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REVIEW

Toxoplasma gondii and schizophrenia: a review of published RCTs

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Abstract Over the last 60 years, accumulating evidence has suggested that acute, chronic, and maternal *Toxoplasma gondii* infections predispose to schizophrenia. More recent evidence suggests that chronically infected patients with schizophrenia present with more severe disease. After acute infection, parasites form walled cysts in the brain, leading to lifelong chronic infection and drug resistance to commonly used antiparasitics. Chronic infection is the most studied and closely linked with development and severity of schizophrenia. There are currently four published randomized controlled trials evaluating antiparasitic drugs, specifically azithromycin, trimethoprim, artemisinin, and artemether, in patients with schizophrenia. No trials have demonstrated a change in psychopathology with adjunctive treatment. Published trials have either selected drugs without evidence against chronic infection or used them at doses too low to reduce brain cyst burden. Furthermore, trials have failed to achieve sufficient power or account for confounders such as previous antipsychotic treatment, sex, age, or rhesus status on antiparasitic effect. There are currently no ongoing trials of anti-*Toxoplasma* therapy in schizophrenia despite ample evidence to justify further testing.

Keywords *Toxoplasma* · Schizophrenia · Treatment · Chronic

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Introduction

Schizophrenia exacts a significant global burden of disease: it was the 12th leading cause of years lost to disability in 2015, placing it ahead of osteoarthritis, chronic obstructive pulmonary disease, and Alzheimer's disease (Vos et al. 2016). Yet, despite significant research, the complex interplay of genetic and environmental factors in its pathogenesis is unclear. Since at least the 1950s, there has been a hypothesized connection between schizophrenia and *Toxoplasma gondii* infection (Buentello 1958). *T. gondii* is an intracellular parasite with tropism for the muscle and brain; upon oral, intravenous, or sexual introduction into immunocompetent hosts, fast-replicating tachyzoites migrate to these organs, convert to bradyzoites, and form cysts that persist for the host's life. Bradyzoites are resistant to almost all clinically available anti-*Toxoplasma* drugs, and treatment is currently only used in acute toxoplasmosis (Neville et al. 2015). Latent *Toxoplasma* infection is classically considered asymptomatic, affecting over 20% of the population in South America, Central and Eastern Europe, the Middle East, Southeast Asia, and Africa (Pappas et al. 2009).

Recent meta-analyses confirm that there is a greater prevalence of both IgG and IgM antibodies, as well as greater IgG titres, in patients with schizophrenia (Monroe et al. 2015; Sutterland et al. 2015). Importantly, the vast majority of studies have examined the epidemiological and pathophysiological link between latent *Toxoplasma* infection, marked by IgG-seropositivity, and schizophrenia in the same individual (Sutterland et al. 2015). A smaller number of studies have also supported development of schizophrenia after acute *Toxoplasma* infection, marked by IgM seropositivity, or maternal infection on foetal development of disease. Current evidence suggests that chronic *Toxoplasma*-induced neuroinflammation and cytokine imbalance alter neurotransmitter

metabolism, tryptophan metabolism, host immune function, and systemic hormone levels (Elsheikha et al. 2016). In rodents, one of the most studied pathways connects chronic *T. gondii* infection with increased brain concentrations of dopamine via parasite-encoded tyrosine hydroxylases and host nitric oxide-mediated dopamine release (Elsheikha et al. 2016). In humans, anti-*Toxoplasma* IgG titres are lower in patients with more severe psychopathology, suggesting that long-term infection leads to worsening of disease over time (Holub et al. 2013).

Not only does *Toxoplasma* infection predispose to schizophrenia, there is mounting evidence that IgG-positive schizophrenia cases are distinct and more severe compared with seronegative cases (Flegr 2015). Three independent studies show more intense positive symptoms (e.g. hallucinations, delusions, and disorganized thought) in seropositive cases (Wang et al. 2006; Amminger et al. 2007; Holub et al. 2013). Furthermore, Çelik et al. (2015) show that seropositive cases have significantly greater risk for continuous disease, need for electroconvulsive therapy, and lack of insight into illness. Holub et al. (2013) show that seropositive cases have longer hospitalizations and are more likely to require high-dose antipsychotics. Fond et al. (2015) show that seropositive patients with schizophrenia or schizoaffective disorder have a higher lifetime number of depressive and manic episodes, suicide attempts, and psychiatric hospitalizations. One imaging study corroborates these observed clinical differences: seropositive patients with schizophrenia had significantly reduced grey matter volume bilaterally in the caudate, median cingulate, thalamus, and occipital cortex and in the left cerebellar hemispheres compared with seronegative patients with schizophrenia. No difference in the brain morphology between seronegative patients and controls was observed (Horacek et al. 2012).

Studies to date

Given the close link between *T. gondii* infection and schizophrenia, there have been four published randomized controlled trials (RCTs) evaluating adjunctive antiparasitics in patients with schizophrenia[1] (Table 1). Each trial has significant underlying issues that prevent extrapolating evidence to all anti-*Toxoplasma* treatment in schizophrenia. The first published trial, conducted by Dickerson et al. (2009), randomly evaluated adjunctive azithromycin in 28 patients with IgG-positive schizophrenia or schizoaffective disorder on stable antipsychotic treatment. The treatment group (n = 13) received azithromycin 600 mg daily for 2 weeks and then weekly for an additional 14 weeks. Patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) at baseline and every other week for 16 weeks. PANSS is the most widely used symptom severity scale in schizophrenia and assesses positive symptoms such as hallucinations and delusions, negative symptoms such as emotional and social withdrawal, and global psychopathology such as depression and anxiety. As per previous benchmarking studies, a total PANSS score of 58, 75, 95, and 116 correlate with mild, moderate, marked, and severe disease, respectively (Leucht et al. 2005). In the azithromycin trial, patients had a mean PANSS baseline score of 71.6, were 54% female, and had a mean duration of illness of 22.3 years.

The next trial, conducted by Shibre et al. (2010), examined 6 months of add-on trimethoprim (TMP) at 200 mg per day to usual care in a double-blind RCT. Study participants (n = 91) were all male, had schizophrenia, had an average duration of illness of 13 years, and had a baseline PANSS score of at least 60. The study was powered to detect a 7-point difference in mean PANSS score between study arms over 6 months with 80% power. PANSS was reassessed monthly.

Dickerson et al. (2011) evaluated 100 mg artemisinin twice daily in a double-blind RCT of 66 patients with schizophrenia or schizoaffective disorder. Inclusion criteria were at least moderately severe on one or more PANSS positive symptom scores and/or PANSS negative symptom scores of 4 or more or a total PANSS score of 50 or more containing at least three positive or negative items with scores of 3 or more. Treatment was given for 10 weeks and PANSS assessed at 2-week intervals. Wang et al. (2014) evaluated the related compound artemether in a double-blind RCT of 100 patients with schizophrenia or schizophreniform disorder. Inclusion criteria were IgG- or IgM-seropositive patients naïve to antipsychotics. Risperidone was started at 0.5 mg twice daily in each group and titrated up by the treating psychiatrist. At week 2, participants received 80 mg artemether or placebo daily for 1 week and then again for the fourth week. Participants were also allowed trihexyphenidyl and clonazepam. Participants were evaluated every other week for 8 weeks with PANSS.

No study found any change in PANSS total score or subscale scores with adjunctive antiparasitic treatment. In the artemisinin trial, there was no change in the Repeatable Battery for the Assessment of Neuropsychological Status (originally a tool to assess dementia) or the University of California Performance-Based Skills Assessment (an evaluation of day to day functioning). In the artemether trial, there was no change in the Clinical Global Impressions Scale (a subjective assessment by the treating physician of disease severity) or the Brief Assessment of Cognition in Schizophrenia (an assessment of memory, attention, and executive function). Furthermore, artemisinin and artemether did not significantly alter IgG-seropositivity to *Toxoplasma* at the end of each trial, and the other two studies did not assess this outcome.

[1] Search strategy included querying Medline, Cochrane Controlled Trials Register, PsychInfo, and Embase with query "Toxoplasm* AND schizophreni*". Resulting abstracts were screened for relevant randomized controlled trials in humans. Reference lists of included trials were screened for additional trials.

Table 1 Summary of published RCTs evaluating anti-*Toxoplasma* therapy in patients with schizophrenia

Trial	Year	Treatment	Inclusion criteria	Follow-up length in weeks (including treatment duration)	Outcomes assessed	Any significant treatment effect
Dickerson et al.	2009	Azithromycin 600 mg PO daily for 2 weeks, then weekly for 14 weeks	• IgG+ • Schizophrenia or schizoaffective disorder • 18–65 years old • At least moderately severe symptoms on PANSS • Stable antipsychotic treatment	16	PANSS	No
Shibre et al.	2010	Trimethoprim 200 mg PO daily for 6 months	• Schizophrenia • Male • 15–49 years old • PANSS ≥ 60	24	PANSS	No
Dickerson et al.	2011	Artemisinin 100 mg PO BID for 10 weeks	• Schizophrenia or schizoaffective disorder • 18–65 years old • Stable antipsychotic treatment • At least moderately severe on 1 or more PANSS positive symptom scores, and/or PANSS negative symptom scores of 4 or more, or a total PANSS score of 50 or more containing at least 3 positive or negative items with scores of 3 or more	10	PANSS, RBANS, UPSA, IgG	No
Wang et al.	2014	Artemether 80 mg PO daily for the 2nd and 4th weeks	• IgM+ or IgG+ • Schizophrenia or schizophreniform disorder • 16–40 years old • Antipsychotic naïve • Illness duration < 2 years • PANSS ≥ 60	8	CGI, PANSS, TESS, BACS, IgG, IgM	No

Please see text for additional explanations of outcome assessment tools

BID twice daily, *PO* by mouth, *PANSS* Positive and Negative Syndrome Scale, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status. *UPSA* University of California Performance-Based Skills Assessment, *CGI* Clinical Global Impressions Scale, *TESS* Treatment Emergent Symptom Scale. *BACS* Brief Assessment of Cognition in Schizophrenia

Drug selection and dosing

All published studies suffered from selection of drugs without established activity against *Toxoplasma* bradyzoites in comparable animal models. Azithromycin has previously been tested in at least two mouse models of chronic *Toxoplasma* infection (Dumas et al. 1994; Mahmoud 2006). In the Dumas et al. experiment, mice were treated for the same duration (14–19 weeks) as the human trial (16 weeks) but received treatment daily for the full duration instead of weekly for weeks 3 to 16. Each treatment dose was roughly equivalent between studies after correcting for inter-species differences (488 mg daily human equivalent vs. 600 mg daily) (Nair and Jacob 2016). Despite in vitro evidence for azithromycin against bradyzoites (Huskinson-Mark et al. 1991), no in vivo reduction in brain cysts was seen in this experiment. One explanation is that drug concentrations in mouse brain were too low to exert antiparasitic activity: In the second experiment (Mahmoud 2006), a human equivalent dose of 1220 mg daily azithromycin was used for 13 weeks, and this dose led to a decrease in the number of cysts in the brains of chronically infected mice. While Mahmoud used a more virulent, albeit still chronic, cystogenic strain of *T. gondii*, additional evidence comes from inhibiting efflux of other macrolides, such as spiramycin, from the brain. Achieving sufficient drug concentration in the brain is challenging because macrolides are effluxed via multidrug-resistant protein 2 and P-glycoprotein (Sugie et al. 2004; Munić et al. 2010), resulting in drug concentrations 10- to 100-fold lower than in other organs of *Toxoplasma*-infected mice (Araujo et al. 1991). Adjunctive metronidazole, an efflux inhibitor, increased maximum spiramycin concentration in chronically infected mouse brain by 72% and reduced cyst burden by 10-fold compared with spiramycin alone (Chew et al. 2012). Given the weekly dosing

of azithromycin in the human schizophrenia trial and the lack of evidence at equivalent daily doses in mice, it is unlikely that human patients saw any reduction in cyst burden, precluding changes in PANSS.

The choice of TMP as the active agent in the Shibre et al. trial is perplexing and likely led to negative study results. A literature search could identify no studies evaluating TMP alone against chronic *Toxoplasma*. Studies examining TMP with sulphamethoxazole (SMX) in chronic infection found the combination, which is synergistic, could not eradicate cysts from mouse brain (Nguyen and Stadtsbaeder 1983) but could increase survival (Dumas et al. 1999) compared with placebo. In a mouse model of acute toxoplasmosis, mice treated with TMP alone did not have increased survival, whereas addition of SMX protected all animals from death (Dumas et al. 1999). Shibre et al. rationalize their choice of active drug by stating that TMP is used for toxoplasmosis prophylaxis in immunocompromised hosts. This argument is invalid as TMP is almost always prescribed with SMX; for example, current HIV guidelines do not recommend TMP alone (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2017).

Finally, there is no direct evidence that artemisinin or artemether, related compounds used to treat malaria, has activity against bradyzoites (Sharif et al. 2016; Loo et al. 2017). Artemether, which is twice as potent as artemisinin against tachyzoites in vitro (Hencken et al. 2010), failed to reduce cyst burden in chronically infected mice (Schultz et al. 2014). Artemether was given daily for 16 days at a human equivalent of 49 mg, longer but at 5/8th the dose of the human schizophrenia trial. One derivative of artemisinin did reduce cyst burden in this study, but given lack of activity of artemether and three other artemisinin derivatives in vivo (Dunay et al. 2009; Schultz et al. 2014), this effect cannot be extrapolated to the class.

Study power and inclusion criteria

Aside from the selection of potentially inappropriate antimicrobial therapy, most published studies have design flaws that further precluded meaningful results. Three (Dickerson et al. 2009; Shibre et al. 2010; Dickerson et al. 2011) out of four studies omitted sample size calculation from their manuscript and were likely inappropriately powered to detect significant difference. Only two studies (Dickerson et al. 2009; Wang et al. 2014) excluded *Toxoplasma*-seronegative patients, further decreasing power, with the TMP evaluation including 11% IgG-negative patients.

Including patients already on a stable course of antipsychotics could have confounded analysis of the remaining IgG-positive patients. It has been reported that select antipsychotics possess activity against *Toxoplasma* tachyzoites in vitro (Jones-Brando et al. 2003; Goodwin et al. 2011; Fond et al. 2014). In a subacute toxoplasmosis rat model, treatment with haloperidol reduced behavioural disturbance more than a pyrimethamine/dapsone combination, which was superior to valproic acid (Webster et al. 2006). Interestingly, these reductions occurred in proportion to the number of animals with *Toxoplasma*-staining neurons and glia in each treatment arm, and each treatment had the opposite effect in uninfected rats (i.e. they increased behavioural disturbance). The authors speculate that the anti-*Toxoplasma* activity of each drug led to behavioural improvement; however, the relevance of these findings to chronic infection in schizophrenia is unclear. Treatment in this rat model started on day 14 when most *T. gondii* cells were in tachyzoite stage, although brain cysts have been reported to form as early as day 8 post-infection (Lainson 1958). As well, pyrimethamine and dapsone both have activity against tachyzoites and bradyzoites as monotherapy (Chang et al. 1994). In humans, one retrospective cohort study failed to find a difference in treatment response between IgG-positive patients treated with antipsychotics active against tachyzoites (Fond et al. 2015). Future RCTs evaluating adjunctive antiparasitic treatment should avoid confounding by only including patients on antipsychotics with no known antiparasitic activity.

Only one RCT (Shibre et al. 2010) accounted for an interaction between *Toxoplasma* infection and sex by study design (excluding females from their trial), and no trials used statistical analysis to account for sex. It has been reported that *Toxoplasma* infection presents differently in each sex: In a cohort of 251 patients, schizophrenia presented 1 year earlier and 2.5 years later in males and females, respectively (Holub et al. 2013). In the same cohort, males, but not females, scored significantly higher in negative PANSS scores, reality distortion, disorganization, and cognitive composite scores than uninfected counterparts. These changes are consistent with sex differences of latent infection on human behaviour (Lindová et al. 2006; Lindová et al. 2013) and modifications to *T. gondii* susceptibility and immune response with experimental manipulation of sex hormones (Roberts et al. 2001). Given that sex hormones change in a non-linear fashion throughout life, the effect of age on sex and *Toxoplasma* infection must also be taken into account.

Further complicating the interaction of sex, age, and *T. gondii* infection is the rhesus factor. At least five studies report that the RhD blood group positivity protects from effects of latent *T. gondii* infection, including prolongation of reaction time, increased risk of traffic accidents, and excessive pregnancy weight gain (Flegr 2013). In 185 patients with schizophrenia, RhD status significantly interacted with sex, protecting RhD-positive females from greater PANSS positive and distortion of reality scores (Holub et al. 2011). Given the complex interplay between genetic and environmental factors in schizophrenia, careful analysis will be necessary to

understand treatment effect and target therapy to appropriate subgroups.

Future research

The time is ripe to evaluate antiparasitic drugs in *Toxoplasma*-infected patients with schizophrenia. At the time of writing (February 2017), there are no ongoing trials registered with the Stanley Medical Research Institute evaluating antiparasitic drugs in schizophrenia, with the exception of minocycline. There is an additional study (NCT02118610) registered with ClinicalTrials.gov evaluating L-tetrahydropalmatine, an anti-inflammatory agent with anti-protozoal properties; however, this agent is not market-approved in North America or Europe. A recent review (Neville et al. 2015) highlighted currently approved and investigational drugs with activity against different stages of *Toxoplasma*. Future research should examine agents with demonstrable activity against the chronic, bradyzoite stage of *T. gondii* in patients with schizophrenia. Notably, recent studies have demonstrated activity of spiramycin combined with metronidazole (Chew et al. 2012), didanosine (Sarciron et al. 1997), miltefosine (Eissa et al. 2015), sulfadiazine (Araujo and Remington 1974; Eissa et al. 2015), and atovaquone combined with clindamycin (Djurković-Djaković et al. 2002) against chronic *Toxoplasma* infection in vivo.

Minocycline, a broad-spectrum tetracycline antibiotic, also has activity against *T. gondii* cysts in an in vivo model (Chang et al. 1991). Interestingly, there is a growing body of evidence that minocycline augmentation therapy in schizophrenia results in lower PANSS total scores, and negative and general subscale scores (Oya et al. 2014). It is currently unknown how minocycline affects the schizophrenic brain; however, there is evidence that it also has antipsychotic properties in an uninfected rat model of schizophrenia (Fujita et al. 2008). Another potential, yet untested, mechanism for therapeutic effect in human schizophrenia is through reduction of *Toxoplasma* cyst burden. Future research should look to delineate the antiparasitic effect of minocycline from its neuromodulatory effect in humans with schizophrenia by IgG stratification.

There is robust evidence that *Toxoplasma* infection increases risk for schizophrenia, and seropositive cases appear to present with worse psychopathology. There have been four trials to date evaluating antiparasitics in *Toxoplasma*-positive patients with schizophrenia; however, there are significant challenges to these trials preventing extrapolation to other anti-*Toxoplasma* agents. Given the significant global burden of schizophrenia, there is a pressing need to evaluate novel therapy approaches.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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