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Trimethoprim as Adjuvant Treatment in Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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Various infectious agents, such as *Toxoplasma gondii*, have been hypothesized to be potentially relevant etiological factors in the onset of some cases of schizophrenia. We conducted a randomized, double-blind, placebo-controlled treatment trial in an attempt to explore the hypothesis that the symptoms of schizophrenia may be related to infection of the central nervous system with *toxoplasma gondii*. Systematically selected patients with ongoing and at least moderately severe schizophrenia from Butajira, in rural Ethiopia, were randomly allocated to trimethoprim or placebo, which were added on to participants' regular antipsychotic treatments. Trial treatments were given for 6 months. The Positive and Negative Syndrome Scale (PANSS) was used to assess outcome. Ninety-one patients were included in the study, with 80 cases (87.9%) positive for *T. gondii* immunoglobulin G antibody. Seventy-nine subjects (87.0%) completed the trial. The mean age of subjects was 35.3 (SD = 8.0) years, with a mean duration of illness of 13.2 (SD = 6.7) years. Both treatment groups showed significant reduction in the overall PANSS score with no significant between-group difference. In this sample of patients with chronic schizophrenia, trimethoprim used as adjuvant treatment is not superior to placebo. However, it is not possible to draw firm conclusion regarding the etiological role of toxoplasmosis on schizophrenia based on this study because the timing and the postulated mechanisms through which toxoplasmosis produces schizophrenia are variable.

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Introduction

The etiology of schizophrenia is undetermined; however, various infectious agents have been hypothesized as potentially relevant agents, including cytomegalovirus (CMV),[1,2] influenza virus,[3] herpes zoster virus type I and II,[4] and a protozoan parasite—*Toxoplasma gondii (T. gondii)*—to some cases of schizophrenia.[5,6] *T. gondii* is an interesting candidate in this regard. It can establish continuous infection within the central nervous system (CNS), change intermediate host behavior, and can cause neurological and psychiatric symptoms in some infected individuals.[7,8] Infection with *T. gondii* has also been associated with increased incidence of schizophrenia.[9,10] Moreover, medications used to treat schizophrenia have been demonstrated to possess anti–*T. gondii* properties.[8,11] Taken together, these evidence support the hypothesis that at least in some cases with schizophrenia infection by the Toxoplasma parasite may be etiologically relevant. Possible mechanisms by which Toxoplasma might contribute to schizophrenia would include the stimulation of cytokines within the brain,[12] activation of endogenous retroviruses,[13] or direct effect on cerebral microarchitecture.[14] However, testing the role of toxoplasmosis or other infectious agents in the onset and maintenance of schizophrenia directly is extremely difficult. As implied above, the proposition has been primarily based on epidemiological associations, i.e., finding higher rate of toxoplasmosis among those with schizophrenia. Although prospective follow-up of Toxoplasma-infected individuals without symptoms of schizophrenia may be considered theoretically possible, the rarity of schizophrenia makes such a study impossible. Ecological studies may also be considered,[15] but the distribution of schizophrenia is such that ecological studies are not likely to contribute substantially.

Treatment trials may help explore the role of some etiological factors. In an animal model, it has been possible to show changes in the behavior of a rat infected with toxoplasmosis that improved following treatment with haloperidol.[8] Such study is not possible to replicate in

humans. Nevertheless, one indirect way of testing whether *T. gondii* might be relevant in this regard is by providing treatment against toxoplasmosis to see if inhibition of replication of *T. gondii* would result in improvement of the symptoms of schizophrenia. Trimethoprim is a relatively safe drug that has been used alone or in combination with sulfamethoxazol as cotrimoxazol as a drug of choice for dual prophylaxis and treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis. It has also been tested as a prophylaxis against various other infections with daily doses of up to 100–600 mg given over 4–12 months.[16–18]

We attempted to explore the hypothesis that some symptoms of schizophrenia may be related to infection of the CNS with *T. gondii* by conducting an adjuvant trimethoprim therapy in a double-blind, randomized, placebo-controlled trial. It has been suggested that inhibiting replication of Toxoplasma parasites using medication may result "in a decrease in the symptoms of schizophrenia and an alteration in the clinical course of the disease."[19]

Methods

Design

The study design was a randomized, double-blind, placebo-controlled trial. Patients were assigned to specific treatments using block randomization. The randomization list was generated using a random number table and was then transferred to a series of sealed envelopes. Patients, investigators, assessors, and the trial statistician were masked to treatment allocation.

Setting and Participants

The study was conducted in Butajira, a predominantly rural district located 135 km south of the capital city, Addis Ababa. The participants were selected from patients already under prospective follow-up to determine the course and outcome of schizophrenia. The initial cohort was identified following standard case ascertainment procedures among the adult (15–49 y old) population of the district.[20,21] The case ascertainment procedure consisted of initial case screening using the Composite International Diagnostic Interview[22] augmented by key informants. This was followed by a diagnostic assessment using the Schedules for Clinical Assessment in Neuropsychiatry.[23,24] Three hundred twenty-one cases with schizophrenia were identified. By the time this clinical trial was planned, 35 cases had died, 20 had out-migrated, and 11 had become vagrants. Thus, 255 cases were available for possible recruitment in the clinical trial (please refer to trial flow diagram).

Entry Criteria

Patients were included in the study if they were consenting male adults, with a diagnosis of schizophrenia according to the *International Classification of Diseases, Tenth Revision*,[25] and had significant ongoing symptoms as evidenced by a Positive and Negative Syndromes Scale (PANSS)[26] score of at least 60. Patients were excluded if they had acute or chronic liver, renal or hematological disease, and a history or evidence of focal neurological or space-occupying lesions of the brain. Female patients were excluded from the study because of the possible adverse effect of the trimethoprim on the fetus if they become pregnant.

Patients were withdrawn from the trial if hemoglobin level dropped by 4 g/dL from baseline, white blood cell count dropped to less than 2500/ml^3, platelet count dropped to less than 100 000/ml^3 or if the patient developed any abnormal liver or renal function tests.

Intervention

Subjects in the intervention group received trimethoprim 200 mg/d, and those on the placebo arm received a medication identical in appearance and taste to the intervention drug (trimethoprim). The content of the placebo was lactose monohydrate. The trial tablets were distributed by pharmacy technicians and were supplied to patients on a daily basis by trained health workers (Community Health Agents [CHAs]), working locally. The CHAs were also trained to refer patients with medical complaints to the local hospital for a review by qualified medical doctor. The trial medications were administered for 6 months. Medication supply and coordination of treatment was based on a trial protocol that enabled supervised administration of medication, collaboration with families of patients, and monitoring of medication use. The study also had protocol for compliance, follow-up, and adverse event reporting during the study period and for up to 6 months after the study was completed.

Assessment

The main outcome assessment was based on the PANSS. PANSS assessment was conducted on a monthly basis by trained psychiatric residents. Additionally, clinical examination and laboratory tests were performed at the end of the second, fourth, and sixth months of the trial. Enzyme-linked immunosorbent assay tests for *T. gondii* antibody titer and human immunodeficiency virus (HIV) were also done.

Data Analysis

The primary outcome was the change in PANSS score from baseline to end of trial (6 mo). Items in the PANSS were also categorized into 6 symptom domains[27]: positive symptoms (5 items), negative symptoms (10 items), depression/anxiety symptoms (5 items), excitement symptoms (5 items), cognitive symptoms (3 items), and suspiciousness (1 item). Change in overall mean score and change in the mean score in the 6 symptom domains

were compared between the 2 treatment groups using Students *t* test.

Further secondary analysis was conducted after participants were stratified on serological status for toxoplasmosis, comparing the treatment groups. An intention-to-treat analysis was performed using data from subjects who received at least 2 weeks of treatment with either drug. Results were considered significant if *P* value is less than .05.

Sample Size

The sample size was necessarily dictated by the size of the available sample from the existing cohort base. However, the total number of eligible cases from this cohort ($n = 91$) enables detection of a 7 point difference in mean reduction of PANSS score between active intervention and placebo group with assumption of PANSS SD of 16, a 1:1 allocation ratio, 80% power, and 95% confidence.[28]

Ethical Considerations

The study protocol was reviewed by the Addis Ababa University, Faculty of Medicine Ethical Review Board, and the health division of the Ethiopian Science and Technology Agency. All patients gave informed consent to participate in the study. First-degree relatives were allowed to give informed consent on behalf of patients who could not give consent because of severe symptoms. A Data Safety Monitoring Board (DSMB) was established comprising of an internist, clinical epidemiologist, a pharmacologist, and a lay representative of the community. The DSMB was responsible for monitoring the conduct of the trial.

Results

Of the 255 patients with schizophrenia initially considered for inclusion, 65 were women and were automatically excluded while 28 refused. Thus, 162 cases were available for inclusion and assessed using PANSS. Of these, 104 subjects (64%) had an average PANSS score of at least 60 and were eligible to participate in the trial. Out of the 104 subjects, additional 3 refused further participation and the remaining 101 individuals had further laboratory investigations. From this group, 9 patients were excluded because of abnormal liver function test results. Thus, 91 patients were included in the trial (see trial flow diagram).

Of the 91 cases with schizophrenia included in the study, 9 (3 from the placebo and 6 from the treatment arm) were not started on the trial drugs although they consented for the study and had been randomized. This was because they did not come to receive the allocated treatment. Of the remaining 82 patients, 79 (96%) completed the study. Reasons for dropout after starting medication were as follows: 2 excluded due to a reduction in their hemoglobin level by 4 gm/dL below baseline value (one from the placebo arm, after 2 mo in the study, and one from the trimethoprim arm after 5 mo in the study) and 1 in the trimethoprim arm committed suicide after 5 months.

Table 1. Baseline Age, Duration of Illness, and Mean PANSS Score of Patients in the Trimethoprim and Placebo Groups. Butajira, Ethiopia, 2005

	N	Mean	SD	*t* Test	*P* Value
Age at enrollment into the trial (y)					
Trimethoprim	46	36.1	7.6	0.987	.326
Placebo	45	34.5	8.5		
Illness duration at enrollment into the trial (y)					
Trimethoprim	46	12.5	5.6	0.905	.368
Placebo	45	13.8	7.8		
PANSS score at baseline					
Trimethoprim	46	78.5	14.9	0.335	.738
Placebo	45	79.6	17.6		

Note: PANSS, Positive and Negative Syndrome Scale.

Included subjects had a mean age of 35.3 (SD = 8.0) years, with a mean duration of illness of 13.2 (SD = 6.7) years. The PANSS mean score at baseline was 79.0 (SD = 16.2). Eighty cases (87.9%) were positive for *T. gondii* (immunoglobulin G [IgG]) antibody, but none of the subjects were HIV positive. There was no significant difference between the treatment and the placebo groups in terms of mean age, total duration of illness at enrollment, and PANSS scores at baseline. There was also no difference in PANSS scores at the end of the second and fifth months (at the time when the 1 participant in the placebo arm and the 2 participants in the trimethoprim arm withdrew from the study) and their Toxoplasma antibody titers (tables 1 and 2).

Both treatment groups showed a reduction in their overall mean PANSS score at all measurement points compared with baseline scores (table 3), but there was no significant difference between the 2 groups. On a separate analysis of the 6 symptom domains, a significant reduction between baseline and 6 months was also demonstrated with no significant between-group difference (table 3). When data on treatment was stratified on IgG antibody status, the symptom reduction was also replicated with no significant between-group differences.

Discussion

Effectiveness of Intervention and Etiological Implication

The etiology of psychotic disorders such as schizophrenia is by and large unknown. This study was conducted based on the growing literature, epidemiological and otherwise, providing evidence for the co-occurrence of schizophrenia and *T. gondii*.[2,5,9] We aimed to indirectly explore the

Table 2. *Toxoplasma gondii* Serum Reactivity Rates Among the Trimethoprim and Placebo Groups at Baseline. Butajira, Ethiopia, 2005.

Toxoplasma Status	Trimethoprim	Placebo	χ^2	*P* Value
IgG				
Nonreactive	4	6	0.518	.157
Reactive	42	38		
IgM				
Nonreactive	17	13	2.00	.641
Reactive	25	25		
Borderline	4	6		

Note: Ig, immunoglobulin.

role of toxoplasmosis in the etiology of schizophrenia by providing standard anti-Toxoplasma treatment in a double-blind, randomized, placebo-controlled trial. The assumption was that if symptoms of schizophrenia were caused by *T. gondii* infection, it may be possible to improve the symptoms through inhibition of Toxoplasma replication.[19] Although antipsychotic medications are considered to have anti-Toxoplasma properties, the sample consisted of patients with chronic schizophrenia of at least moderate severity, despite having received antipsychotic medication for several years prior to their inclusion in this study. Thus, patients would drive additional benefit if treatment with trimethoprim was found to be effective. Most of the recruited subjects were successfully followed up.

Patients in both treatment groups (the trimethoprim and placebo group) showed significant reduction in the overall PANSS score, without significant between-group differences. This lack of significant difference suggests that treatment with trimethoprim is not superior to placebo in improving symptoms of schizophrenia in this particular setting. The general improvement in symptom severity despite patients having been on antipsychotic medication for many years previously may be due to enhanced adherence occasioned by strict follow-up during the trial period. The reduction in symptom severity appears to be due primarily to a gross reduction in all symptoms domains. Because there were no significant between-group differences, the improvement in these symptom domains also appears to be due to the ongoing treatment with antipsychotic medications. Some researchers[37] have described excess positive and cognitive symptom domains measured with the PANSS among

Table 3. Mean Score and PANSS Cluster Score of Trimethoprim and Placebo Groups Overtime. Butajira, Ethiopia, 2005.

	N	Trimethoprim, Mean (SD)	*N*	Placebo, Mean (SD)	*t* Test	*P* Value
PANSS overall score						
Baseline	46	78.5 (14.9)	45	79.6 (17.6)	0.335	.738
Month 1	40	75.4 (21.0)	42	74.6 (28.1)	0.138	.891
Month 2	40	67.9 (22.3)	42	73.6 (26.3)	1.074	.286
Month 3	40	68.8 (19.9)	41	72.6 (22.3)	0.804	.424
Month 4	40	66.1 (19.5)	41	72.0 (21.2)	1.340	.196
Month 5	40	64.6 (19.6)	41	68.8 (23.0)	0.873	.386
Month 6	38	61.9 (18.0)	41	65.5 (17.6)	0.897	.375
PANSS clusters score						
Positive symptoms						
Baseline	46	10.5 (4.5)	45	10.7 (4.0)	0.283	.776
6 mo	38	8.3 (2.7)	41	8.9 (3.9)	0.779	.439
Negative symptoms						
Baseline	46	35.0 (8.5)	45	36.4 (10.7)	0.702	.485
6 mo	38	27.7 (10.6)	41	30.4 (11.1)	1.107	.272
Excitement						
Baseline	46	10.5 (4.4)	45	9.7 (4.2)	0.893	.374
6 mo	38	8.2 (3.5)	41	7.8 (3.1)	0.584	.561
Anxiety/depression						
Baseline	46	11.5 (4.2)	45	10.9 (3.1)	0.701	.485
6 mo	38	7.4 (2.4)	41	8.3 (2.8)	1.531	.130
Cognitive						
Baseline	46	7.5 (3.3)	45	7.9 (3.2)	0.532	.596
6 mo	38	7.3 (3.8)	41	7.2 (3.8)	0.081	.936
Suspiciousness						
Baseline	46	2.2 (1.5)	45	2.2 (1.6)	0.013	.989
6 mo	38	1.8 (1.1)	41	1.7 (1.2)	0.210	.834

Note: PANSS, Positive and Negative Syndrome Scale.

Toxoplasma-seropositive patients compared with -seronegative patients. Studies have also shown significant correlations between latent toxoplasmosis and certain personality shifts[29] and deterioration of psychomotor performance (increased reaction time) compared with controls indicating a decline in the long-term ability of infected individuals to concentrate.[30] The general improvement observed in the PANSS symptoms, which are also shown in the placebo group could just be due to placebo effect as well.[31–33] To our knowledge, there are no reports regarding the effects of trimethoprim on symptoms of schizophrenia to compare our findings with.

We were unable to compare the PANSS scores of those who were IgG antibody reactive, showing chronic infection against those who were not reactive because of high seroprevalence in our cases. A high prevalence of seropositivity for toxoplasmosis in humans in general[34] and among people with schizophrenia in particular is well recognized.[2] However, the prevalence is higher among our sample, even compared with that reported in Ethiopia in an earlier study.[35] This may be a reflection of the patients living conditions and that of the general dietary habit in this rural setting where eating raw meat is widely acceptable. Cats, which are the definitive hosts to *T. gondii*,[19] are also common in this setting and may have contributed to the high prevalence.

The overall safety of trimethoprim appeared comparable to placebo, with one participant from each group having to be withdrawn from the study due to a reduction in hemoglobin. One participant from the trimethoprim group committed suicide after the fifth month of treatment with trimethoprim. The act followed a family discord and did not appear to be directly related to receiving trimethoprim. To our knowledge, there are no reported associations between trimethoprim and suicide. No adverse incident was reported in the 6-month postintervention period.

Limitations

The participants in this study were cases with chronic schizophrenia with average illness duration of about 13 years. Thus, our finding is not generalizable to those with a shorter duration of illness. The relatively small sample size, the lack of objective measure of medication compliance, and the fact that PANSS was used as the only outcome measure may also limit and might also have affected the results of the study.

Conclusion

Patients receiving trimethoprim as an adjuvant treatment for schizophrenia did not show any significant improvement in symptoms compared with placebo. However, this should not be interpreted to mean toxoplasmosis does not contribute to the onset of schizophrenia. Some of the etiology of schizophrenia has been ascribed to early neurodevelopmental abnormalities.[35,36] If toxoplasmosis is relevant in such circumstances, its effect could be early in life during brain development adversely impacting critical structural and functional development of the brain.[15] These changes, which may form the underlying neuropathology of schizophrenia in some cases, are less likely to be reversed with trimethoprim.

Additionally, the improvement caused by the enhanced adherence by the strict follow-up regimen during the trial period may have drowned out any subtle additional improvement that could have occurred with the trimethoprim-treated group.

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