37	6	16
chloroquine	2	3	2	5	1	3
furazolidone	7	12	4	11	7	19
mebendazole	13	22	8	21	10	27
metronidazole	39	65	24	63	25	68
nitazoxanide	7	12	6	16	5	14
ornidazole	6	10	2	5	4	11
quinacrine	3	5	2	5	3	8
secnidazole	9	15	6	16	7	19
tinidazole	18	30	12	32	9	24
other	11	18	4	11	6	16

[a]WHO regions included the following countries: Africa: Tanzania ($n = 1$); Americas: Brazil ($n = 5$), Cuba ($n = 12$), Mexico ($n = 6$), Peru ($n = 3$); Eastern Mediterranean: Egypt ($n = 2$), Iraq ($n = 2$), Iran ($n = 6$); Europe: Finland ($n = 2$), Israel ($n = 1$), Kazakhstan ($n = 1$), Spain ($n = 3$), Turkey ($n = 4$); South-East Asia: Bangladesh ($n = 4$), India ($n = 6$), Thailand ($n = 2$).

a lesser degree evidence of higher efficacy of other 5-NIs, such as tinidazole, ornidazole (OZN) or secnidazole (SCZ), compared with other drugs[15,19] Conversely, another systematic review suggested that albendazole was as effective as metronidazole, but with substantially fewer side effects.[20] For the remaining drugs fewer RCTs were available, and the evidence regarding their efficacy and side effects is uncertain.[16] Inclusion criteria and search strategies focusing on few single pairwise comparisons or drug classes may have contributed to these inconsistent findings.

Previous systematic reviews only considered pairwise comparisons between treatments. Multiple treatments or network meta-analysis (NMA) offers a solution to situations in which many treatments need to be compared, but there is little to no direct evidence for some of the comparisons.[21]

We aimed to collect all the available evidence on parasitological cure and side effects from RCTs of drugs for the treatment of giardiasis and combine this evidence using NMA.

Methods

Search strategy and selection criteria

This systematic review and NMA was conducted according to the PRISMA guidelines extension.[22] We included all RCTs from previous systematic reviews and meta-analyses[15–20] that compared the efficacy of drugs for the treatment of giardiasis. In addition, the literature search from all previously published systematic reviews and meta-analyses was integrated (see search terms and strategy in Appendix 1 and Table S1, available as Supplementary data at *JAC* Online) and updated from the end date of the broadest systematic review[15] (May 2013) to May 2016. Language was restricted to English, Spanish and Portuguese. The references of all included studies and relevant experts' narrative reviews[23–26] were also searched for eligible studies that may have been missed by previous systematic reviews.

Inclusion and exclusion criteria

All RCTs comparing two or more giardiasis treatments or placebo in children and/or adults were included. A study was considered randomized if the article reported that treatments were allocated at random. All settings (outpatient and inpatient) were included. RCTs had to report parasitological cure rates to be included. We did not focus on clinical cure rate because of its potential subjectivity and methodological variability. Studies that only compared a single drug at different doses were excluded.

Data extraction

Two authors (J. M. O. M. and T. R. F.) independently extracted the following data: name of first author, year of publication, country, sample size, age of participants, setting, patients' characteristics, length of follow-up, treatment/drug assigned, dosage (including dose, daily frequency and duration), number of patients initially assigned to the drug, number treated and number cured at end of follow-up. If a drug was administered at different dosages in different arms of a trial, these arms were combined. Data for the following side effects were extracted: any side effect, metallic taste, abdominal pain, nausea, vomiting, diarrhoea, dizziness, yellow urine, headache (or cephalgia), sickness, loss of appetite (or hyporexia/anorexia), vertigo, somnolence/drowsiness, urticaria (or hives or skin rash), weakness (or fatigue) and jaundice (or yellow skin).

Table 2. Summary of drug efficacy

Drug[a]	No. of RCTs	Patients cured	Patients treated	Pooled efficacy (95% CI)		Heterogeneity I^2 (%)	Heterogeneity *P*
Albendazole	17	757	983	0.79	(0.69–0.86)	89	<0.001
A. graveolens	1	14	14	1.00	(0.78–1.00)	NA	NA
Chloroquine	2	95	111	0.86	(0.78–0.91)	NA	NA
Furazolidone	7	149	180	0.86	(0.75–0.92)	53	0.05
Mebendazole	13	348	493	0.66	(0.51–0.79)	88	<0.001
Mentha crispa	1	22	50	0.44	(0.31–0.58)	NA	NA
Metronidazole	39	1284	1532	0.88	(0.83–0.91)	84	<0.001
Nitazoxanide	7	214	300	0.71	(0.63–0.78)	51	0.05
Oleozon	1	63	112	0.56	(0.47–0.65)	NA	NA
Ornidazole	6	223	351	0.80	(0.60–0.92)	91	<0.001
Placebo	3	13	64	0.01	(0.00–0.88)	NA	NA
Propolis	2	102	153	0.63	(0.45–0.79)	NA	NA
Paromomycin	1	54	59	0.92	(0.82–0.96)	NA	NA
Praziquantel	1	17	30	0.57	(0.39–0.73)	NA	NA
Quinacrine	3	140	161	0.87	(0.81–0.91)	NA	NA
Sausalin	1	107	125	0.86	(0.78–0.91)	NA	NA
Secnidazole	9	523	595	0.88	(0.83–0.91)	45	0.08
Tinidazole	18	791	957	0.85	(0.79–0.89)	78	<0.001

NA, not assessed.
[a]In addition, albendazole was administered in combination with nitazoxanide in one trial, and in combination with praziquantel in another trial.

Assessment of risk of bias and quality of the evidence

The reporting quality of included studies was assessed by two investigators (J. M. O. M. and T. R. F.) independently. Disagreements were resolved through discussion. Studies were rated as low, unclear or high risk using the Cochrane Collaboration risk of bias criteria.[27]

Quality of the evidence was assessed using the GRADE working group approach for network meta-analysis.[28]

Data analysis

Analyses were conducted in R (version 3.2.3).[29] Drug efficacy and side effects within a study arm were calculated in the ITT population to avoid bias due to non-random loss of participants. If ITT data were not provided or could not be estimated, PP data were used.

First, exploratory estimates of drug efficacy (i.e. proportion of patients cured) and proportion of patients with side effects were obtained for each treatment separately, using a mixed-effects logistic regression meta-analysis model (the 'metafor' R package).[30] Heterogeneity was assessed with I^2 estimates and Wald *P* values for drugs tested in five or more RCTs. If drug efficacy was estimated in just one RCT, we used the Wilson formula to derive the exact 95% CI.[31]

We performed a random-effects NMA using the R package 'netmeta' (version 0.9-4).[32,33] We estimated a relative risk (RR) and 95% CI, to compare drug efficacies and proportions of patients with side effects for each pair of available treatments. In the case of zero counts, a correction of +0.5 for all arms within the RCT was used. Publication bias was assessed by visual inspection of funnel plots ('metafor' R package).[30]

The assumption of transitivity was tested by looking at the distribution of potential effect modifiers (patients and study characteristics) and treatment allocation in two different subsamples: (i) children and (ii) symptomatic patients. Heterogeneity and inconsistency were assessed by decomposing Cochran's *Q* statistic[34] and using I^2 tests.[35] Sources of inconsistency were visualized with net heat plots.[34]

Results

A flow diagram of the updated literature search is depicted in Figure S1. Briefly, we identified four new RCTs published after the period covered by previous systematic reviews. These were added to the 48 RCTs identified in previous systematic reviews.[15–20] We further identified eight additional RCTs by scanning reference lists of included RCTs and experts' reviews. Thus, 60 RCTs encompassing 6714 patients were eligible. Appendixes 2 and 3 list all included and excluded studies, and sources of identification and reasons for exclusion, respectively.

Table 1 and Table S2 summarize the characteristics of included studies. The majority of RCTs included symptomatic children from outpatient settings. In most studies, the length of follow-up was >2 weeks. Most RCTs were published in the WHO Region of the Americas, particularly in Cuba, followed by the European and South-East Asia regions. The characteristics of RCTs conducted only in children, or only in symptomatic patients, were similar to those of all RCTs.

Table 2 summarizes the characteristics of drugs administered. We found 18 different treatments for giardiasis, metronidazole being the most tested. Most treatments had an efficacy of >80%, although heterogeneity was high. There was high variability in the drug dose, frequency of administration and duration of treatment for metronidazole, albendazole, mebendazole, furazolidone, nitazoxanide and ornidazole (Table S3). For secnidazole or tinidazole in nearly all cases a single dose was administered.

Table 3 and Figure 1 give an overview of the different treatment comparisons. There were 33 different combinations of treatment comparison. The majority of RCTs ($n = 51$) compared just two arms, with the most common study design being

Table 3. Clinical trial design including number of treated and cured patients (sorted by descending number of arms and by treatment in alphabetical order)

First author, year	Design (no. of trials)	Arms	ABZ	AGA	CQ	FZD	MBZ	MEN	MTZ	NTZ	OLZ	OZN	PLA	PPS	PRM	PZQ	QC	SAU	SCZ	TNZ
Chan del Pino, 1999	ABZ/FZD/MTZ/SCZ/TNZ (1)	5	11/17			14/15			13/17										11/15	13/15
Bassily, 1970	FZD/MTZ/PLA/QC (1)	4				16/20			19/20				0/20				20/20			
Escobedo, 2003a	ABZ/CQ/TNZ (1)	3	37/60		43/50															50/55
Speich, 2013	ABZ/NTZ/PLA (1)	3	15/25							12/21			13/25							
Kalayci, 1995	FZD/MBZ/MTZ (1)	3				12/15	11/15		14/15											
Chacon, 1991	FZD/MTZ/SCZ (1)	3				19/20			18/20										12/17	
Bulut, 1996	MBZ/MTZ/OZN (1)	3					12/34		13/15			10/11								
Imani, 2004	MBZ/MTZ/PZQ (1)	3					15/30		28/30							17/30				
Nunez, 2004	MTZ/PPS/PRM (1)	3							71/89					80/108	54/59					
Alizadeh, 2006	ABZ/MTZ (10)	2	54/60						46/60											
Cañete, 2012			62/75						64/75											
Dutta, 1994			73/75						73/75											
Hall, 1993a			112/144						77/78											
Hall, 1993b			122/141						63/63											
Karabay, 2004			27/33						29/34											
Misra, 1995			28/32						29/32											
Rodriguez-Garcia, 1996			21/27						16/22											
Romero-Cabello, 1995			47/50						49/50											
Yereli, 2004			47/52						49/55											
Bances-Garcia, 2013	ABZ/NTZ (1)	2	40/49							43/49										
Mendoza, 2003	ABZ/TNZ (3)	2	17/49																	31/43
Pengsaa, 1999			31/68																	49/63
Pengsaa, 2002			13/26																	25/27
Sahib, 2014	AGA/MTZ (1)	2		14/14					14/14											
Canete, 2010	CQ/MTZ (1)	2			52/61				45/61											
Garg, 1972	FZD/MTZ (3)	2				38/40			38/40											
Nair, 1979						16/20			16/19											
Quiros-Buelna, 1989						34/50			43/50											
Al-Waili, 1992	MBZ/MTZ (4)	2					21/23		18/21											
Gascon, 1989							2/14		8/9											
Gascon, 1990							1/8		10/11											
Sadjjadi, 2001							43/50		45/50											
Davila-Gutierrez, 2002	MBZ/NTZ (2)	2					11/19			18/32										
Rodriguez-Garcia, 1999							33/41			32/41										
Canete, 2006a	MBZ/QC (1)	2					48/61										51/61			
Almirall, 2011	MBZ/SCZ (2)	2					55/64												56/62	
Escobedo, 2003b							57/73												58/73	
Canete, 2006b	MBZ/TNZ (1)	2					39/61													50/61
Teles, 2011	MEN/SCZ (1)	2						22/50											42/50	
Ortiz, 2001	MTZ/NTZ (1)	2							41/55	39/55										
Leite, 1976	MTZ/OZN (2)	2							12/15			13/15								
Oren, 1991									37/37			35/38								
Kavousi, 1979	MTZ/QC (1)	2							75/80								69/80			

Continued

Table 3. *Continued*

First author, year	Design (no. of trials)	Arms	ABZ	AGA	CQ	FZD	MBZ	MEN	MTZ	NTZ	OLZ	OZN	PLA	PPS	PRM	PZQ	QC	SAU	SCZ	TNZ
Cimerman, 1988	MTZ/SCZ (2)	2							52/60										57/62	
Rastegar-Lari, 1996									24/25										27/27	
Fallah, 2007	MTZ/TNZ (7)	2							43/64											37/42
Gazder, 1977									19/50											40/50
Kyronseppa, 1981									19/25											22/25
Nigam, 1991									19/35											39/40
Perez-Choliz, 1989									12/27											23/25
Speelman, 1985a									9/17											16/18
Speelman, 1985b									14/17											15/18
Rossignol, 2001	NTZ/PLA (1)	2								12/17			0/19							
Escobedo, 2008	NTZ/TNZ (1)	2								58/85										57/81
Amoroto, 2002	OLZ/OZN (1)	2									63/112	67/112								
Begaydarova, 2014	OZN/SAU (1)	2										53/125						107/125		
Jokipii, 1982	OZN/TNZ (1)	2										45/50								45/50
Miyares, 1988	PPS/TNZ (1)	2												22/45						17/45
Cimerman, 1997	SCZ/TNZ (2)	2																	116/129	120/138
Cimerman, 1999																			144/160	142/161

ABZ, albendazole; AGA, *Anethum graveolens*; CQ, chloroquine; FZD, furazolidone; MBZ, mebendazole; MEN, *Mentha crispa*; MTZ, metronidazole; NTZ, nitazoxanide; OLZ, oleozon; OZN, ornidazole; PLA, placebo; PPS, propolis; PRM, paromomycin; PZQ, praziquantel; QC, quinacrine; SAU, sausalin; SCZ, secnidazole; TNZ, tinidazole.

albendazole:metronidazole ($n = 10$), followed by metronidazole:tinidazole ($n = 7$). Nine RCTs had a multi-arm design.

Figure 2(a and b) summarizes the assessment of risk of bias. For random sequence generation, allocation concealment and blinding, the majority of studies were judged as having high or unclear risk of bias. For the attrition and reporting bias domains, >66% of RCTs were at low risk.

The results of traditional pairwise meta-analysis and NMA are combined in Table 4. Both metronidazole (RR 1.10, 95% CI 1.01–1.19) and tinidazole (RR 1.35, 95% CI 1.21–1.50) were associated with higher cure rates than albendazole. Tinidazole was associated with a higher cure rate than metronidazole (RR 1.23, 95% CI 1.12–1.35), the WHO-recommended treatment. Tinidazole was associated with significantly or non-significantly higher cure rates on NMA than all other drugs apart from sausalin. Sausalin was statistically significantly associated with higher cure rates than all other drugs, but this was based on data from a single trial against ornidazole, whose efficacy appeared lower in this trial than in other RCTs.

The total variability in effect sizes was substantial ($Q = 176$, df = 55, $I^2 = 68\%$, $P < 0.0001$). Heterogeneity (variability within designs) was also substantial and statistically significant ($Q = 69$, df = 27, $I^2 = 61\%$, $P < 0.0001$). The main contributors to the total heterogeneity were the comparisons albendazole:metronidazole ($Q = 34$, df = 9, $I^2 = 74\%$, $P < 0.0001$), mebendazole:metronidazole ($Q = 12$, df = 3, $I^2 = 76\%$, $P = 0.0062$) and metronidazole:tinidazole ($Q = 17$, df = 6, $I^2 = 65\%$, $P = 0.0080$). Inconsistency (variability between designs) estimated by the full design-by-treatment interaction model was also high ($Q = 71$, df = 27, $I^2 = 61\%$, $P < 0.0001$). The designs contributing most to the total inconsistency were albendazole:tinidazole and metronidazole:tinidazole. Detaching these designs did not result in a loss of statistical significance for the total inconsistency, but increased the inconsistency for many other designs (see net heat plot in Figure S2). There was no evidence of publication bias for designs involving albendazole, metronidazole and tinidazole (Figure S4).

The GRADE assessment of the quality of the evidence for the comparisons metronidazole:albendazole and tinidazole:metronidazole was low, and moderate for tinidazole:albendazole (Table S17).

The number and percentage of side effects reported are shown in Table S4. Of all the RCTs, 85% ($n = 51$) reported some information on side effects. The summary proportion of side effects for each drug is reported in Table S5. The drugs with the highest proportion of patients with any side effects were chloroquine and *Mentha crispa*, although these were assessed in a single RCT for each drug. Heterogeneity was high for metronidazole, ornidazole, quinacrine, secnidazole and tinidazole.

The results of traditional pairwise meta-analysis and NMA for any side effects as a composite outcome are shown in Table S6. The network graph is available in Figure S3. In NMA, metronidazole was not associated with higher risk of any side effects than all other drugs. Tinidazole, ornidazole and nitazoxanide were statistically significantly associated with more side effects than albendazole and mebendazole but not than metronidazole. The total variability in the effect sizes was moderate but statistically significant ($Q = 59$, df = 35, $I^2 = 40\%$, $P = 0.0073$) and could be explained by substantial heterogeneity ($Q = 40$, df = 16, $I^2 = 60\%$, $P = 0.0008$), particularly in the designs albendazole:metronidazole

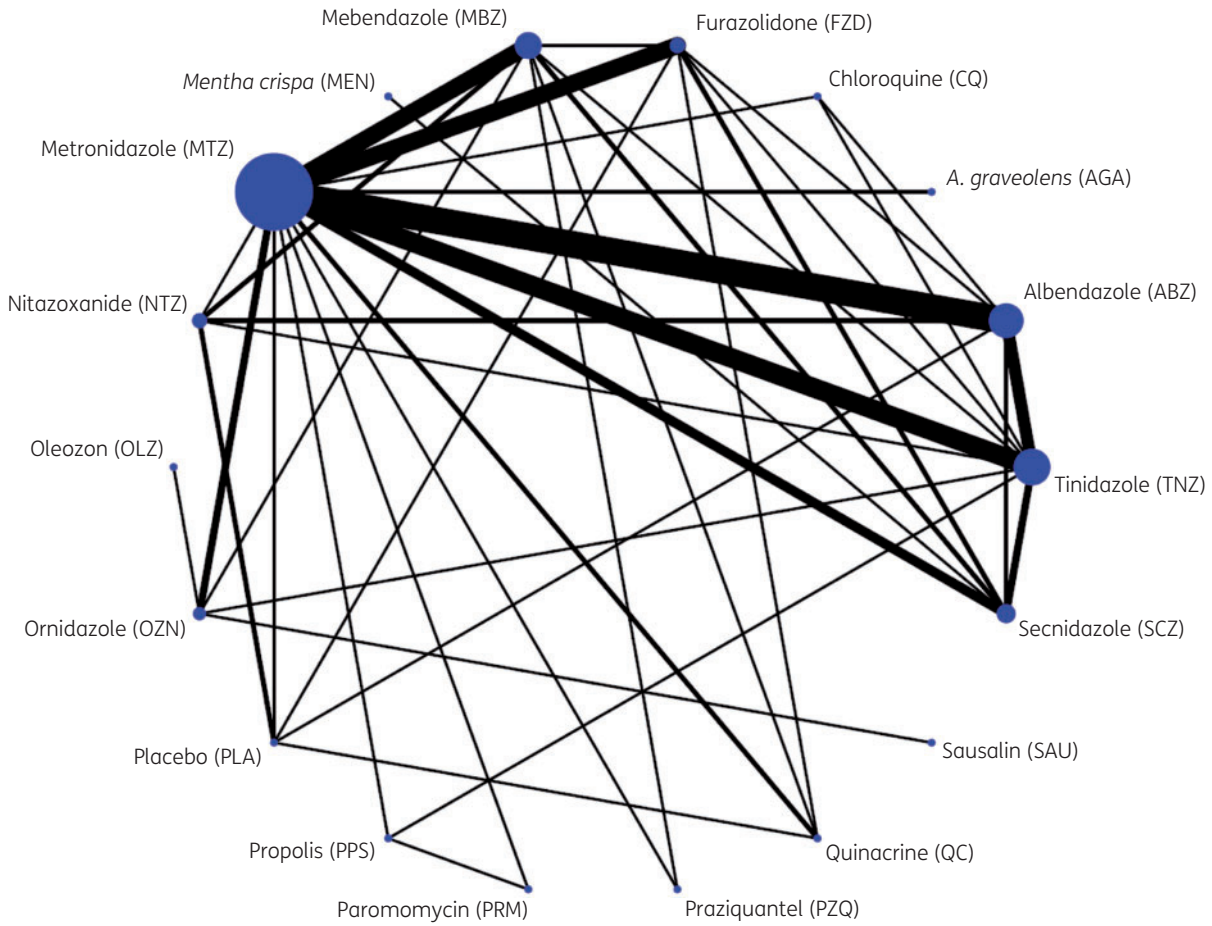

Figure 1. Network graph. The sizes of the nodes and edges are proportional to the number of patients receiving the drug and number of trials comparing these two drugs, respectively. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

($Q = 25$, df = 5, $I^2 = 80\%$, $P = 0.0001$) and mebendazole:secnidazole ($Q = 6.6$, df = 1, $I^2 = 85\%$, $P = 0.0102$). Total inconsistency for this NMA was estimated as zero.

With regard to specific side-effects (Tables S7–S16), tinidazole was associated with higher incidence of metallic taste, nausea and vomiting than albendazole, mebendazole and secnidazole. Compared with metronidazole, tinidazole was only significantly associated with higher incidence of nausea.

A joint evaluation of drug efficacy and side effects is shown in Figure 3. Sausalin ranked higher than all drugs as it was associated with higher efficacy and was generally not associated with higher or lower side effects. Tinidazole ranked higher than albendazole and mebendazole for efficacy but was associated with more side effects. Metronidazole was preferred to albendazole and *Mentha crispa* only.

Discussion

In this large and comprehensive investigation we have applied NMA to all available treatments of giardiasis to evaluate all available trial evidence simultaneously. Previous systematic reviews and traditional meta-analysis have not investigated all treatments, nor provided estimates of the absolute and comparative efficacy of all drugs. Furthermore, we provide a joint assessment of drug efficacy and side effects for each available treatment relative to the others.

Balancing the evidence for drug efficacy and side effects, tinidazole appears to be the best available treatment for giardiasis. It is the only 5-NI associated with a higher parasitological cure rate than metronidazole and it also has a higher cure rate than albendazole. Our estimate of the efficacy of tinidazole relative to albendazole is lower than that from a previous meta-analysis,[19] but our estimate is based on a larger number of trials and total sample size, and is strengthened by indirect evidence from the comparisons tinidazole:metronidazole and metronidazole:albendazole. Tinidazole was associated with a higher incidence of side effects than albendazole, mebendazole and secnidazole, but these are largely mild in nature (metallic taste, nausea and vomiting) and are unlikely to affect compliance as they occur after treatment completion.

Based on its combined performance in the assessment of efficacy and side effects, tinidazole may be an appropriate first-choice treatment for giardiasis. The better adherence possible with a single-dose regimen, which is usual for tinidazole, is likely to be even

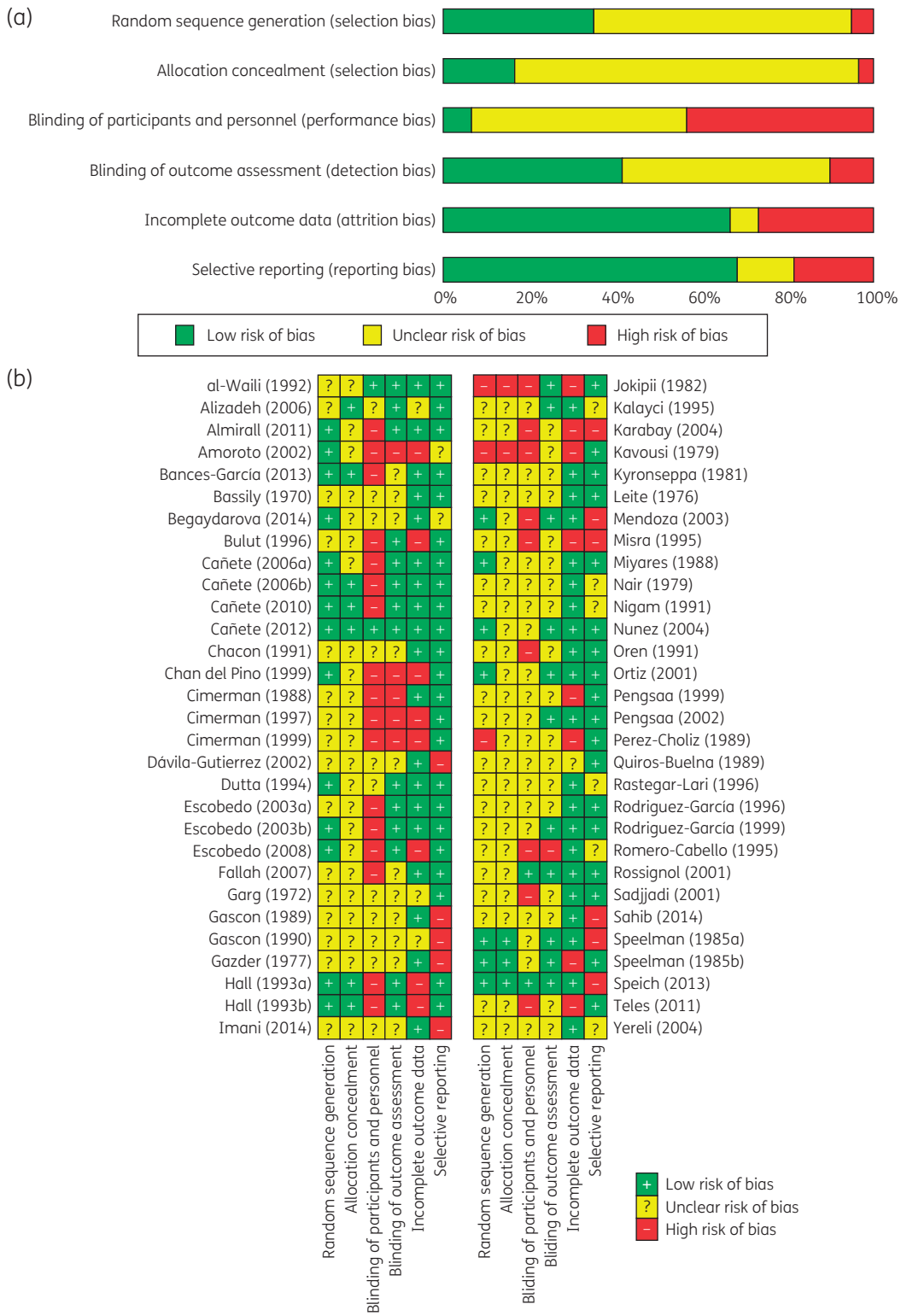

Figure 2. (a) Summary risk of bias assessment. (b) Risk of bias assessment across individual studies. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 4. RRs and 95% CI for the comparative efficacy of drugs for the treatment of giardiasis[a]

ABZ		**1.39 (1.00–1.95)**	1.44 (0.92–2.26)			1.04 (0.96–1.14)	1.05 (0.80–1.36)			0.87 (0.50–1.51)						1.13 (0.67–1.92)	**1.63 (1.36–1.97)**
1.10 (0.82–1.47)	**AGA**					1.00 (0.75–1.33)											
1.30 (1.05–1.60)	1.18 (0.83–1.67)	**CQ**				0.87 (0.64–1.18)											1.06 (0.80–1.41)
1.10 (0.95–1.26)	1.00 (0.74–1.36)	0.85 (0.67–1.07)	**FZD**	0.92 (0.57–1.46)		1.05 (0.92–1.19)				**0.03 (0.00–0.48)**				1.24 (0.88–1.75)		0.76 (0.57–1.02)	0.93 (0.66–1.31)
0.99 (0.86–1.13)	0.90 (0.66–1.22)	**0.76 (0.61–0.96)**	0.90 (0.77–1.05)	**MBZ**		**1.28 (1.09–1.51)**	0.97 (0.73–1.29)		**2.58 (1.48–4.47)**				1.13 (0.66–1.94)	1.06 (0.79–1.44)		1.04 (0.84–1.27)	1.28 (0.92–1.79)
0.60 (0.39–0.93)	**0.55 (0.33–0.92)**	**0.46 (0.29–0.74)**	**0.55 (0.35–0.85)**	**0.61 (0.39–0.94)**	**MEN**											**1.91 (1.26–2.9)**	
1.10 (1.01–1.19)	1.00 (0.75–1.33)	0.85 (0.69–1.04)	1.00 (0.89–1.12)	1.11 (0.99–1.24)	**1.83 (1.19–2.82)**	**MTZ**	0.95 (0.68–1.33)		0.99 (0.82–1.2)	**0.03 (0.00–0.40)**	0.93 (0.69–1.24)	1.15 (0.87–1.52)	**0.61 (0.40–0.92)**	0.98 (0.81–1.19)		0.99 (0.84–1.17)	**1.41 (1.22–1.63)**
1.07 (0.91–1.26)	0.98 (0.71–1.35)	0.83 (0.64–1.06)	0.98 (0.80–1.18)	1.08 (0.91–1.29)	**1.79 (1.13–2.82)**	0.98 (0.83–1.14)	**NTZ**			0.79 (0.45–1.40)							1.03 (0.75–1.42)
1.14 (0.78–1.66)	1.03 (0.65–1.65)	0.88 (0.58–1.33)	1.03 (0.70–1.52)	1.15 (0.78–1.69)	**1.89 (1.07–3.33)**	1.03 (0.71–1.50)	1.06 (0.71–1.58)	**OLZ**	1.06 (0.76–1.48)								
1.21 (1.01–1.44)	1.10 (0.80–1.52)	0.93 (0.72–1.20)	1.10 (0.90–1.34)	**1.22 (1.01–1.48)**	**2.01 (1.27–3.18)**	1.10 (0.94–1.29)	1.13 (0.91–1.4)	1.06 (0.76–1.48)	**OZN**						**2.02 (1.45–2.81)**		1.00 (0.76–1.32)
0.75 (0.46–1.21)	0.68 (0.39–1.20)	**0.58 (0.34–0.97)**	0.68 (0.41–1.12)	0.75 (0.46–1.24)	1.24 (0.65–2.38)	0.68 (0.42–1.11)	0.70 (0.43–1.14)	0.66 (0.36–1.21)	0.62 (0.37–1.03)	**PLA**				**41.0 (2.62–642)**			
1.15 (0.88–1.50)	1.05 (0.72–1.54)	0.89 (0.64–1.23)	1.05 (0.79–1.39)	1.16 (0.88–1.54)	**1.92 (1.16–3.17)**	1.05 (0.81–1.36)	1.07 (0.80–1.45)	1.01 (0.65–1.59)	0.95 (0.71–1.29)	1.54 (0.89–2.68)	**PPS**	1.24 (0.93–1.64)					0.77 (0.45–1.33)
1.34 (1.01–1.77)	1.22 (0.82–1.80)	1.03 (0.74–1.45)	1.22 (0.90–1.64)	**1.35 (1.01–1.82)**	**2.23 (1.34–3.71)**	1.22 (0.93–1.60)	1.25 (0.91–1.71)	1.18 (0.74–1.86)	1.11 (0.81–1.52)	**1.79 (1.02–3.14)**	1.16 (0.88–1.53)	**PRM**					
0.74 (0.49–1.11)	0.67 (0.41–1.10)	**0.57 (0.36–0.89)**	0.67 (0.44–1.02)	0.75 (0.50–1.13)	1.23 (0.68–2.22)	0.67 (0.45–1.01)	0.69 (0.45–1.06)	0.65 (0.38–1.12)	**0.61 (0.40–0.94)**	0.99 (0.53–1.87)	0.64 (0.4–1.04)	**0.55 (0.34–0.90)**	**PZQ**				
1.10 (0.92–1.32)	1.01 (0.73–1.39)	0.85 (0.66–1.10)	1.01 (0.83–1.21)	1.12 (0.94–1.34)	**1.84 (1.16–2.91)**	1.01 (0.86–1.18)	1.03 (0.83–1.28)	0.97 (0.65–1.46)	0.91 (0.73–1.15)	1.48 (0.89–2.48)	0.96 (0.71–1.30)	0.83 (0.60–1.13)	1.49 (0.97–2.30)	**QC**			
2.44 (1.68–3.54)	**2.22 (1.40–3.52)**	**1.88 (1.24–2.85)**	**2.22 (1.51–3.26)**	**2.47 (1.69–3.61)**	**4.06 (2.31–7.14)**	**2.22 (1.54–3.20)**	**2.27 (1.53–3.38)**	**2.15 (1.34–3.43)**	**2.02 (1.45–2.81)**	**3.27 (1.78–6.02)**	**2.12 (1.36–3.31)**	**1.82 (1.16–2.88)**	**3.30 (1.92–5.67)**	**2.21 (1.48–3.29)**	**SAU**		
1.15 (1.00–1.31)	1.04 (0.77–1.41)	0.88 (0.70–1.11)	1.04 (0.89–1.22)	**1.16 (1.02–1.32)**	**1.91 (1.26–2.90)**	1.04 (0.93–1.17)	1.07 (0.89–1.28)	1.01 (0.69–1.48)	0.95 (0.79–1.15)	1.54 (0.93–2.53)	1.00 (0.75–1.32)	0.86 (0.64–1.15)	**1.55 (1.02–2.35)**	1.04 (0.86–1.25)	**0.47 (0.32–0.69)**	**SCZ**	1.00 (0.85–1.19)
1.35 (1.21–1.50)	1.23 (0.91–1.65)	1.04 (0.85–1.28)	**1.23 (1.06–1.42)**	**1.37 (1.20–1.56)**	**2.25 (1.46–3.47)**	**1.23 (1.12–1.35)**	**1.26 (1.07–1.49)**	1.19 (0.82–1.73)	1.12 (0.94–1.32)	**1.81 (1.10–2.97)**	1.17 (0.90–1.53)	1.01 (0.76–1.34)	**1.82 (1.21–2.75)**	**1.22 (1.02–1.47)**	**0.55 (0.38–0.80)**	**1.18 (1.04–1.33)**	**TNZ**

Numbers in bold are statistically significant.

ABZ, albendazole; AGA, *Anethum graveolens*; CQ, chloroquine; FZD, furazolidone; MBZ, mebendazole; MEN, *Mentha crispa*; MTZ, metronidazole; NTZ, nitazoxanide; OLZ, oleozon; OZN, ornidazole; PLA, placebo; PPS, propolis; PRM, paromomycin; PZQ, praziquantel; QC, quinacrine; SAU, sausalin; SCZ, secnidazole; TNZ, tinidazole.

[a]The lower triangle (in grey) shows summary RRs (95% CIs) derived in NMA (taking into account both the direct and indirect evidence) for the comparison of the drug in the row versus the drug in the column as reference. In contrast, the upper triangle (in white) shows summary RRs (95% CIs) derived in traditional pairwise meta-analysis (taking into account direct evidence only) for the comparison of the drug in the column versus the drug in the row as reference. White spaces indicate lack of direct evidence for the given comparison. Thus, for example, for the comparison of TNZ with MTZ, the RRs and 95% CIs were 1.23 (1.12–1.35) and 1.41 (1.22–1.63) according to the results from network and traditional pairwise meta-analyses, respectively.

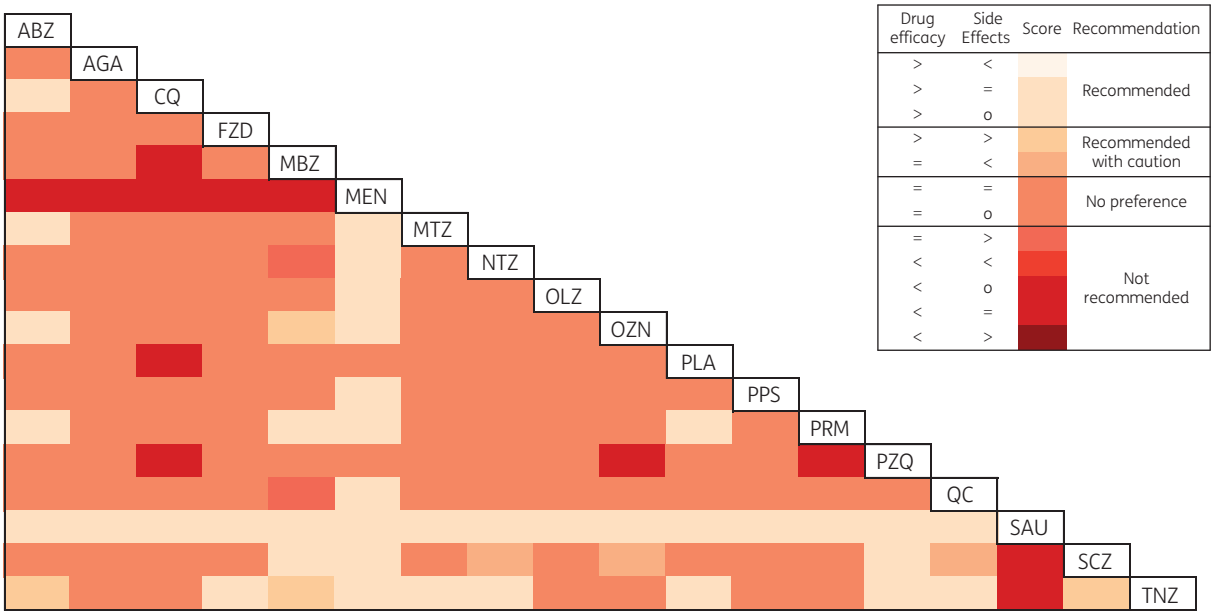

Figure 3. Joint assessment of drug efficacy and side effects (drug in the row compared with drug in the column). Symbols: >, higher drug efficacy, or more side effects than comparator drug; <, lower drug efficacy, or fewer side effects than comparator drug; =, no evidence of higher or lower drug efficacy, or of more or fewer side effects than comparator drug; o, side effects were not assessed for this comparison. ABZ, albendazole; AGA, *Anethum graveolens*; CQ, chloroquine; FZD, furazolidone; MBZ, mebendazole; MEN, *Mentha crispa*; MTZ, metronidazole; NTZ, nitazoxanide; OLZ, oleozon; OZN, ornidazole; PLA, placebo; PPS, propolis; PRM, paromomycin; PZQ, praziquantel; QC, quinacrine; SAU, sausalin; SCZ, secnidazole; TNZ, tinidazole. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

more important in clinical and public health practice than in the more controlled settings of RCTs. We used a measure of efficacy based on parasitological cure of the originally infected individual. Transmission to close contacts and potential reinfection, not generally reported in RCT results, may additionally occur. Greater efficacy of treatments is therefore likely to support better public health control than a single estimate of parasitological cure might suggest.

With regard to costs, in the UK[36] the price per gram of tinidazole (£1.38, Fasigyn 16×500 mg, Pfizer) is slightly higher than that of metronidazole (£1.13, Flagyl 14×400 mg, Zentiva). However, considering the average recommended dosage (400 mg three times a day for 7 days for metronidazole and 1500 mg single dose for tinidazole), a course of tinidazole treatment is likely to be the cheaper. Moreover, since both compounds are out of patent, cost is unlikely to be a barrier to considering tinidazole as a first-line treatment globally. Thus, inclusion of tinidazole in the next update of the WHO Essential Medicines List for the treatment of giardiasis should be considered.

Sausalin was associated with higher cure rates than all other drugs, although CIs were wider than those for tinidazole. Only one RCT used sausalin as a treatment.[37] Although it did not qualify as high risk for any of the biases assessed, risk was judged as unclear for some domains. However, in this RCT the comparator treatment (ornidazole) had a strikingly low efficacy compared with the performance of ornidazole in other trials. This combination of effects thus produces weak evidence for the very high observed relative efficacy of sausalin in indirect comparisons. Additional RCTs are needed to test sausalin in other populations and in direct comparison with front-line treatments. This may be important to guide treatment for those failing 5-NI first-line treatment or to give an evidence base for first-line treatments in areas where NI resistance is common.[3]

Previous systematic reviews and meta-analyses have argued that albendazole is as effective as metronidazole but causes fewer side effects.[16,20] We found that metronidazole was statistically significantly associated with a higher cure rate than albendazole in both traditional and network meta-analysis. Other drugs that were found to be statistically significantly better in treating giardiasis than albendazole are chloroquine, ornidazole, paromomycin, sausalin and tinidazole. Our work does not therefore support a place for albendazole in the treatment of giardiasis.

Our study has many advantages compared with previous systematic reviews, including completeness, broad criteria for inclusion and minimal exclusion criteria, external validity, wider range of treatments, and assessment of efficacy and proportion of patients with side effects for all drugs.

Our investigation has several limitations. Heterogeneity and inconsistency were substantial around designs including metronidazole, which may be a result of the high variability in the dose and duration of metronidazole. Other potential explanatory variables such as patient characteristics or study setting have been previously tested as moderators but they were not found to explain the variability in effect sizes.[15] Owing to the limited number of RCTs within each design we could not explore quantitatively the sources of heterogeneity. Overall, the quality of RCTs was moderate, the biggest problem being the lack of blinding of participants and personnel due to the different regimens (e.g. single dose versus

multiple doses) being administered. Also, because of heterogeneity and inconsistency the quality of the evidence and thus our confidence in the estimates is low to moderate. Drug efficacy is likely to be related to length of follow-up, which varied between studies. We used data from the latest timepoint available, but estimates of drug efficacy may have been influenced by cases who became cured after the end of follow-up or by instances of re-infection after initial cure. We decided *a priori* to combine treatments with different dosages to simplify the network, and so did not assess any dose-related efficacy effects. Nearly every included RCT assessed parasitological cure with microscopy methods, which are considered less sensitive than immunoassay and polymerase chain reaction methods in a single stool specimen, but highly sensitive in three or more faecal samples,[38,39] which was the methodology used by most RCTs in this review. Finally, we were not able to estimate the impact that the different drugs could have on the global public health burden or the impact on the emerging problem of metronidazole-resistant giardiasis owing to the lack of data in the included RCTs.

In this comprehensive investigation of all giardiasis treatments we provide strong evidence in favour of the adoption of tinidazole as a first-line treatment, given its higher efficacy and comparable side effects to the current mainstay therapy, metronidazole. Thus, inclusion of tinidazole in the WHO Essential Medicines List for the treatment of giardiasis should be considered. Further research is needed to clarify whether newer therapies such as sausalin may be more effective, particularly given the evidence of emerging nitroimidazole resistance.[3]

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Transparency declarations

None to declare.

Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

Supplementary data

Appendixes 1 to 3, Tables S1 to S17 and Figures S1 to S4 are available as Supplementary data at *JAC* Online.

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