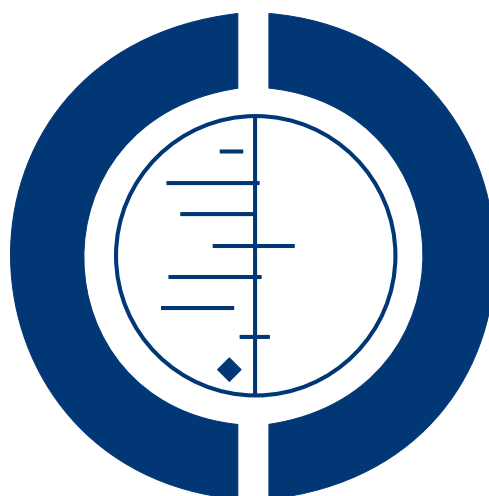


# Trypanocidal drugs for chronic asymptomatic *Trypanosoma cruzi* infection (Review)

Villar JC, Villar LA, Marin-Neto JA, Ebrahim S, Yusuf S



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[Intervention Review]

# Trypanocidal drugs for chronic asymptomatic *Trypanosoma cruzi* infection

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## ABSTRACT

### Background

Prior guidelines stated that trypanocidal therapy should not be used for treating chronic asymptomatic *Trypanosoma cruzi* infections. However, the recent availability of clinical trials reporting high rates of parasitologic cure in children with early chronic *T. cruzi* infection have produced changes of these recommendations in some countries. Because of the uncertainty regarding best treatment for this stage of *T. cruzi* infections, the literature was reviewed systematically for a synthesis of the available evidence.

### Objectives

To assess the effects of trypanocidal therapy for chronic asymptomatic *T. cruzi* infection

### Search methods

We searched The Cochrane Controlled Trials Register (Issue 1, 2000), MEDLINE (start-Nov 1999), EMBASE (start - Feb 2000), LILACS (start - Feb 2000) and the Tropical Diseases Research Division of WHO database (Start - Feb 2000) . Reference lists of articles were searched for relevant material.

### Selection criteria

Published RCTs of trypanocidal therapy for people with chronic, asymptomatic *T. cruzi* infections

### Data collection and analysis

Two reviewers independently screened papers for inclusion criteria, quality assessment and data extraction. Forms were used to collect data. Reviewers resolved differences by discussion then a third reviewer if necessary.

### Main results

Of 43 papers assessed for inclusion, five RCTs (total population=756) met the inclusion criteria. The quality of the trials was rated as low (n=3) or intermediate (n=2). Two RCTs tested benznidazole in school children and three tested different agents in adults. The Odds Ratios and their 95%CI (Fixed models) were: Incidence of ECG abnormalities: 0.41 (0.09, 1.85); Negative seroconversion (AT

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ELISA): 10.91 (6.07, 19.58); Negative xenodiagnosis during the follow up: 5.37 (3.34, 8.64); Standardised mean reduction of antibody titres: 0.54 (0.31, 0.84). Nitroimidazolic derivatives substantially and significantly modified parasite-related outcomes compared to placebo. Other agents showed borderline or not significant effect.

### Authors' conclusions

Despite major public health importance, trypanocidal-therapy for chronic asymptomatic *T. cruzi* infection has been tested in few, small size RCTs which were designed to assess parasitic-related, but not clinical outcomes. Therefore, the potential of trypanocidal therapy to prevent Chagas' disease among asymptomatic, chronically infected subjects is promising, but remains to be evaluated. Trypanocidal therapy, particularly nitroimidazolic derivatives given to children or adults with positive xenodiagnosis improve parasite-related outcomes. The large contrast between the burden of Chagas disease and the existing evidence on its prevention points the need to test these or newer agents in more and larger RCTs that include clinical endpoints.

## PLAIN LANGUAGE SUMMARY

### Studies testing anti-parasitic drugs for people infected, but still free of Chagas' disease, are scarce and fail to provide evidence about them as preventive medications.

*Trypanosoma cruzi*, a parasite causing Chagas' disease, infects about 18 million people living across Latin America. About 30% of them develop a major heart disease in their 30s or 40s, after decades of silent infection. No treatment is considered useful for preventing the disease among those infected, but still healthy. Drugs aimed to destroy the parasites may have this potential. Reviewers found only five published trials including 756 participants testing such agents. Although the anti-parasitic activity of most of these compounds was documented, no study addressed the efficacy of the drugs in terms of signs or symptoms of the disease.

## BACKGROUND

Chagas' heart disease (CHAD) is the result of human infection by *Trypanosoma cruzi*. Ninety years after its first description (Chagas 1909) Chagas heart disease is endemic in 21 Latin American countries, where the WHO estimates that 16-18 million people are infected and 100 million are at risk (WHO 2000). It accounts for the loss of 2,740,000 disability adjusted life years (Murray 2000), four times the burden caused by malaria, schistosomiasis, leprosy and leishmaniasis altogether in the Americas (Schmunis 1994). Once primary infection is acquired, spontaneous clinical resolution occurs in 95%-99% of cases (WHO 1991, Laranja 1956). Then, chronically infected individuals become seropositive and remain asymptomatic for the next 10-30 years, when, if the electrocardiogram is normal and no evidence of cardiomegaly or digestive megavisera is observed at X rays, they are known to be in the indeterminate phase (IP) (WHO 1991). Of these individuals, about 30% will progress to the chronic phase (CP), which is characterised by an irreversible dilated cardiomyopathy (Prata; WHO 1991; Laranja 1956). Until now, the only measure useful to reduce the burden of Chagas heart disease has been the vector control, a policy responsible for the interruption of the transmission of Chagas heart disease in southern South America (PAHO

1998, Schmunis 1996). Despite these advances in reducing the incidence of *T. cruzi* infection, the burden of Chagas heart disease is expected to continue in the future since virtually all the burden of Chagas heart disease comes from individuals already infected who progress from the indeterminate phase to the chronic phase. Unfortunately, the trypanocidal treatment currently available considered useful only for treating either the acute phase or the reactivation of Chagas heart disease (WHO 1991, Sosa 1999, Fragata 1995). Thus, an effective treatment for chronic *T. cruzi* infection, particularly for those individuals still in the indeterminate phase of Chagas heart disease is a high priority and will be a necessary complement to the vector control policy to achieve a sustained reduction of the burden of Chagas heart disease in the mid and long term.

Nitrofurans, the first trypanocide agents developed, were introduced to treat *T. cruzi* infections in 1962. Since then, two new trypanocidal treatments have become available for use in humans. These are the nitroimidazolic derivatives, nifurtimox (NFTMX) and benznidazole (BZD) (Cançado 1976, Brener 1975; Apt 1985). However, severe side effects mean that in most endemic countries BZD alone is used to treat *T. cruzi* infections (Fragata 1995, Sosa 1999).

Unfortunately, only a small number of additional agents (other imidazolic derivatives, purine-analogue agents or ergosterol-synthesis blockers) have been tested in animal or phase I/ phase II clinical trials (Marr 1986, Urbina 1999, De Castro 1993). In addition, logistic constraints, limited knowledge of the natural history of Chagas heart disease as well as the lack of diagnostic tools to evaluate the success of treatment have made it difficult to define appropriate follow-up periods and clinical endpoints in clinical trials (Moncayo 1994).

Other factors have also discouraged the enthusiasm for trypanocidal treatments for Chagas heart disease. The observation of scarce number of parasites in blood or tissues in hearts of people with Chagas disease caused doubt about the aetiology of Chagas heart disease. Moreover, it has been thought that demonstration of *T. cruzi* in the blood and tissues is not sufficient cause to develop Chagas disease. As a result, mechanisms of disease independent of the effect of parasitic load were proposed (Rossi 1995). More recently however, observations have challenged this concept, giving to the parasites a critical importance for causation of Chagas heart disease.

·DNA hybridisation techniques have shown that circulating parasitic load and parasitic DNA/antigens in tissues correlate with the degree of inflammation, which targets only affected organs (Marinho 1999, Jones 1993, Higuchi 1997).

·Clinical trials using better diagnostic tests and research designs have reported high rates of cure in children with early chronic *T. cruzi* infection and recommend trypanocidal therapy for the indeterminate phase of Chagas disease. (Sosa 1998, de Andrade 1996).

In addition lack of data on the long term efficacy of trypanocidal treatments contributed to lack of enthusiasm for their use.

Thus, the debate on the role of parasites in the disease and the recommendation of trypanocidal therapy for the indeterminate phase of Chagas heart disease has been re-opened (Bestetti 1996, Bestetti 1997, Andrade 1997, Ianni 1998). Because of the uncertainty regarding best treatment for this stage of *T. cruzi* infections a systematic review of the trial data is appropriate.

## OBJECTIVES

To provide a synthesis of the best evidence available on the effects of trypanocidal treatment of asymptomatic *T. cruzi* infection.

## METHODS

### Criteria for considering studies for this review

### Types of studies

We included published trials that randomly allocated participants with chronic *T. cruzi* infection, without symptomatic Chagas' heart disease, to one or more of the trypanocidal drugs (as listed in De Castro 1993) or to a control treatment or placebo

### Types of participants

Participants must not have symptomatic Chagas' heart disease. No restrictions on age, gender, country or language were set.

### Types of interventions

Oral trypanocidal therapies e.g. Nitroimidazolic derivatives such as nifurtimox (NFTMX) and benznidazole (BZD). Other oral trypanocidal therapies allopurinol (ALLOP) and itraconazole (ITRA). In any dose given for at least 30 days and compared against a control or placebo.

### Types of outcome measures

Studies had to include at least one of the following outcomes

#### CLINICAL OUTCOMES:

All-cause mortality

Sudden death

Incidence of heart failure

Side effects of treatment.

#### PARASITE-RELATED OUTCOMES

At present there are no direct methods to measure *T. cruzi* parasite load. Therefore, some surrogate measures are used to assess this indirectly. The most common are the serology, where the presence or absence of "anti-*T. cruzi*" antibodies found in the blood stream is measured and a technique of parasitologic diagnosis called "xenodiagnosis".

Serology is carried out in clinical laboratories and has two elements, quantitative, "what is the concentration of antibodies (proteins called immunoglobulins) in the blood? ", and qualitative "is the quantity sufficient for this laboratory to state the patient is positive for this disease?". There are several methods for measuring the presence of antibody in the blood. The most commonly used methods to diagnose Chagas' disease are ELISA (Enzyme linked immunosorbent assay), indirect haemagglutination and indirect immunofluorescence (IIF). Each has different units of measurement that can be approximated to the quantity of antibody. Laboratories express the amount of antibodies found in a test depending on the technique used. For example "titres", when the technique requires to dilute (with water) the serum being tested for antibodies 2,4,8,16 times etc. Other techniques measure changes in light absorbance in a colour-producing reaction linked to enzymes (ELISA) or the amount of (antibodies in the) serum needed for producing certain amount of fluorescent light (immunofluorescence). Typically, after any assessment of antibodies for a given

infectious disease the laboratory will assign a "status" to the reaction as positive or negative i.e. the patient is defined as seropositive - has the disease, or seronegative, does not have the disease. Each laboratory has its own "boundaries" for assigning this status depending on the serological technique used. Thus, the serological status is, in the end, a qualitative assumption resulting from a quantitative assessment.

Xenodiagnosis is a test for parasite infection, in which another species is used as growth medium for the parasite sought. The natural vector of *T.cruzi* (reduviduae) are laboratory bred to ensure they do not carry any parasites. Reduviduae nymphs are allowed to feed on the blood of the individual being tested. After their blood meal the nymphs are reared for some days. The gut contents of nymphs are then searched for *T.cruzi* parasites. If parasites are found in the reduviduae insects, the patient has *T.cruzi* infection or "positive xenodiagnosis".

#### OUTCOME 1 NEGATIVE SEROCONVERSION

Seroconversion for this review was defined as a qualitative change in the serological status against *T.cruzi* after treatment.

"Negative seroconversion" is defined as a change to the serological reaction against *T. cruzi* from being "seropositive" before randomisation, to become "seronegative" after the treatment. Seropositive and Seronegative are defined by the laboratories in which the blood was analysed.

#### OUTCOME 2. ANTIBODY TITRES MEAN REDUCTION

We also looked at the mean reduction of antibody titres after treatment as an outcome.

#### OUTCOME 3. NEGATIVE XENODIAGNOSIS AFTER TREATMENT

The proportion of patients with negative xenodiagnosis after treatment was also considered as outcome of this review.

### Search methods for identification of studies

The following electronic sources of biomedical information were consulted: MEDLINE (start - Nov 1999), EMBASE (start - Feb 2000), LILACS (Start - Feb 2000), The Cochrane Controlled Trials Register (CCTR, Issue 1, 2000) and Tropical Diseases Research Division at the WHO (start - Feb 2.000). The search was complemented with a hand search of review articles retrieved in previous systematic appraisal of these studies (Villar 2000).

Except in the case of the CCTR, for consistency, we used the same search strategy criteria in all databases, with the equivalent English, Spanish and Portuguese terms for ["Trypanosomiasis" or "Chagas"] and ["Chemotherapy" or "Treatment"] in the title or abstract.

Relevant papers were identified in a two step process.

#### Step 1

Titles and abstracts (or full papers if no abstract available) of all retrieved citations were screened for pre-selection. References were pre-selected for further exam when they referred to all the following:

- a) human participants
- b) treatment of Chagas disease
- c) trypanocidal agents.

#### Step 2

Full papers of all pre-selected references were appraised by two reviewers independently for inclusion criteria. Differences in opinion were resolved by consensus and a third reviewer opinion if necessary.

### Data collection and analysis

#### DATA ABSTRACTION AND SYNTHESIS

A "data abstraction" form was designed for collecting information from relevant studies. It included general characteristics of the studies, information on demographics, disease, intervention, follow-up, outcomes and a quality assessment (Jadad 1996). Two independent reviewers abstracted the information from each study, and their eventual differences were resolved by discussion and a third reviewer opinion if necessary. Agreement between reviewers for quality assessment was calculated. All Kappa coefficients were calculated by using the PC AGREE program (1994, McMaster University). A descriptive review of the trials was performed.

#### DATA ANALYSIS - Clinical endpoints

When appropriate, pooled effect estimates and their 95% confidence intervals of the individual clinical endpoints were obtained by computing odds ratios (OR) using the method proposed by Yusuf and Peto (Yusuf 1985) and the random models statistical approach.

#### DATA ANALYSIS - Diagnosis of trypanosomiasis and assessment of parasite load

#### SEROLOGICAL STATUS, "ANTI-T.cruzi" ANTIBODY TITRE, XENODIAGNOSIS

Changes in serology were examined quantitatively by pooling the standardised weighted mean differences after intervention. Individual differences were computed by subtracting the mean antibody titre after treatment from the mean antibody titre at baseline. For each study the variance of the mean differences was inferred using the methodology suggested by Follmann (Follmann 1992). When available, for parasite-related outcomes, both symptomatic and asymptomatic *T. cruzi* chronically infected patients were included in the analysis.

If appropriate, further stratified analysis by categories (i.e. type of participants, type of agents) was planned. All computations were performed using Metaview 4.1 (2000, The Cochrane collaboration software).

## RESULTS

## Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

All five studies were phase-three RCTs. Four of the five had parallel design and the other re-allocated patients initially on placebo to either of two active treatment arms ([Apt 1998](#)). In this trial the comparison All trials were reported as randomised, double blind and placebo-controlled. General characteristics of the included studies are described in the Table of Included Studies.

Three of the studies were published originally in English, one in Portuguese and one in Spanish. Two Studies were conducted in Brazil ([Andrade, Coura 1997](#)), one was conducted in Chile ([Apt 1998](#)), one in Argentina ([Sosa-Estani](#)) and one in Bolivia ([Gianella 1997](#)). Three studies included participants from one location covering suburban and/or rural populations and two were multi centre studies. The total number of randomised participants in the five studies was 756. Four papers were published in specialised journals in parasitology or tropical medicine ([Sosa 1998](#), [Apt 1998](#), [Gianella 1997](#), [Coura 1997](#)) and the other in a general Journal ([de Andrad 1996](#)). No association with pharmaceutical companies or other potential conflicts of interest were declared in the reports. In the three studies where the ECG status of participants at baseline was reported, at least 70% of trial participants were in the Indeterminate Phase of Chagas disease. Two studies tested BZD in school children ([Andrade, Sosa-Estani](#)) the whereas the other three ([Apt 1998](#), [Coura, Gianella](#)) randomised adults to treatment with either BZD, NFTMX, allopurinol (ALLOP) or itraconazole (ITRA). Only one study ([Andrade](#)) reported clearly the gender distribution of participants. In that study 70 of 129 (54.2%) of participants were male.

Control of re-infection

Three studies ([Sosa-Estani, Andrade, Coura](#)) were performed in endemic areas which were, or had been under epidemiologic vigilance by vector control campaigns. The trialists documented the probability of re-infection by screening and surveying periodically the rates of seroconversion. Control of re-infection was not reported in the trials by [Apt 1998](#) and [Gianella](#).

Diagnosis of *T. cruzi* infection

At least two positive serological tests (ELISA, Indirect haemagglutination and Indirect Immunofluorescence) were required to diagnose chronic *T. cruzi* infection in all studies. Xenodiagnosis was used as one of the outcomes of the effects of trypanocidal therapy in three of them ([Apt 1998, Gianella, Coura](#)) and was employed as a diagnostic sub study in another ([Sosa-Estani](#)). DNA hybridization methods for parasite counting were not used in any of the studies. Further biochemical or genetic characterisation of *T. Cruzi* were not performed either.

Interventions

Four trypanocidal agents, BZD, ALLOP, NFTMX and ITRA were tested in the included studies. Three studies tested the effect of BZD (BZD) with different regimens: [Sosa-Estani](#) tested BZD 5 mg/kg/day for 8 weeks; [Andrade](#) tested BZD 7.5 mg/kg/day for

8 weeks and [Coura](#) tested BZD 5 mg/kg/day for 30 days. [Apt 1998](#) and [Gianella](#) tested ALLOP in similar regimens (8.5 mg/kg/day or 300 mg T.I.D). The [Apt 1998](#) study tested the effect of ITRA (6.5 mgs/kg/day for 16 weeks) and [Coura](#) tested NFTMX (5 mg/kg/day for 30 days). All studies were placebo-controlled. No co-interventions were done in any study. The summary of the interventions in the included studies is shown in the summary table of included studies.

Follow-up and drop-outs

Overall follow-up varied from 12 months ([Coura, Gianella](#)) to 48 months ([Apt 1998, Sosa-Estani](#)). Up to 5-6 time points were used to perform serological tests and clinical assessments (if needed). [Andrade](#) reported that 86% of participants finished the protocol. Only one of seventeen dropouts was attributable to side effect of the medication (BZD). Participants who dropped out of this study had no clinical or serological differences to the population remaining in the study. [Sosa-Estani](#) reported that 6 of 55 (11%) BZD-treated children dropped out because of side effects (defined in the study protocol as the need to stop study medication, but no need for hospitalisation). [Apt 1998](#) reported 62/217 (28.6%) dropouts in those who received itraconazole compared to 2/187 (1.1%) subjects (symptomatic and asymptomatic) allocated to ALLOP and attributed that to the length of treatment required with ITRA as the main cause. [Gianella](#) reported 10 dropouts, five for each arm of treatment.

## Risk of bias in included studies

None of the included trials reported methods for randomisation, methods for concealing the treatment allocation, or methods of blinding for outcome assessment. None described the characteristics of the placebo either. Two, [Andrade](#) and [Sosa-Estani](#), described the details of the withdrawals during the trial. [Andrade](#) performed an intention-to-treat analysis and reported a sample size calculation beforehand.

## Effects of interventions

Study selection

Five randomised controlled trials were identified as eligible for inclusion in this systematic review. Taking all the sources of studies together, 1306 abstracts were screened for eligibility, from which 87 (6.7%) were considered as potentially relevant. Because of the overlap among databases, a total of 44 of these studies were pre-selected for further appraisal. 6 of these studies were located in LILACS (6) and the Tropical Diseases Research Division database (1) exclusively, whereas 36 (81.8%) appeared in MEDLINE, overlapping with the references placed in EMBASE (17) or the CCTR (13). Of the 44 papers evaluated in full, 5 (11.4%) met the inclusion criteria. The 39 excluded studies did not contain original data (n=18), were experimental studies other than RCTs (n=14), did



not include the target population of this review (n=5), were observational studies (n=5) or contained duplicated information (n=1). The Characteristics of excluded studies table summarises the reasons for exclusion of these papers. Putting together all the reasons for exclusion, agreement for inclusion/exclusion was reached in 42 of the 44 papers (Kappa=0.807, p<0.001) between reviewers. Of the two studies classified differently in the independent assessment, one was finally considered as an observational study and the other as a preliminary report of an RCT whose data had been duplicated by the authors in a further publication. Both studies were excluded. No third reviewer's opinion was necessary.

#### Outcomes and data synthesis

Primary and secondary outcomes were pre-defined in three studies (Sosa-Estani, Andrade, Gianella). The only clinical outcome evaluated was the incidence of ECG changes in those participants in the indeterminate phase of Chagas disease in two studies (Andrade, Sosa-Estani, n=198). Another report (Apt 1998) showed data on electrocardiogram, but not by allocated treatment. Conversely, all studies reported parasitic-related outcomes before and after the trypanocidal therapy, using study-specific definitions. Serological status was reported in three studies (Andrade, Coura, Sosa-Estani, n=277). Negative seroconversion was assessed as outcome using different techniques: Coura and Sosa-Estani assessed this outcome by conventional serology, whereas Andrade used the AT ELISA technique (Almeida 1995). Sosa-Estani's RCT AT ELISA results were reported in a separate publication (Almeida 1999). Xenodiagnosis (in terms of rate of randomised participants with negative tests after treatment) were reported by four studies (Apt 1998, Coura, Gianella, Sosa-Estani, n=693). Finally, differences in antibody titres after receiving trypanocidal therapy were reported in three studies (Andrade, Sosa-Estani, Gianella, n=230).

The pooled Odds ratios (OR) and their 95% confidence intervals, as computed by the Yusuf-Peto and the random models methods were respectively: Incidence of ECG Changes: 0.41 (0.09, 1.85) and 0.41 (0.07, 2.35); Negative seroconversion, as assessed by AT ELISA:

10.91 (6.07, 19.58) and 22.33 (8.92, 55.89); Negative xenodiagnosis after treatment: 5.37 (3.34, 8.64) and 4.97 (3.08, 8.02); The pooled antibody titres standardised mean reductions (by subtracting titres before trypanocidal therapy from titres after trypanocidal therapy) using Indirect Immunofluorescence were 0.58 (0.31, 0.84) and 0.54 (0.19, 0.89). Data synthesis results for pooled outcomes including all information available are shown in the comparisons under the tables section.

After pooling the data for these outcomes, heterogeneity among studies was found for xenodiagnosis (heterogeneity test, p<0.001). The analysis of this outcome by different categories is shown in the comparison tables for negative xenodiagnosis across different categories. Both populations and agents used in the trials were observed to account for heterogeneity in the results for this outcome. Among adults included in the trials heterogeneity was observed (p<0.001). Adults treated with Nitrosamine derivatives (NFTMX or BZD)

had significantly higher rates of negative xenodiagnosis compared to adults treated with other agents ALLOP or ITRA. Similar results were observed when the children and adults treated with BZD, compared to those treated with no nitrosamine derivatives. Individually, BZD and NFTMX treated participants achieved substantial and significant differences in the rates of negative xenodiagnosis after treatment compared to ALLOP and ITRA treated participants. For adults treated with BZD and NFTMX (Coura) the OR (95% CI, Yusuf-Peto method) were 31.44 (10.35, 95.47) and 14.82 (4.82, 45.59). It decreased to 2.53 (1.14, 5.64) and 1.54 (0.77, 3.08) in adults treated with ITRA (Apt 1998) and ALLOP (Apt 1998 and Gianella) respectively. The xenodiagnosis at baseline was also a source of heterogeneity in the results for this outcome. The OR (95% CI, using the Yusuf-Peto method) for negative xenodiagnosis after treatment in participants with positive xenodiagnosis at the baseline was 16.4 (7.91, 34.03), whereas for those with negative xenodiagnosis when randomised was 1.30 (0.43, 3.94).

For negative seroconversion, data using conventional serology differ from the pooled outcome using AT ELISA shown above: Coura reported no changes in the serological status in any of the adults allocated to either treatment group (Not estimable OR). Sosa-Estani reported negative seroconversion in 5 of 44 BZD-treated children and 2 of 44 of placebo-treated children (2P=0.433, Fisher's exact test).

#### Side effects

Of two studies testing BZD in children, 7 of 115 treated dropped out of the study because of side effects. However, the criteria for discontinuation were different in both studies. Andrade reported that less than 5% of participants complained of a variety of minor symptoms, but rash and pruritus were reported as higher in those receiving the drug (8/64 with BZD versus 2/65 with Placebo, p=0.094). Sosa-Estani stated a general good tolerance of children to BZD and reported no severe side effects, but a 11% incidence of moderate side effects who dropped out as stated above. Overall, this study estimated the incidence of side effects as less than 20%. The only study testing BZD in adults reported a non quantified variety of mild side effects (skin reactions, peripheral neuropathy, digestive disturbances), but stated that they were less intense than those seen with NFTMX.

Side effects were also reported in studies testing ALLOP or ITRA. Apt 1998 stratified tolerance into satisfactory, moderate and unsatisfactory and reported no significant differences between placebo and active treatment. A proportion of 10.3%, 9.7% and 6.7% of those receiving ALLOP, ITRA and Placebo respectively reported moderate side effects (p=0.412). However, one case of Stevens-Johnson syndrome was observed among 155 patients treated with ALLOP in this study. Gianella also reported one case of severe skin reaction requiring hospitalisation and steroid treatment among 13 patients evaluated who were allocated to ALLOP. Three studies (Apt 1998, Andrade, Sosa-Estani) evaluated blood chemistry (liver enzymes, blood cell counts) but did not report abnormalities in



children under trypanocidal therapy. [Apt 1998](#) reported a transient increase in aspartate aminotransferase and alkaline phosphatase in three of 185 patients receiving ITRA.

## DISCUSSION

Chagas heart disease is one example of the contrast between the burden of a disease and the intensity with which it is researched. As observed in this review, despite major public health importance, until now trypanocidal therapy for chronic asymptomatic *T. cruzi* infection has been tested in 756 participants, randomised in five studies, all of them published after 1995. These trials were not designed to assess clinical outcomes and failed to report key methodological issues. In addition, because of the sparsity of data reported, none of the pooled outcomes included all randomised participants. Thus, all observations on the effects of these agents for chronic asymptomatic *T. cruzi* infection should be interpreted in the light of the small number of participants in studies not intended to evaluate clinical outcomes. Hence, at present, no experimental evidence is available to support any recommendation on the clinical use of trypanocidal therapy for improving clinical outcomes in chronic asymptomatic *T. cruzi* infection.

The most important finding in this review was that trypanocidal therapy, in particular Nitroimidazolic derivatives, improved parasite-related outcomes. BZD had the greatest effect, it

significantly reduced the proportion of positive xenodiagnoses in both children and adults, produced negative seroconversion in children, when serology was tested (using the AT ELISA technique) and reduced the antibody titres in children (as assessed by IIF). Conversely studies testing ALLOP or ITRA demonstrated a substantially lower, though not significant effect on these outcomes. In addition to the lower effect on parasite load, all the severe side effects reported in the trials included in this review occurred in participants treated with these agents (1.1%). Although these results are in favour of the use of BZD in children and either NFTMX or BZD for adults for reducing antibodies or the parasite load respectively, whether this effect will result in clinical benefit remains to be proven. Moreover, although effective for parasite clearance, a variety of side effects were reported in up to 20% of participants treated with nitroimidazolic derivatives. While these promising results with parasite-related outcomes provide a spur to reduce the uncertainty about the clinical effect of these agents, they also make a case for the development of more and safer trypanocidal agents available for clinical practice, as suggested by others ([Urbina 1999](#)).

Most data presented in this review comprised parasite-related outcomes, assessed either by xenodiagnosis or serology. Xenodiagnosis was the most widely used test across the studies included in this review. Despite its obvious problems for patients' comfort while

being tested, it has remained the best available tool to recover *T. cruzi*. However, it fails to detect circulating parasites in 40-80% of cases, particularly in the Indeterminate Phase of Chagas disease when parasitaemia is thought to be low ([Castro 1999](#)). Such a lack of sensitivity is in itself a problem to reliably evaluate parasitic cure ([Britto 1999](#)). Indeed, only 70 of 296 (23.6%) of the xenodiagnosis performed were positive during the follow-up among seropositive participants randomised to placebo. The relevance of this issue is highlighted by the fact that patients with positive xenodiagnosis (and perhaps higher parasite loads) at baseline seem to benefit more from trypanocidal therapy. "Conventional" serology, the other diagnostic tool, is used to define an individual as infected, if confirmed by at least two different techniques (i.e. indirect haemagglutination and ELISA tests accordingly positive in a given individual) most commonly using "whole" *T. cruzi* antigens. Its value as a tool for assessment of parasite clearance is still to be proven. Indeed, both Coura and Sosa-Estani found a significantly lower number of positive xenodiagnosis in participants treated with nitrosamine derivatives, but all treated adults kept their serological status ([Coura](#)) and children (when tested with conventional serology) did not have a significantly different rate of negative seroconversion ([Sosa-Estani](#)). Conversely, when participants' serological status was diagnosed by a more specific serological technique, such as AT ELISA, this outcome turned out to be highly significant. Thus, the extent to which antibodies (in terms of either serological status or antibody titres) correlates with parasitic load (in terms of xenodiagnosis, haemoculture or polymerase chain reaction) also remains unclear and adds complexity to the evaluation of chemotherapy for Chagas heart disease. Although the efficacy of nitroimidazolic derivatives was demonstrated in terms of parasite-related outcomes as compared to placebo, assessing the absolute trypanocidal effect is still an unsolved problem. Hence, beside newer trypanocidal agents to be tested, better diagnostic techniques are also needed for improved appraisal of their effectiveness.

Clinical outcomes were not considered in the RCTs included in this review. Only two studies reported the incidence of ECG abnormalities in participants with Indeterminate Phase of Chagas heart disease at baseline. Despite a remarkable completion of a three or four year follow-up of school children of suburban areas of Brazil and Argentina, only seven abnormal ECGs out of 198 (3.5%) were found. Although such low number of events does not allow further speculation, it points to the need to take into account the low-rate of events in the design of further studies. Likewise, data provided by this review are not sufficient to address the relationship between parasitic-related and clinical outcomes. Thus, a better understanding of both the natural history and the pathogenic role of parasites in Chagas heart disease is needed for future trypanocidal therapy trials.

## AUTHORS' CONCLUSIONS

## Implications for practice

Few clinical events were recorded in the trials included in this review. There remains uncertainty in the belief that reducing parasitic load may modify the natural history of *T. cruzi* infection and therefore the severity of any subsequent heart disease. An additional issue for clinicians is the relatively high rate of side effects found with the use of anti-trypanocidal drugs. If trypanocidal therapy were indicated on individual basis, our review provides evidence on the differential effect of nitrosamine derivatives over other type of drugs. Since trypanocidal therapy seems to be more effective in people with positive xenodiagnosis, these patients would have higher possibility of benefit from treatment.

## Implications for research

Further clinical research in Chagas heart disease embraces many challenges: conducting more and larger trials that test newer agents; using better techniques for parasite identification, and using risk stratification tools for a better estimation of the number of events. Recording clinical events in trials involving *T. cruzi*-infected populations is likely to be more reliable than parasite-related outcomes and is necessary to provide more definitive, clinically relevant answers on the efficacy of these agents. Prospective analysis based on clinical outcomes will also provide a better understanding of the pathogenesis of the disease. Meanwhile, recommendations about trypanocidal therapy in Indeterminate Phase of Chagas disease should be considered as valid only for parasite-related outcomes and based on small pieces of evidence. Research to provide evidence that is lacking remains a high priority for governments of Latin America and a challenge for the regional scien-

tific community.

## Conclusion

Trypanocidal therapy for chronic asymptomatic *T. cruzi* infection has been tested in five randomised controlled trials including 756 randomised participants that were designed to evaluate parasite-related, but not clinical outcomes. Nitroimidazolic derivatives, especially BZD improve parasite-related outcomes in both adults and children. Other agents, such as itraconazole or allopurinol have much lower, or neutral effect on these outcomes. These promising results in parasite load reduction are to be considered together with the rate of side effects reported in the trials of 10% to 20%. Given the importance of Chagas heart disease for public health in Latin America, randomised controlled trials should be done that can add more information to these results should be done so the effects and harms can be confirmed for clinical endpoints along with parasitic endpoints.

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\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Andrade

Methods	4
Participants	School children (90% in IP)
Interventions	BZD (n=64) 7.5 mg/k/d (8 wk) Placebo (n=65)
Outcomes	Serological status recorded Antibody titres reported Incidence of ECG abnormalities
Notes	Brazil, 1996

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

#### Apt

Methods	1
Participants	Adults (70% in IP)
Interventions	ALLOP (n=187) 8.5 mg/k/d (8 wk) ITRA (n=217) 6 mg/k/d (16 wk) Placebo (n=24)
Outcomes	Xenodiagnosis recorded ECG changes reported but not described by treatment allocation Side effects
Notes	Chile, 1998

#### *Risk of bias*

Item	Authors' judgement	Description
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**Apt** (Continued)

Allocation concealment?	No	C - Inadequate
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**Coura**

Methods	2	
Participants	Adults (% in IP NA)	
Interventions	BZD (n=26) 5 mg/k/d (4 wk) NFTMX (n=27) 5 mg/k/d (4 wk) Placebo (n=24)	
Outcomes	Serological status recorded Xenodiagnosis recorded	
Notes	Brazil, 1997	

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Gianella**

Methods	2	
Participants	Adults (% in IP NA)	
Interventions	ALLO (n=20) 300mg TID (8wk) Placebo	
Outcomes	Antibody titres recorded Xenodiagnosis recorded	
Notes	Bolivia, 1997	

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Sosa-Estani**

Methods	3
Participants	School children (95% in IP)
Interventions	BZD (n=55) 5 mg/k/d (8wk) Placebo
Outcomes	Serological status recorded Antibody titres recorded Xenodiagnosis recorded Incidence of ECG abnormalities
Notes	Argentina, 1998

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Methods were assessed by using the scale described by Jadad et al 1996. A point is awarded if

- 1 the study was described as randomised (additional point given if method to generate sequence was given and was appropriate a point deducted if described and inappropriate).
- 2 The study is described as double blind ( additional point given if method of blinding described and appropriate, a point deducted if described and inappropriate) and
- 3 the number of withdrawals and drop outs are reported

IP: Indeterminate phase

NA: Not available in the report

BZD: Benznidazole

NFTMX: Nifurtimox

ALLO: Allopurinol

ITRA: Itraconazole

**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Abitbol	Study not reporting original data
Aguilera	Original studies, other than RCTs
Amato	Study not reporting original data

(Continued)

Amato (a)	Study not reporting original data
Andrade (a)	Original studies, other than RCTs Study population out of the scope
Andrade (b)	Original studies, other than RCTs Study population out of the scope
Apt (a)	Study not reporting original data
Apt (b)	Duplicated data
Bestetti	Study not reporting original data
Bocca Tourres	Original studies, other than RCTs Study population out of the scope
Brener	Study not reporting original data
Carpintero	Original studies, other than RCTs
Coura (a)	Study not reporting original data
De Araujo Malta	Study not reporting original data
De Oliveira	Original studies, other than RCTs Study population out of the scope
De Oliveira (a)	Original studies, other than RCTs
Fernandez	Original studies, other than RCTs Study population out of the scope
Fragata	Study not reporting original data
Gallerano	Original studies, other than RCTs
Gallerano (a)	Original studies, other than RCTs
Gonnert	Original studies, other than RCTs
Gutteridge	Study not reporting original data
Ivanovic	Study not reporting original data
Levi	Original studies, other than RCTs

(Continued)

Levi (a)	Study not reporting original data
López-Antuñaño	Study not reporting original data
Maldonado	Original studies, other than RCTs
Marr	Study not reporting original data
Meirovich	Original studies, other than RCTs
Mendoza	Study not reporting original data Study related to drugs other than trypanocidal therapy
Prata	Original studies, other than RCTs
Rassi	Study not reporting original data
Romeu Cançado	Study not reporting original data
Rubio	Original studies, other than RCTs
Santana	Study not reporting original data
Viotti	Original studies, other than RCTs
Wegner	Original studies, other than RCTs Study population out of the scope
Wegner (a)	Original studies, other than RCTs Study population out of the scope

## DATA AND ANALYSES

### Comparison 1. Incidence of ECG abnormalities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 BZD Children	2	198	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.09, 1.85]

### Comparison 2. Negative seroconversion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 BZD - AT ELISA - CHILDREN	2	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.91 [6.07, 19.58]

### Comparison 3. Negative xenodiagnosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All populations- All tested agents	4	693	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.37 [3.34, 8.64]
2 Children - BZD	1	85	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.61 [3.76, 24.58]
3 Adults - All tested agents	3	608	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.40 [2.54, 7.63]
4 Adults - Nitrosamine derivatives	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	22.24 [8.45, 58.56]
5 Adults - Drugs other than nitrosamine derivatives	2	531	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.04, 3.96]
6 BZD - Children and adults	2	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	15.75 [7.69, 32.27]
7 NFTMX - Adults	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	14.82 [4.82, 45.59]
8 ITRA - Adults	1	319	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.53 [1.14, 5.64]
9 ALLOP - Adults	2	377	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.77, 3.08]
10 Positive xenodiagnosis at baseline (Adults)	3	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	16.40 [7.91, 34.03]
11 Negative xenodiagnosis at baseline (Adults / Drugs other than nitrosamine derivatives)	1	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.43, 3.94]



#### Comparison 4. Reduction of antibody titres

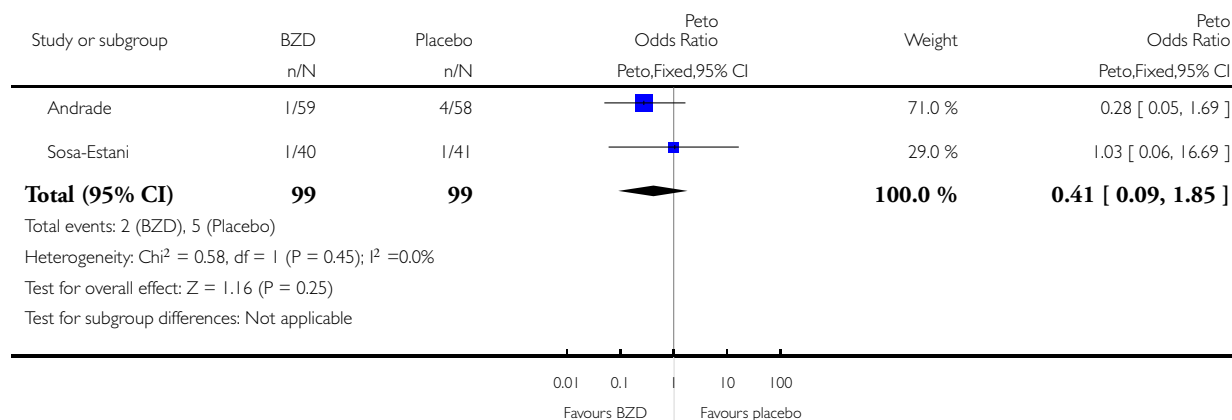
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All available studies (Indirect immunofluorescence)	3	230	Std. Mean Difference (IV, Fixed, 95% CI)	0.58 [0.31, 0.84]

#### Analysis 1.1. Comparison 1 Incidence of ECG abnormalities, Outcome 1 BZD Children.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 1 Incidence of ECG abnormalities

Outcome: 1 BZD Children

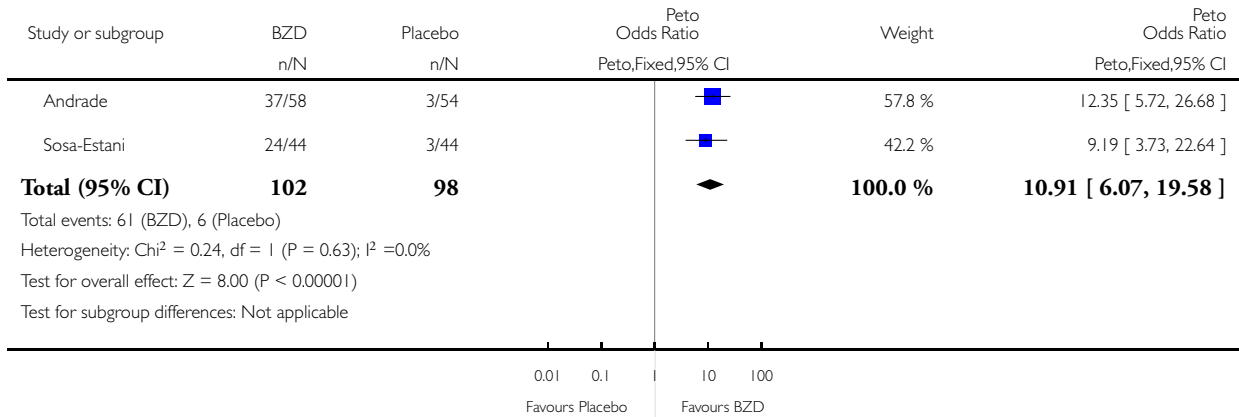


### Analysis 2.1. Comparison 2 Negative seroconversion, Outcome 1 BZD - AT ELISA - CHILDREN.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 2 Negative seroconversion

Outcome: 1 BZD - AT ELISA - CHILDREN

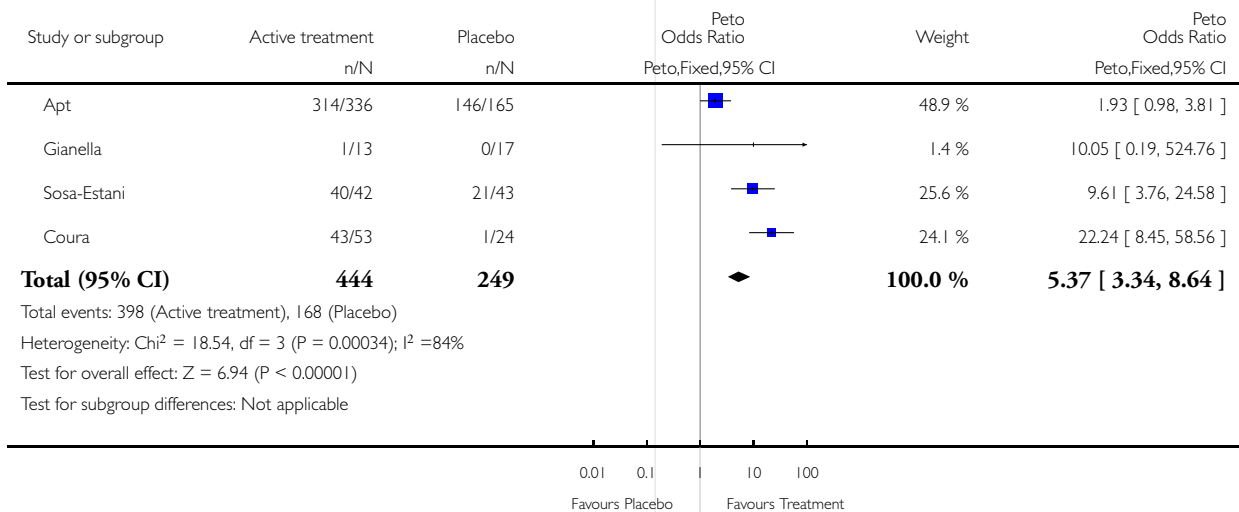


### Analysis 3.1. Comparison 3 Negative xenodiagnosis, Outcome 1 All populations- All tested agents.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 1 All populations- All tested agents

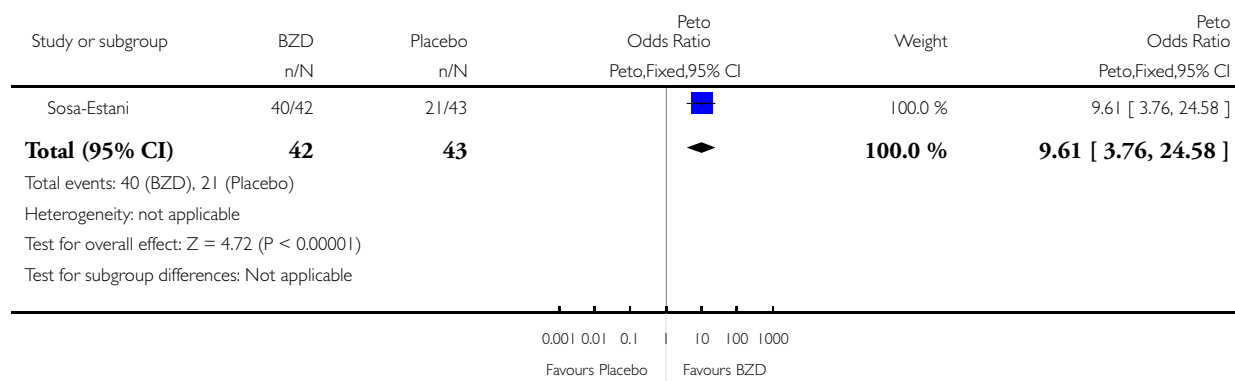


### Analysis 3.2. Comparison 3 Negative xenodiagnosis, Outcome 2 Children - BZD.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 2 Children - BZD

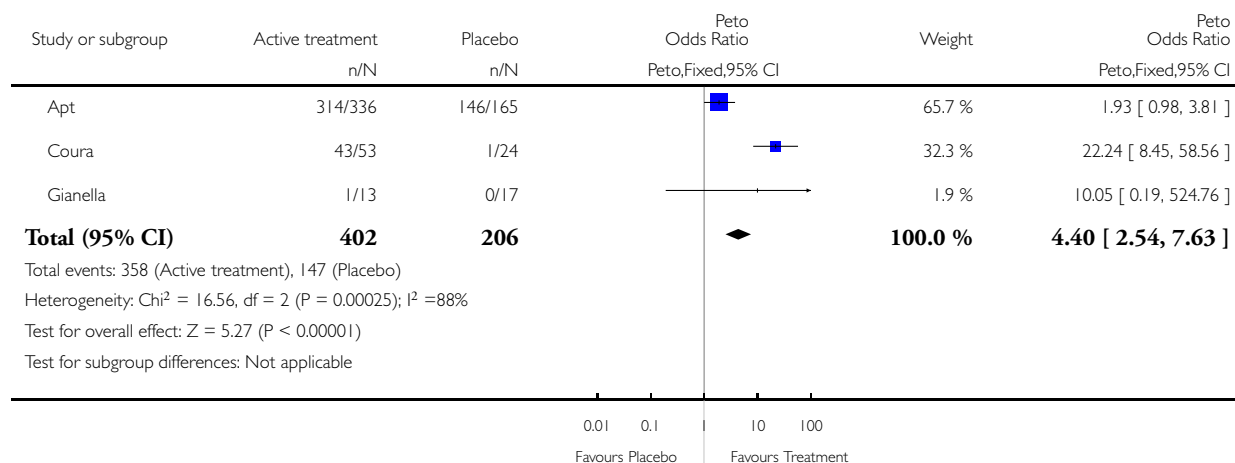


### Analysis 3.3. Comparison 3 Negative xenodiagnosis, Outcome 3 Adults - All tested agents.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 3 Adults - All tested agents

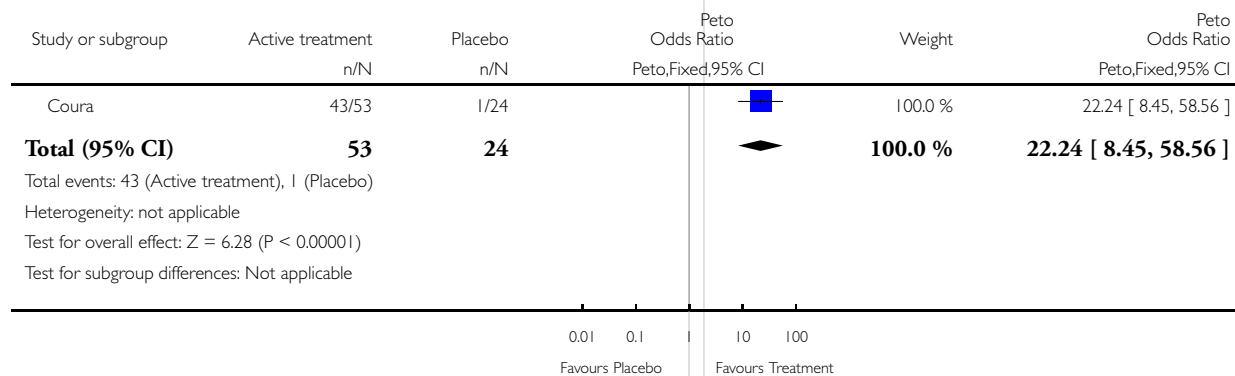


### Analysis 3.4. Comparison 3 Negative xenodiagnosis, Outcome 4 Adults - Nitrosamine derivatives.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 4 Adults - Nitrosamine derivatives

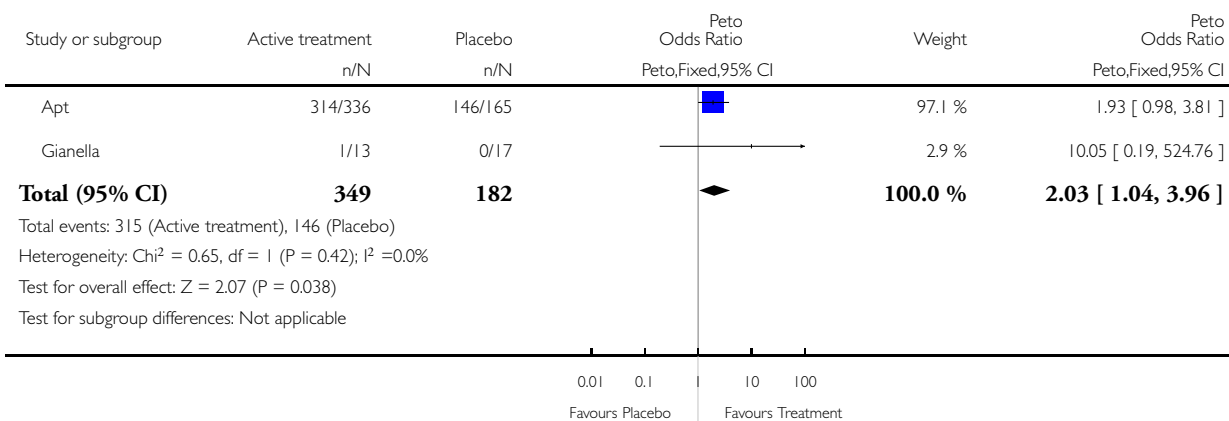


### Analysis 3.5. Comparison 3 Negative xenodiagnosis, Outcome 5 Adults - Drugs other than nitrosamine derivatives.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 5 Adults - Drugs other than nitrosamine derivatives

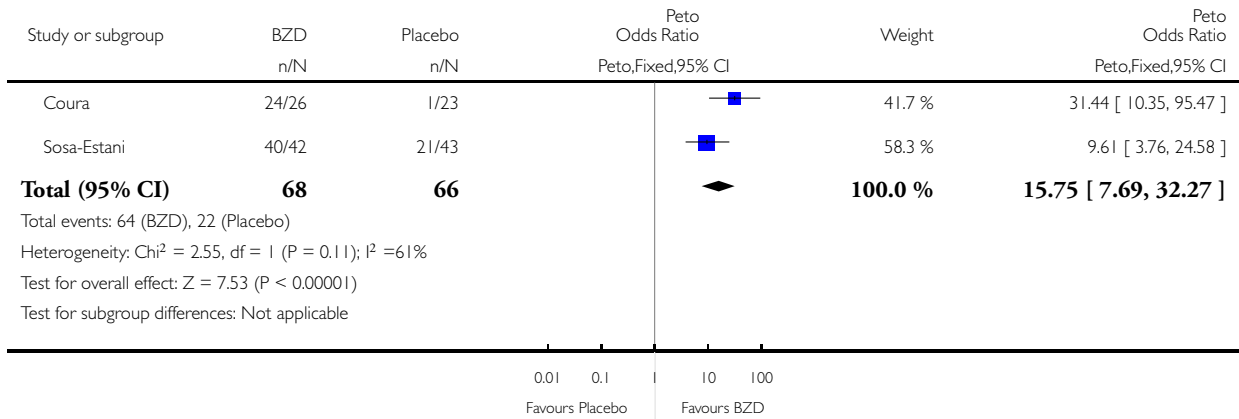


### Analysis 3.6. Comparison 3 Negative xenodiagnosis, Outcome 6 BZD - Children and adults.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 6 BZD - Children and adults

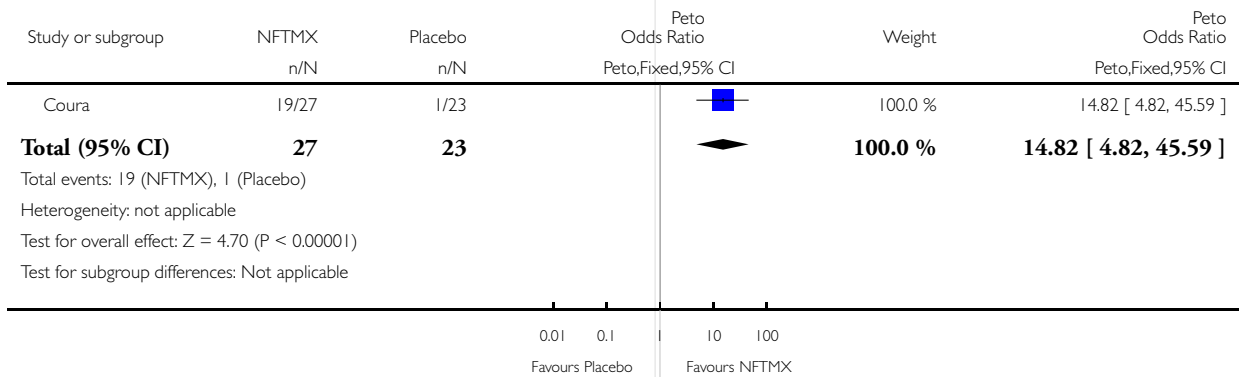


### Analysis 3.7. Comparison 3 Negative xenodiagnosis, Outcome 7 NFTMX - Adults.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 7 NFTMX - Adults



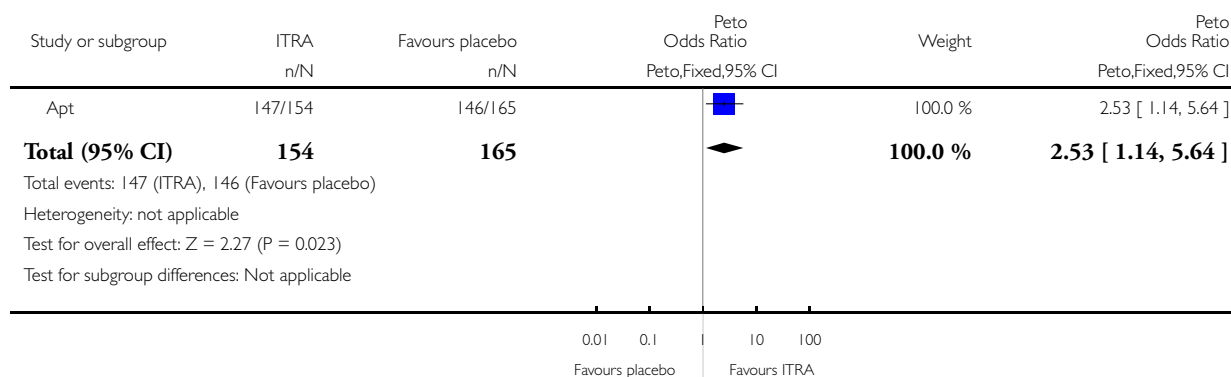


### Analysis 3.8. Comparison 3 Negative xenodiagnosis, Outcome 8 ITRA - Adults.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 8 ITRA - Adults

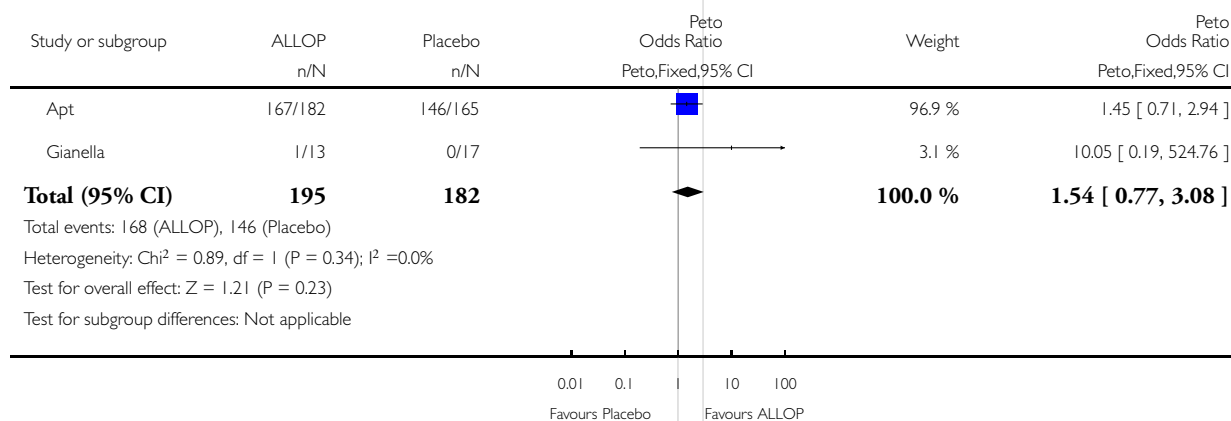


### Analysis 3.9. Comparison 3 Negative xenodiagnosis, Outcome 9 ALLOP - Adults.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 9 ALLOP - Adults

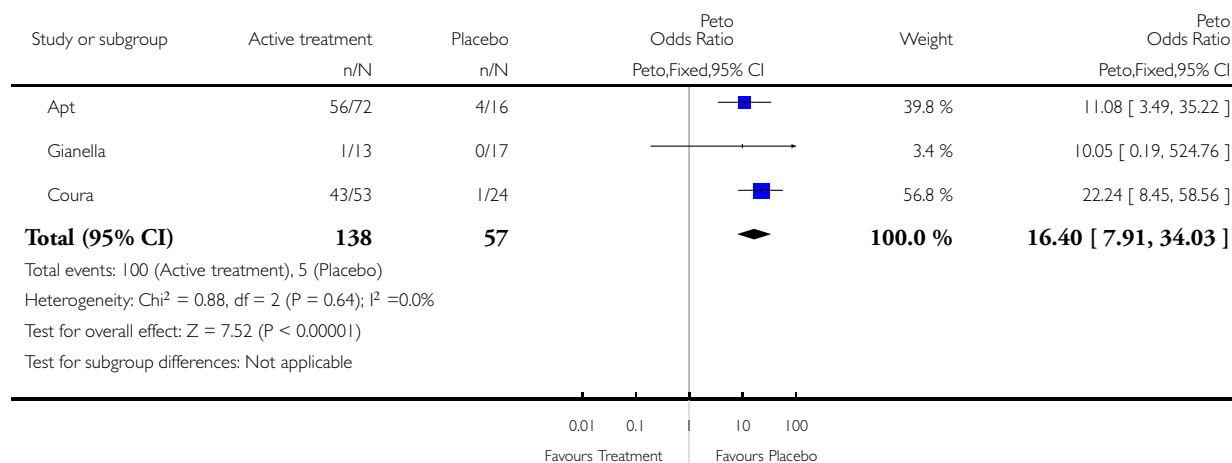


### Analysis 3.10. Comparison 3 Negative xenodiagnosis, Outcome 10 Positive xenodiagnosis at baseline (Adults).

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 10 Positive xenodiagnosis at baseline (Adults)

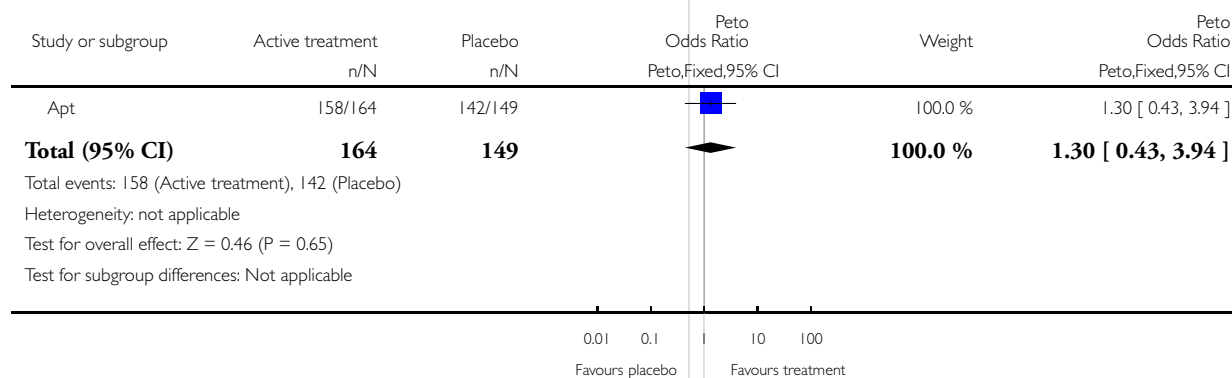


### Analysis 3.11. Comparison 3 Negative xenodiagnosis, Outcome 11 Negative xenodiagnosis at baseline (Adults / Drugs other than nitrosamine derivatives).

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 3 Negative xenodiagnosis

Outcome: 11 Negative xenodiagnosis at baseline (Adults / Drugs other than nitrosamine derivatives)

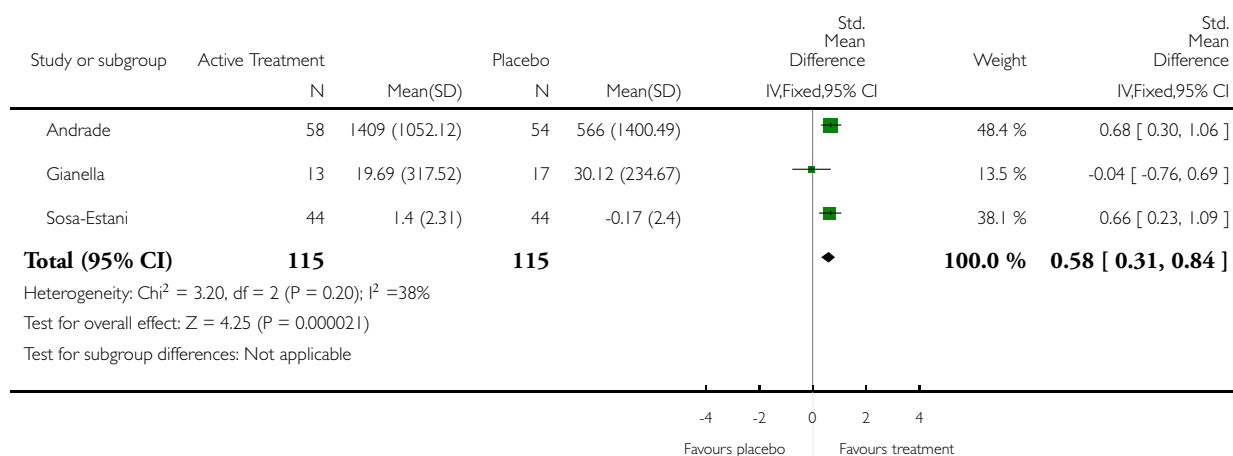


### Analysis 4.1. Comparison 4 Reduction of antibody titres, Outcome 1 All available studies (Indirect immunofluorescence).

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: 4 Reduction of antibody titres

Outcome: 1 All available studies (Indirect immunofluorescence)



## WHAT'S NEW

Last assessed as up-to-date: 31 October 2001.

Date	Event	Description
18 June 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 1, 2002

## CONTRIBUTIONS OF AUTHORS

Juan C Villar Drafted the protocol, Searched the references, select the included papers, extracted the data and drafted the manuscript.

Villar LA co-selected the included papers, co-extract the data and co-reviewed the draft manuscripts.

Marin-Neto JA gave input to the protocol, verified the data extraction and co-reviewed the draft manuscripts

Ebrahim S gave input to the protocol, co-reviewed both the protocol and the draft manuscripts

Yusuf S Proposed the study, got together the authors and co-reviewed both the protocol and the draft manuscripts

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- Universidad Autonoma de Bucaramanga, Colombia.
- Population Health Institute, McMaster University, Canada.
- Faculdade de Medicina de Riberirao Preto USP, Brazil.
- University of Bristol, UK.
- Universidad Industrial de Santander, Colombia.

### External sources

- No sources of support supplied

## INDEX TERMS

### Medical Subject Headings (MeSH)

Chagas Disease [\*drug therapy]; Chronic Disease; Randomized Controlled Trials as Topic; Trypanocidal Agents [\*therapeutic use];  
Trypanosoma cruzi

## **MeSH check words**

Animals; Humans