Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection (Review)

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

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Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Juan Carlos Villar1, Luis Angel Villar2, Jose Antonio Marin-Neto3, Shah Ebrahim4, Salim Yusuf5

1Sabatical: Research Fellow, Department of Medicine, Population Health Institute, McMaster University, Hamilton, Canada. 2Basic medical sciences, Universidad Industrial de Santander, Santander, Colombia. 3Faculdade de Medicina de Ribeirão Preto USP, Ribeirão Preto, Brazil. 4Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, London, UK. 5Division of Cardiology, Hamilton Health Sciences, HGH-McMaster Clinic, Hamilton, Canada

Contact address: Juan Carlos Villar, Sabatical: Research Fellow, Department of Medicine, Population Health Institute, McMaster University, 237 Barton St East, Hamilton, Ontario, L8L 2X2, Canada. jvillar@unab.edu.co.

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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
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 megaviscera 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 haemaglutination 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 (reduvidae) are laboratory bred to ensure they do not carry any parasites. Reduviae 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 reduvidae 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 2000). 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 urban 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 Andrade 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 haemaglutination 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 haemaglutination 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 nitroamine 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 scientific 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.

ACKNOWLEDGEMENTS

We would like to specially thank Dr Sergio Sosa-Estani for his helpful suggestions to improve the display and accuracy of the data presented in this review. Juan C Villar holds a educational grant from the Universidad Autonoma de Bucaramanga; Salim Yusuf holds a research chair from the Heart and Stroke Foundation of Canada. J. A. Marin-Neto holds a research grant on Chagas’ heart disease from the Conselho Nacional de Pesquisa e Desenvolvimento (CNPq, Brazil).

REFERENCES

Implications for practice

Andrade (published data only)

Apt (published data only)

Coura (published data only)

Sosa-Estani (published data only)

Abitbol (published data only)
Abitbol H. Tratamiento de la enfermedad de Chagas [Treatment of Chagas disease]. An R Acad Nac Med (Madr )

Andrade (published data only)

Apt (published data only)

Coura (published data only)

Sosa-Estani (published data only)

Abitbol (published data only)
Abitbol H. Tratamiento de la enfermedad de Chagas [Treatment of Chagas disease]. An R Acad Nac Med (Madr )

Aguilera [published data only]

Amato [published data only]

Amato (a) [published data only]

Amato (b) [published data only]

Apt (a) [published data only]

Apt (b) [published data only]

Bestetti [published data only]
Bestetti RB. Should benznidazole be used in chronic Chagas’ disease?. *Lancet* 1997;349:653.

Bocca Tourres [published data only]

Brenes [published data only]

Carpintero [published data only]

Coura (a) [published data only]

De Araujo Malta [published data only]

De Oliveira [published data only]

De Oliveira (a) [published data only]

Fernandez [published data only]

Fragata [published data only]

Gallerano [published data only]

Gallerano (a) [published data only]

Gonnert [published data only]

Gutteridge [published data only]

Ivanovic [published data only]

Levi [published data only]

Levi (a) [published data only]
Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection (Review)

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López-Antuñaño [published data only]

Maldonado [published data only]

Marr [published data only]

Meirovich [published data only]

Mendoza [published data only]

Prata [published data only]

Rassi [published data only]

Romeu Cançado [published data only]

Rubio [published data only]

Santana [published data only]

Viotti [published data only]

Wegner [published data only]

Wegner (a) [published data only]

Additional references

Almeida 1995

Almeida 1999

Andrade 1997

Apt 1985

Apt 1998

Bestetti 1996

Bestetti 1997

Brener 1975

Brener 1994

Britto 1999

Cançado 1976
Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection (Review)

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Castro 1999

Chagas 1909

Coura 1997

de Andrade 1996

De Castro 1993

Follmann 1992

Fragata 1995

Gianella 1997

Higuchi 1997

Ianni 1998

Jadad 1996

Jones 1993

Laranja 1956

Marinho 1999

Marr 1986

Moncayo 1994

Murray 2000

PAHO 1998

Prata 1976

Rossi 1995

Schmunis 1994

Schmunis 1996

Sosa 1998
Sosa 1999

Urbina 1999

Villar 2000

WHO 1991

WHO 2000

Yusuf 1985

* Indicates the major publication for the study.
## Characteristics of studies  [ordered by study ID]

**Andrade**

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<td>Participants</td>
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<tr>
<td>Interventions</td>
<td>BZD (n=64) 7.5 mg/k/d (8 wk) Placebo (n=65)</td>
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<tr>
<td>Outcomes</td>
<td>Serological status recorded Antibody titres reported Incidence of ECG abnormalities</td>
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### Risk of bias

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**Apt**

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<tr>
<td>Interventions</td>
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<tr>
<td>Outcomes</td>
<td>Xenodiagnosis recorded ECG changes reported but not described by treatment allocation Side effects</td>
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<td>Adults (% in IP NA)</td>
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<tr>
<td>Interventions</td>
<td>BZD (n=26) 5 mg/k/d (4 wk) NFTMX (n=27) 5 mg/k/d (4 wk) Placebo (n=24)</td>
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<tr>
<td>Outcomes</td>
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<tr>
<td>Notes</td>
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### Risk of bias

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<td>Participants</td>
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<tr>
<td>Interventions</td>
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<td>Outcomes</td>
<td>Antibody titres recorded Xenodiagnosis recorded</td>
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### Sosa-Estani

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<td>Participants</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Outcomes</td>
<td>Serological status recorded Antibody titres recorded Xenodiagnosis recorded Incidence of ECG abnormalities</td>
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#### Risk of bias

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<td>Allocation concealment?</td>
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<td>B - Unclear</td>
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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]

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<th>Study</th>
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<td>Abitbol</td>
<td>Study not reporting original data</td>
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<tr>
<td>Aguilera</td>
<td>Original studies, other than RCTs</td>
</tr>
<tr>
<td>Amato</td>
<td>Study not reporting original data</td>
</tr>
<tr>
<td>Study/Reference</td>
<td>Result</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Amato (a)</td>
<td>Study not reporting original data</td>
</tr>
</tbody>
</table>
| 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 |
<p>| 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 |</p>
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<tr>
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<th>Study Type</th>
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<td>Levi (a)</td>
<td>Study not reporting original data</td>
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<tr>
<td>López-Antuñaño</td>
<td>Study not reporting original data</td>
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<tr>
<td>Maldonado</td>
<td>Original studies, other than RCTs</td>
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<tr>
<td>Marr</td>
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<td>Mendoza</td>
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<td></td>
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<td>Prata</td>
<td>Original studies, other than RCTs</td>
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<td>Rassi</td>
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<td>Romeu Cançado</td>
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</tr>
<tr>
<td>Rubio</td>
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<td>Viotti</td>
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<td>Wegner</td>
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<td>Wegner (a)</td>
<td>Original studies, other than RCTs</td>
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## DATA AND ANALYSES

### Comparison 1. Incidence of ECG abnormalities

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BZD Children</td>
<td>2</td>
<td>198</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.41 [0.09, 1.85]</td>
</tr>
</tbody>
</table>

### Comparison 2. Negative seroconversion

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

### Comparison 3. Negative xenodiagnosis

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

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<th>Outcome or subgroup title</th>
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<th>No. of participants</th>
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<th>Effect size</th>
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<tbody>
<tr>
<td>1 All available studies (Indirect immunofluorescence)</td>
<td>3</td>
<td>230</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.58 [0.31, 0.84]</td>
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---

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Placebo n/N</th>
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<td>71.0 %</td>
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<tr>
<td>Sosa-Estani</td>
<td>1/40</td>
<td>1/41</td>
<td>29.0 %</td>
<td>1.03 [0.06, 16.69]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>99</strong></td>
<td><strong>99</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.41 [0.09, 1.85]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (BZD), 5 (Placebo)

Chi² = 0.58, df = 1 (P = 0.45); I² =0.0%

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>BZD n/N</th>
<th>Placebo n/N</th>
<th>Peto Odds Ratio Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade</td>
<td>37/58</td>
<td>3/54</td>
<td>57.8 % 12.35 [ 5.72, 26.68 ]</td>
<td></td>
</tr>
<tr>
<td>Sosa-Estani</td>
<td>24/44</td>
<td>3/44</td>
<td>42.2 % 9.19 [ 3.73, 22.64 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>102</strong></td>
<td><strong>98</strong></td>
<td><strong>100.0 % 10.91 [ 6.07, 19.58 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 61 (BZD), 6 (Placebo)  
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); 𝐼^2 = 0.0%  
Test for overall effect: Z = 8.00 (P < 0.00001)  
Test for subgroup differences: Not applicable

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment n/N</th>
<th>Placebo n/N</th>
<th>Peto Odds Ratio Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>314/336</td>
<td>146/165</td>
<td>48.9 % 1.93 [ 0.98, 3.81 ]</td>
<td></td>
</tr>
<tr>
<td>Gianella</td>
<td>1/13</td>
<td>0/17</td>
<td>1.4 % 10.05 [ 0.19, 524.76 ]</td>
<td></td>
</tr>
<tr>
<td>Sosa-Estani</td>
<td>40/42</td>
<td>21/43</td>
<td>25.6 % 9.61 [ 3.76, 24.58 ]</td>
<td></td>
</tr>
<tr>
<td>Coura</td>
<td>43/53</td>
<td>1/24</td>
<td>24.1 % 22.24 [ 8.45, 58.56 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>444</strong></td>
<td><strong>249</strong></td>
<td><strong>100.0 % 5.37 [ 3.34, 8.64 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 398 (Active treatment), 168 (Placebo)  
Heterogeneity: Chi² = 18.54, df = 3 (P = 0.00034); 𝐼^2 = 84%  
Test for overall effect: Z = 6.94 (P < 0.00001)  
Test for subgroup differences: Not applicable
Analysis 3.2. Comparison 3 Negative xenodiagnosis, Outcome 2 Children - BZD.

Review: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection

Comparison: Negative xenodiagnosis

Outcome: 2 Children - BZD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>BZD</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed,95% CI</td>
<td></td>
<td>Peto,Fixed,95% CI</td>
</tr>
<tr>
<td>Sosa-Estani</td>
<td>40/42</td>
<td>21/43</td>
<td>100.0 %</td>
<td>9.61 [ 3.76, 24.58 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td>43</td>
<td>100.0 %</td>
<td>9.61 [ 3.76, 24.58 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 40 (BZD), 21 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 4.72 (P < 0.00001)
Test for subgroup differences: Not applicable
### 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  

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>314/336</td>
<td>146/165</td>
<td>1.93 [0.98, 3.81]</td>
<td>65.7 %</td>
<td>1.93 [0.98, 3.81]</td>
</tr>
<tr>
<td>Coura</td>
<td>43/53</td>
<td>1/24</td>
<td>22.24 [8.45, 58.56]</td>
<td>32.3 %</td>
<td>22.24 [8.45, 58.56]</td>
</tr>
<tr>
<td>Gianella</td>
<td>1/13</td>
<td>0/17</td>
<td>10.05 [0.19, 524.76]</td>
<td>1.9 %</td>
<td>10.05 [0.19, 524.76]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 402 / 206

Total events: 358 (Active treatment), 147 (Placebo)

Heterogeneity: Chi² = 16.56, df = 2 (P = 0.00025); I² = 88%

Test for overall effect: Z = 5.27 (P < 0.00001)

Test for subgroup differences: Not applicable

### 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  

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coura</td>
<td>43/53</td>
<td>1/24</td>
<td>22.24 [8.45, 58.56]</td>
<td>100.0 %</td>
<td>22.24 [8.45, 58.56]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 53 / 24

Total events: 43 (Active treatment), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 6.28 (P < 0.00001)

Test for subgroup differences: Not applicable
**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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apt</td>
<td>314/336</td>
<td>146/165</td>
<td><strong>1.93 [0.98, 3.81]</strong></td>
<td>97.1 %</td>
<td><strong>1.93 [0.98, 3.81]</strong></td>
</tr>
<tr>
<td>Gianella</td>
<td>1/13</td>
<td>0/17</td>
<td><strong>10.05 [0.19, 524.76]</strong></td>
<td>2.9 %</td>
<td><strong>10.05 [0.19, 524.76]</strong></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>349</strong></td>
<td><strong>182</strong></td>
<td><strong>2.03 [1.04, 3.96]</strong></td>
<td>100.0 %</td>
<td><strong>2.03 [1.04, 3.96]</strong></td>
</tr>
</tbody>
</table>

Total events: 315 (Active treatment), 146 (Placebo)

Heterogeneity: Chi$^2$ = 0.65, df = 1 (P = 0.42); I$^2$ = 0.0%

Test for overall effect: Z = 2.07 (P = 0.038)

Test for subgroup differences: Not applicable

---

Favours Placebo Favours Treatment
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>BZD</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Coura</td>
<td>24/26</td>
<td>1/23</td>
<td>41.7%</td>
<td>31.44 [ 10.35, 95.47 ]</td>
</tr>
<tr>
<td>Sosa-Estani</td>
<td>40/42</td>
<td>21/43</td>
<td>58.3%</td>
<td>9.61 [ 3.76, 24.58 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>68</strong></td>
<td><strong>66</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>15.75 [ 7.69, 32.27 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 64 (BZD), 22 (Placebo)

Heterogeneity: Chi$^2 = 2.55$, df = 1 ($P = 0.11$); $I^2 = 61$

Test for overall effect: $Z = 7.53$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NFTMX</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>Peto,Fixed, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Coura</td>
<td>19/27</td>
<td>1/23</td>
<td>100.0%</td>
<td>14.82 [ 4.82, 45.59 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>27</strong></td>
<td><strong>23</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>14.82 [ 4.82, 45.59 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 19 (NFTMX), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: $Z = 4.70$ ($P < 0.00001$)

Test for subgroup differences: Not applicable
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

| Study or subgroup | ITRA  | Favours placebo | Peto Odds Ratio | Weight
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>147/154</td>
<td>146/165</td>
<td>2.53 [1.14, 5.64]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 154 165 100.0 % 2.53 [1.14, 5.64]

Total events: 147 (ITRA), 146 (Favours placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 2.27 (P = 0.023)
Test for subgroup differences: Not applicable

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

| Study or subgroup | ALLOP | Placebo | Peto Odds Ratio | Weight
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>167/182</td>
<td>146/165</td>
<td>1.45 [0.71, 2.94]</td>
<td>96.9 %</td>
</tr>
<tr>
<td>Gianella</td>
<td>1/13</td>
<td>0/17</td>
<td>10.05 [0.19, 524.76]</td>
<td>3.1 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 195 182 100.0 % 1.54 [0.77, 3.08]

Total events: 168 (ALLOP), 146 (Placebo)
Heterogeneity: Chi² = 0.89, df = 1 (P = 0.34); I² = 0.0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable
### 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)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>56/72</td>
<td>4/16</td>
<td>39.8%</td>
<td>1.08</td>
<td>3.49, 35.22</td>
</tr>
<tr>
<td>Gianella</td>
<td>1/13</td>
<td>0/17</td>
<td>3.4%</td>
<td>10.05</td>
<td>0.19, 524.76</td>
</tr>
<tr>
<td>Coura</td>
<td>43/53</td>
<td>1/24</td>
<td>56.8%</td>
<td>22.24</td>
<td>8.45, 58.56</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>138</strong></td>
<td><strong>57</strong></td>
<td>100.0%</td>
<td>16.40</td>
<td>7.91, 34.03</td>
</tr>
</tbody>
</table>

Total events: 100 (Active treatment), 5 (Placebo)

Heterogeneity: Chi² = 0.88, df = 2 (P = 0.64); I² = 0.0%

Test for overall effect: Z = 7.52 (P < 0.00001)

Test for subgroup differences: Not applicable

### 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)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apt</td>
<td>158/164</td>
<td>142/149</td>
<td>100.0%</td>
<td>1.30</td>
<td>0.43, 3.94</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>164</strong></td>
<td><strong>149</strong></td>
<td>100.0%</td>
<td>1.30</td>
<td>0.43, 3.94</td>
</tr>
</tbody>
</table>

Total events: 158 (Active treatment), 142 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable
## 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)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active Treatment</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Andrade</td>
<td>58</td>
<td>1409 (1052.12)</td>
<td>54</td>
<td>566 (1400.49)</td>
<td>48.4 % 0.68 [ 0.30, 1.06 ]</td>
</tr>
<tr>
<td>Gianella</td>
<td>13</td>
<td>19.69 (317.52)</td>
<td>17</td>
<td>30.12 (234.67)</td>
<td>13.5 % -0.04 [ -0.76, 0.69 ]</td>
</tr>
<tr>
<td>Sosa-Estani</td>
<td>44</td>
<td>1.4 (2.31)</td>
<td>44</td>
<td>-0.17 (2.4)</td>
<td>38.1 % 0.66 [ 0.23, 1.09 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>115</strong></td>
<td><strong>115</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>100.0 % 0.58 [ 0.31, 0.84 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 3.20, \text{df} = 2, P = 0.20 \); I\(^2\) = 38%

Test for overall effect: \( Z = 4.25, P = 0.000021 \)

Test for subgroup differences: Not applicable

### WHAT’S NEW

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 June 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>
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 Ribeirao 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