



Antipsychotics and Mood Stabilizers as Potential Anti-Toxoplasma Agents: A Critical Mechanistic Review of Molecular, Anti-inflammatory, and Histopathological Evidence

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Article Info	Abstract
Document Type: Review Paper Received 08/06/2026 Received in revised form 11/07/2026 Scientific Accepted 20/07/2026 Published 28/10/2026 Keywords: <i>Toxoplasma gondii</i>, Antipsychotics, Mood stabilizers, Valproic acid, Haloperidol, Risperidone, Neuroinflammation	<i>Toxoplasma gondii</i> is a neurotropic protozoan parasite that can establish long-term infection in the central nervous system. Chronic cerebral infection has been associated with neuroinflammation, altered neurotransmission, and increased susceptibility to neuropsychiatric disorders, particularly schizophrenia and bipolar disorder. Current anti-Toxoplasma therapies mainly target actively replicating stages and show limited efficacy against established tissue cysts, while toxicity and treatment tolerance remain important concerns. These limitations have increased interest in psychiatric drugs with reported antiparasitic and immunomodulatory properties. This critical mechanistic review evaluates evidence on selected antipsychotics and mood stabilizers, mainly valproic acid, haloperidol, and risperidone, as possible adjunctive candidates against <i>T. gondii</i> infection. The analysis focuses on parasite-related outcomes, including parasite burden, REP-529 copy number, and BAG1 expression, as well as host inflammatory responses, particularly TNF-α expression, microglial activation, and cytokine-associated neuroinflammation. Histopathological evidence related to cyst establishment, perivascular infiltration, glial nodules, encephalitis, and preservation of brain tissue integrity is also considered. Available findings suggest that these drugs may affect parasite persistence and infection-associated inflammation under defined experimental conditions. However, inconsistencies across in vitro assays, animal models, and limited clinical observations indicate that their therapeutic relevance remains uncertain. Further mechanistic, pharmacological, and translational studies are required before these agents can be considered for clinical application in toxoplasmosis.

1. Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite with a broad host range and a marked capacity to establish long-term infection in neural and muscular tissues. Human infection mainly occurs through ingestion of oocyst-contaminated food or water, or through consumption of undercooked meat containing tissue cysts. *Toxoplasma gondii* infection affects a substantial proportion of the global population, with seroprevalence rates estimated to range from approximately 30% to 50% worldwide, varying significantly by geographic region and socioeconomic conditions. Importantly, accumulating epidemiological evidence has linked chronic infection with an increased risk of neuropsychiatric disorders, including schizophrenia and mood-related conditions. Given the high global exposure burden and the limited efficacy of current treatments against tissue cyst stages, these observations provide a strong rationale for exploring host-directed repurposing strategies involving psychotropic agents (Saadatnia & Golkar, 2012; Weiss &

Kim, 2011). After host entry, the parasite can disseminate as rapidly replicating tachyzoites and reach different tissues, including the central nervous system (Mendez & Koshy, 2017). Under immune pressure, tachyzoites convert into slow-replicating bradyzoites enclosed within tissue cysts, allowing chronic persistence of the parasite in the host (Lyons *et al.*, 2002; Weiss & Kim, 2011). This stage conversion is a central challenge in toxoplasmosis treatment, because established cysts are less responsive to conventional anti-Toxoplasma chemotherapy than actively replicating stages (Dunay *et al.*, 2018; Sullivan Jr. *et al.*, 2009).

The persistence of *T. gondii* in the brain has generated sustained interest in its possible contribution to neuropsychiatric disorders. Experimental studies indicate that cerebral infection can affect glial function, neuronal activity, immune signaling, and neurotransmitter-associated pathways (Boillat *et al.*, 2020; Carruthers & Suzuki, 2007; Mendez & Koshy, 2017; Tedford & McConkey, 2017). Infection of microglia, astrocytes, and neurons has been associated with inflammatory gene

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expression, microglial activation, and changes in dopaminergic and serotonergic regulation, which overlap with biological pathways implicated in schizophrenia and bipolar disorder (Fond *et al.*, 2015; Luder *et al.*, 1999; Müller *et al.*, 2015; Tyebji *et al.*, 2019). Epidemiological and serological studies have reported a higher frequency of *T. gondii* seropositivity among patients with schizophrenia compared with control populations (Burgdorf *et al.*, 2019; Torrey *et al.*, 2012; Torrey & Yolken, 2003). However, this association should be interpreted cautiously, because seropositivity does not establish causality, and differences in population background, exposure history, disease stage, and clinical classification may influence the reported relationship (Burgdorf *et al.*, 2019; Tyebji *et al.*, 2019). Recent comprehensive reviews have continued to emphasize the epidemiological and mechanistic links between chronic *T. gondii* infection and psychotic disorders, while also highlighting the ongoing uncertainty regarding the therapeutic utility of psychotropic drugs in this context (Mares *et al.*, 2024).

Current anti-Toxoplasma treatment mainly targets active parasite replication. Pyrimethamine-based regimens and related combinations can reduce tachyzoite proliferation, but their activity against established tissue cysts remains limited, and toxicity remains an important practical concern (Dunay *et al.*, 2018). These limitations have encouraged interest in drug repurposing strategies that may affect both parasite persistence and host inflammatory responses. Psychotropic drugs are relevant in this context because several antipsychotics and mood stabilizers can cross the blood-brain barrier and modulate biological processes that are also involved in chronic cerebral toxoplasmosis, including calcium signaling, microglial activation, cytokine production, oxidative stress, and epigenetic regulation (Baumeister *et al.*, 2016; Chen *et al.*, 2014; Mizoguchi *et al.*, 2014; Monti *et al.*, 2009; Patel *et al.*, 2023).

The anti-Toxoplasma relevance of psychotropic drugs remains unresolved. Early in vitro studies reported that drugs used in schizophrenia and bipolar disorder, including haloperidol and valproic acid, could inhibit *T. gondii* invasion or replication (Jones-Brando *et al.*, 2003; Pezzella *et al.*, 1997). Other studies, however, reported weak, inconsistent, or absent anti-Toxoplasma activity for several tested agents, including some antipsychotics and mood stabilizers (Fond *et al.*, 2014; Goodwin *et al.*, 2011; Strobl *et al.*, 2007). In animal models, valproic acid and haloperidol were reported to alter infection-related behavioral outcomes in rats, whereas other mouse studies failed to demonstrate protection against acute or chronic infection (Goodwin *et al.*, 2008; Saraei *et al.*, 2016; Saraei *et al.*, 2015; Webster *et al.*, 2006). Clinical observations have also suggested possible associations between antipsychotic treatment, anti-Toxoplasma activity, and improved outcomes in selected patient groups, but these findings remain indirect and cannot establish therapeutic efficacy (Fond *et al.*, 2015; Leweke *et al.*, 2004). A 2025 study by the same research group extended these findings by demonstrating that risperidone significantly reduced BAG1, SAG1, and REP529 copy numbers in the brains of chronically infected mice, with concomitant reductions in TNF- α expression and histopathological lesions

(Enshaeieh *et al.*, 2025). This inconsistency indicates that the potential value of psychotropic drugs against *T. gondii* cannot be judged from isolated positive or negative reports. Differences in parasite stage, treatment timing, infection model, drug dose, and outcome measurement may strongly affect the interpretation of efficacy (Ferguson & Hutchison, 1987; Goodwin *et al.*, 2008; Watts *et al.*, 2015). For example, late initiation of treatment may reduce the chance of detecting effects on cyst development, because bradyzoite replication decreases as chronic infection becomes established (Babaie *et al.*, 2017; Ferguson & Hutchison, 1987; Watts *et al.*, 2015). In this context, molecular endpoints such as REP-529 copy number and BAG1 expression may provide more informative measures of parasite and cyst-associated burden than cyst counting alone. REP-529 is a highly repetitive genomic element of *Toxoplasma gondii* that is widely used as a sensitive molecular marker for parasite detection and estimation of parasite burden because of its high copy number. In contrast, BAG1 (bradyzoite antigen 1) is a stage-specific marker expressed during bradyzoite differentiation and is commonly used to assess tissue cyst formation and chronic infection. Although these markers provide valuable information regarding parasite burden and developmental stage, they should be interpreted together with inflammatory and histopathological findings, as changes in their expression do not necessarily reflect parasite viability or overall disease severity (Berizi *et al.*, 2021; Enshaeieh *et al.*, 2021; Homan *et al.*, 2000).

Valproic acid, haloperidol, and risperidone are frequently discussed candidates because they combine neuropharmacologic activity with mechanisms that may be relevant to chronic cerebral toxoplasmosis. Valproic acid may affect host and parasite responses through calcium channel modulation, histone deacetylase inhibition, oxidative stress regulation, and inflammatory signaling (Johannessen, 2000; Monti *et al.*, 2009; Suh *et al.*, 2010; Ximenes *et al.*, 2012). Haloperidol has been linked to calcium channel blockade, calmodulin-related effects, and modulation of inflammatory cell responses, which may be relevant to calcium-dependent parasite invasion, replication, and egress (Enyeart *et al.*, 1992; Ito *et al.*, 1996; Matsumoto *et al.*, 2015; Pace *et al.*, 2014; Pezzella *et al.*, 1997). Risperidone may contribute through modulation of dopaminergic and serotonergic signaling and suppression of inflammatory pathways in activated glial cells, although its direct antiparasitic activity has been less consistent across models (Fond *et al.*, 2014; Kato *et al.*, 2011; MacDowell *et al.*, 2013; Mizoguchi *et al.*, 2014). These mechanisms are biologically plausible, but their direct contribution to parasite control remains incompletely defined.

This review evaluates the evidence for antipsychotics and mood stabilizers as possible adjunctive candidates against *T. gondii* infection, with emphasis on valproic acid, haloperidol, and risperidone. The discussion is organized around three connected levels of evidence. The first concerns parasite-related outcomes, including parasite burden, cyst persistence, REP-529 copy number, and BAG1 expression (Berizi *et al.*, 2021; Enshaeieh *et al.*, 2021; Homan *et al.*, 2000). The second concerns host inflammatory responses, particularly TNF- α -associated signaling, microglial activation, and cytokine-mediated

neuroinflammation (Baumeister *et al.*, 2016; Enshaiehi *et al.*, 2021; Patel *et al.*, 2023). The third concerns histopathological outcomes in infected brain tissue, including cyst establishment, perivascular inflammation, glial nodules, encephalitis, and preservation of tissue integrity (Enshaiehi *et al.*, 2021; Hermes *et al.*, 2008; Li, Severance *et al.*, 2019). By examining these levels together, the review aims to identify where current evidence is supportive, where it remains inconsistent, and which mechanistic and translational gaps should be addressed before clinical relevance can be inferred. This review does not aim to comprehensively cover all antipsychotic and mood-stabilizing agents. Instead, it specifically focuses on valproic acid, haloperidol, and risperidone, as these agents currently have the most substantial experimental evidence regarding their potential anti-Toxoplasma gondii activity, including molecular, anti-inflammatory, and histopathological outcomes. Drugs such as lithium, although clinically important as mood stabilizers, were not included because comparable experimental evidence addressing these parasite-related endpoints remains limited. Although psychotropic drugs have been increasingly recognized for their immunomodulatory and neurobiological effects, current evidence regarding their role in Toxoplasma gondii infection remains dispersed and methodologically heterogeneous. To address this gap, the present review deliberately focuses on valproic acid, haloperidol, and risperidone, as these agents represent the most extensively studied compounds in experimental toxoplasmosis across molecular, inflammatory, and histopathological dimensions. This targeted approach enables a more rigorous and internally consistent evaluation of mechanistic evidence, while avoiding dilution of conclusions by pharmacological agents with insufficient or non-comparable experimental data. The conceptual framework of the reviewed evidence is summarized in Figure 1. Accordingly, this review is intentionally focused

on valproic acid, haloperidol, and risperidone, which collectively represent the most extensively investigated psychotropic agents in experimental Toxoplasma gondii research, thereby allowing a more coherent and mechanistically comparable synthesis of the available evidence.

2. Evidence Landscape of Psychotropic Drugs against Toxoplasma gondii

The anti-Toxoplasma relevance of psychotropic drugs has been examined through in vitro assays, animal models, and limited clinical observations. These evidence levels address different biological questions and should not be interpreted with the same weight. In vitro studies are useful for identifying direct effects on parasite invasion or replication, but they do not reproduce the pharmacokinetic, immune, and tissue-specific conditions of chronic cerebral infection.

Animal models provide stronger biological relevance, particularly when molecular parasite markers, inflammatory responses, and histopathological outcomes are assessed together. Clinical and serological observations may support translational relevance, but they remain indirect unless parasite-specific endpoints are included. Therefore, the current evidence should be evaluated according to model type, parasite stage, treatment timing, drug exposure, and the endpoint used to define efficacy.

A structured comparative synthesis was applied across in vitro, in vivo, and indirect clinical evidence to enhance interpretive rigor beyond descriptive reporting. Each evidence tier provides distinct but non-equivalent biological information: in vitro systems capture direct cellular and molecular effects, in vivo models integrate immune-mediated and systemic responses, and clinical observations reflect highly heterogeneous and multifactorial disease contexts.

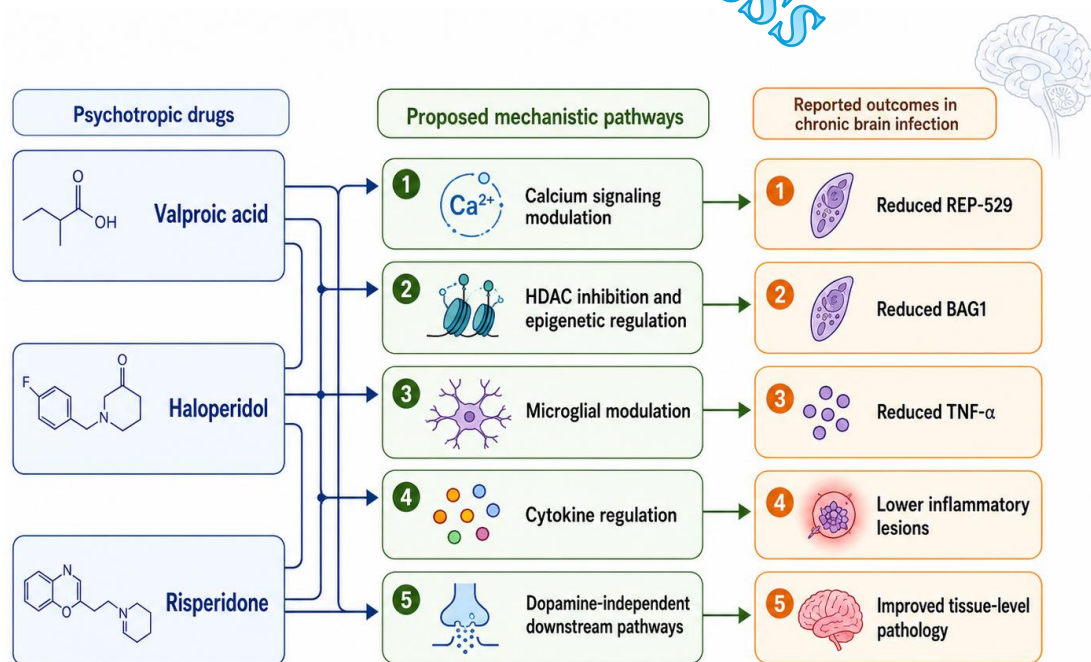


Figure 1. Proposed mechanistic framework linking selected psychotropic drugs with molecular, inflammatory, and tissue-level outcomes during chronic *T. gondii* infection (Enshaiehi *et al.*, 2021; Fond *et al.*, 2014; Jones-Brando *et al.*, 2003; Pezzella *et al.*, 1997).

Discrepancies across these levels are expected and are likely attributable to variations in parasite developmental stage, host immune status, pharmacological exposure, and experimental endpoints. Accordingly, greater interpretive weight was assigned to cross-model consistency rather than isolated findings within a single experimental domain.

2.1. In vitro evidence and limits of direct parasite inhibition

Early in vitro studies provided the first basis for considering psychotropic drugs as potential anti-Toxoplasma candidates. Jones-Brando *et al.* reported that several drugs used in schizophrenia and bipolar disorder could inhibit *T. gondii* replication in cell culture, including haloperidol and valproic acid (2003). Trifluoperazine, a calmodulin antagonist, was also shown to interfere with tachyzoite invasion, supporting the relevance of calcium- and calmodulin-dependent processes in parasite entry (Pezzella *et al.*, 1997). These findings were important because they suggested that some neuropsychiatric drugs may affect parasite biology through mechanisms beyond their canonical psychiatric targets.

However, subsequent in vitro findings were not fully consistent. Later studies reported weak or negligible anti-Toxoplasma activity for some agents, including valproic acid, haloperidol, and risperidone, whereas other compounds such as phenothiazine derivatives showed stronger inhibitory effects (Fond *et al.*, 2014; Goodwin *et al.*, 2011; Strobl *et al.*, 2007). This inconsistency indicates that anti-Toxoplasma activity cannot be generalized to all antipsychotics or mood stabilizers. It also suggests that the observed effects may depend on drug structure, concentration range, host-cell type, parasite strain, exposure time, and the method used to measure parasite inhibition. Therefore, in vitro activity should be considered as preliminary mechanistic evidence rather than proof of therapeutic efficacy.

2.2. In vivo evidence and the importance of infection stage

Animal studies have produced a more complex picture. Webster *et al.* reported that valproic acid and haloperidol modified behavioral changes in *T. gondii*-infected rats, suggesting that these drugs may affect infection-associated neurological outcomes in vivo (2006). However, other mouse studies failed to demonstrate clear protection against acute or chronic infection after treatment with antipsychotics or mood stabilizers. Goodwin *et al.* reported that valproic acid did not prevent toxoplasmosis in mice or reduce tissue cyst burden under the tested conditions (Goodwin *et al.*, 2008). Similarly, studies by Saraei *et al.* reported limited or absent protective effects for selected psychotropic drugs in mouse models of acute or chronic toxoplasmosis (2015, 2016).

These negative findings are important and should not be treated as methodological failure alone. They may indicate real pharmacological limitations of these drugs against established infection. At the same time, treatment timing is a critical factor in chronic toxoplasmosis. Bradyzoite replication and cyst maturation are dynamic during early

chronic infection and become less active as cysts mature (Ferguson & Hutchison, 1987; Watts *et al.*, 2015). It has also been reported that BAG1 transcript levels differ between earlier and later infection stages, supporting the view that treatment initiated after cyst establishment may have reduced capacity to affect cyst-associated parasite activity (Babaie *et al.*, 2017). Therefore, differences in the timing of drug administration may partly explain why some studies failed to detect effects on chronic infection.

A more recent in vivo study reported that valproic acid, haloperidol, and risperidone reduced molecular indicators of parasite and cyst burden in chronically infected mice. Enshaeieh *et al.* treated mice infected with the Tehran strain of *T. gondii* and quantified REP-529 copy number and BAG1 expression in brain samples using qPCR. The three drugs significantly reduced both markers, and the observed effects were comparable to cotrimoxazole under the tested experimental conditions (Enshaeieh *et al.*, 2021). This study is relevant because it used molecular endpoints rather than relying only on direct microscopic cyst counting. However, the interpretation should remain model-specific. The findings depend on the mouse strain, parasite strain, dose, route of administration, treatment window, and selected molecular markers. They support possible in vivo activity, but they do not establish general therapeutic efficacy. More recent in vivo work has provided additional support for the anti-Toxoplasma activity of selected psychotropic drugs. Enshaeieh *et al.* (2025) reported that risperidone treatment in chronically infected NMRI mice significantly inhibited chronic infection, decreasing BAG1, SAG1, and REP529 copy numbers, and reduced brain TNF- α expression and histopathological lesions to levels comparable to cotrimoxazole. These findings, however, remain limited to a small number of experimental models and require independent replication.

A notable limitation of the current evidence base is its reliance on a small number of experimental studies, particularly a limited set of in vivo investigations. While these studies provide important preliminary insights into potential anti-Toxoplasma gondii effects of psychotropic agents, the overall evidence remains insufficient to support broad generalization. The predominance of findings derived from a single or limited number of in vivo models constrains interpretability and increases susceptibility to model-specific bias. Therefore, independent replication across diverse experimental systems is essential to validate the robustness and translational relevance of the proposed mechanisms.

2.3. Clinical and serological observations

Clinical evidence remains limited and mostly indirect. Fond *et al.* reported that patients with schizophrenia or bipolar disorder who were seropositive for *T. gondii* and received drugs classified as having in vitro anti-Toxoplasma activity showed better clinical outcomes than patients receiving drugs without such activity (Fond *et al.*, 2015).

Leweke *et al.* also reported higher anti-Toxoplasma IgG levels in serum and cerebrospinal fluid of untreated patients with recent-onset schizophrenia, followed by a reduction after antipsychotic treatment (2004). These

findings are relevant because they connect psychotropic treatment, infection-associated markers, and psychiatric outcomes.

Recent clinical investigations have continued to explore the relationship between *T. gondii* seropositivity, antipsychotic treatment, and psychiatric outcomes. A 2025 cohort study in patients with severe mental illness found that *T. gondii* IgG seropositivity was associated with elevated cortisol levels and altered psychotic symptom scores, with antipsychotic treatment status as a relevant covariate (Andreou *et al.*, 2025). These observations remain indirect, but they reinforce the need for infection-specific endpoints in future clinical studies.

Nevertheless, these clinical observations should be interpreted cautiously. Improved psychiatric outcomes do not necessarily indicate parasite suppression, and changes in antibody levels do not directly demonstrate reduction of cerebral cyst burden.

In addition, clinical studies in psychiatric populations are affected by confounding factors such as disease severity, medication history, immune status, exposure background, and differences in diagnostic criteria. Therefore, available clinical data are better viewed as hypothesis-generating evidence. They may justify further investigation, but they cannot confirm that antipsychotics or mood stabilizers act as effective anti-Toxoplasma therapies in humans.

2.4. Sources of inconsistency across experimental models

The divergence among available studies appears to arise from several sources. First, parasite stage is a major

determinant of drug response. Drugs that affect tachyzoite invasion or replication in vitro may not affect established bradyzoite cysts in the brain. Second, treatment timing strongly influences the probability of detecting an effect on cyst formation or cyst-associated activity. Interventions applied after chronic infection is established may show weaker effects than interventions applied during the transition from acute to chronic infection. Third, outcome measurement differs across studies.

Cyst counting, survival analysis, behavioral testing, REP-529 quantification, BAG1 expression, TNF- α transcription, and histopathological scoring do not measure the same biological process. Fourth, drug concentration and exposure differ markedly between cell culture, animal models, and clinical treatment. These differences explain why the field contains both supportive and negative findings.

The available evidence does not justify a broad claim that antipsychotics and mood stabilizers are established anti-Toxoplasma drugs. It does, however, support a more restricted conclusion. Selected psychotropic drugs, particularly valproic acid, haloperidol, and risperidone, may affect parasite-associated and host inflammatory endpoints under defined experimental conditions. Their value should therefore be discussed as conditional, mechanism-dependent, and model-specific. A reliable interpretation requires integrated assessment of parasite burden, cyst-associated molecular markers, inflammatory mediators, and tissue-level pathology rather than reliance on a single endpoint. The comparative structure and interpretive weight of the available evidence are summarized in Figure 2.

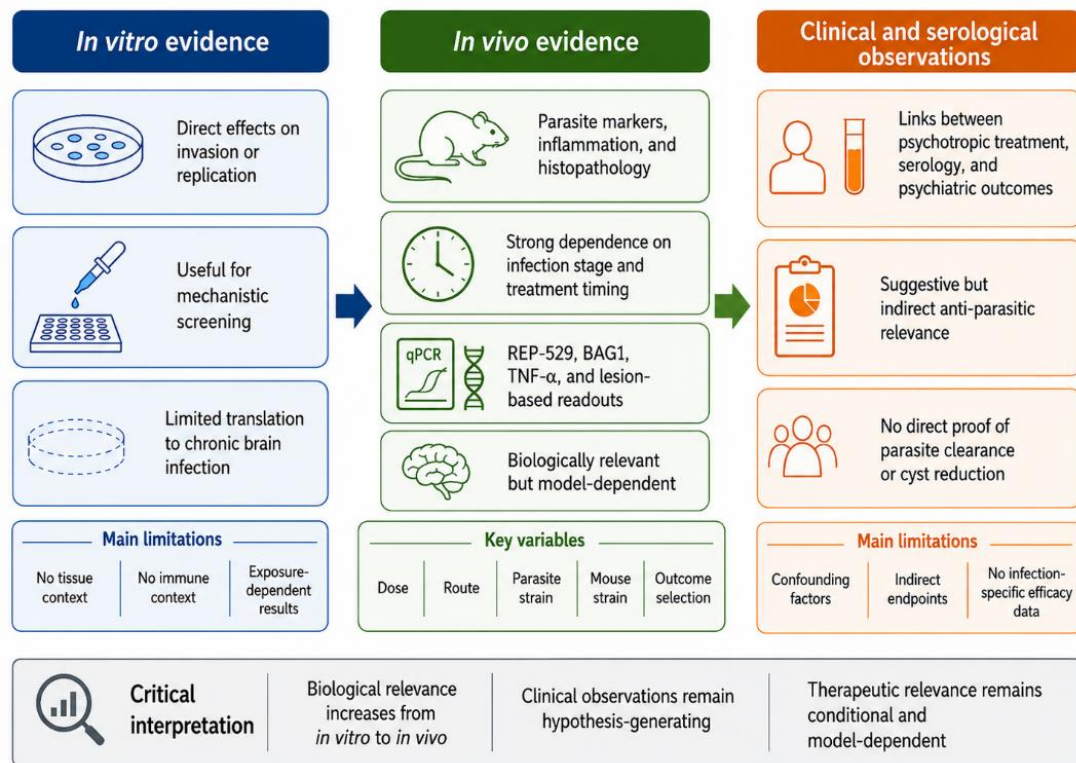


Figure 2. Comparative evidence landscape for psychotropic drugs across in vitro, in vivo, and clinical or serological observations in chronic *Toxoplasma gondii* infection, highlighting the main strengths, limitations, and model-dependent nature of the available evidence.

3. Mechanistic Links between Psychotropic Drugs and Chronic Toxoplasmosis

The possible effects of psychotropic drugs on chronic toxoplasmosis are unlikely to arise from a single pharmacological pathway. These drugs were not developed as antiparasitic agents, and their reported activity against *T. gondii* should be interpreted through overlapping effects on parasite biology, infected host cells, and inflammatory responses in the brain. This distinction is important because reduced parasite-associated markers, lower cytokine expression, and improved histopathology are related outcomes, but they do not necessarily reflect the same biological mechanism. Interpretation of the proposed mechanisms should be made with caution because systematic dose-response evidence remains limited. The available studies vary substantially in experimental design, dosing strategies, exposure duration, and biological endpoints, preventing robust comparison of pharmacodynamic effects across models. Consequently, it is not yet established whether modulation of host inflammatory or signaling pathways occurs within the same concentration range required for direct anti-Toxoplasma gondii activity. Addressing this gap through well-designed dose-response studies will be essential for distinguishing mechanistic associations from clinically relevant antiparasitic effects and for improving the translational value of future investigations.

For clarity, mechanistic findings in this review are categorized based on the strength of supporting evidence. Mechanisms that have been directly demonstrated in experimental Toxoplasma gondii models are described as evidence-based findings, whereas pathways inferred from related biological systems or indirect experimental observations are explicitly indicated as hypothetical or putative. This distinction is intended to ensure appropriate interpretation of the available evidence and to avoid overextension of conclusions beyond the current experimental data.

3.1. Parasite-stage biology and cyst persistence

The transition from tachyzoites to bradyzoites is central to chronic toxoplasmosis. Tachyzoites mediate acute dissemination, whereas bradyzoites persist within tissue cysts and support long-term infection in neural and muscular tissues (Lyons *et al.*, 2002; Sullivan Jr *et al.*, 2009). Therefore, the evaluation of psychotropic drugs against *T. gondii* should not be based only on tachyzoite inhibition in cell culture. Chronic infection requires endpoints that reflect total parasite burden, cyst-associated persistence, and stage-specific activity. Molecular markers such as REP-529 and BAG1 are useful in this context, but their interpretation depends on parallel assessment of inflammation and tissue pathology (Berizi *et al.*, 2021; Homan *et al.*, 2000; Lyons *et al.*, 2002).

It is important to interpret changes in REP-529, BAG1, TNF- α expression, and histopathological outcomes with appropriate caution. These parameters should be considered surrogate markers of parasite burden and host inflammatory response rather than direct evidence of parasite clearance or therapeutic efficacy. Accordingly, reductions in these markers reflect modulation of host–

parasite interactions and disease-associated pathology, but do not necessarily indicate complete eradication of Toxoplasma gondii or definitive clinical benefit.

From a translational perspective, interpretation of experimental anti-Toxoplasma gondii effects must consider pharmacokinetic and pharmacodynamic constraints. Clinically achievable plasma and brain concentrations, blood–brain barrier permeability, protein binding, and metabolic clearance all influence whether experimentally effective doses can be replicated in humans. In several cases, concentrations required to modulate host signaling pathways or parasite viability in experimental models may exceed those safely attainable in clinical practice. Furthermore, dose–response relationships remain insufficiently characterized across studies, limiting direct extrapolation from preclinical findings. Therefore, safety profiles and maximum tolerated doses must be integrated into the evaluation of repurposing potential to avoid overestimation of clinical efficacy based solely on experimental data.

3.2. Calcium-dependent invasion, replication, and egress

Calcium signaling provides a biologically plausible link between psychotropic drugs and *T. gondii* biology. Calcium flux contributes to gliding motility, host-cell invasion, intracellular replication, and egress from infected cells (Lovett & Sibley, 2003; Pace *et al.*, 2014; Triana *et al.*, 2018). Genomic and functional studies also support the presence of calcium-regulated systems in apicomplexan parasites, indicating that calcium-dependent processes are important for parasite survival and virulence-associated traits (Nagamune & Sibley, 2006; Prole & Taylor, 2011).

Several psychotropic drugs can influence calcium-related pathways. Haloperidol has been reported to block T-type and L-type calcium channels and interact with calmodulin-related mechanisms (Enyeart *et al.*, 1992; Ito *et al.*, 1996; Ogata *et al.*, 1989; Tarabová *et al.*, 2009). Trifluoperazine, a calmodulin antagonist, was shown to interfere with tachyzoite invasion, further supporting the relevance of calcium and calmodulin in parasite entry (Pezzella *et al.*, 1997). Valproic acid and risperidone may also influence ion fluxes or intracellular signaling, although direct evidence linking these effects to parasite control in chronic brain infection remains incomplete (Fond *et al.*, 2014; Johannessen, 2000; Perucca, 2002; Wu, Jan *et al.*, 2000).

3.3. Valproic acid, epigenetic regulation, and stress-related pathways

Valproic acid is mechanistically distinct from antipsychotic drugs because it combines mood-stabilizing activity with effects on sodium and calcium channels, GABAergic signaling, and histone deacetylase inhibition (Johannessen, 2000; Monti *et al.*, 2009; Perucca, 2002). The histone deacetylase inhibitory activity is relevant because chromatin regulation contributes to parasite differentiation, stress adaptation, and stage conversion (Saksouk *et al.*, 2005; Sullivan Jr. & Hakimi, 2006). Histone deacetylase inhibitors can also induce oxidative stress, DNA damage, and altered cell-cycle progression in

eukaryotic systems, processes that may be relevant to *T. gondii* because of its atypical cell-cycle organization and sensitivity to oxidative damage (Cornago *et al.*, 2014; Francia & Stripen, 2014; Gubbels *et al.*, 2008; Murray & Cohn, 1979). However, reduced parasite-associated markers after valproic acid treatment do not prove that epigenetic regulation is the primary antiparasitic mechanism. Direct parasite-stage assays and host-cell-specific analyses are still required.

3.4. Host-directed regulation of neuroinflammation

Chronic cerebral toxoplasmosis is shaped by parasite persistence and sustained inflammatory responses. Infection can activate microglia and astrocytes and increase inflammatory mediators such as TNF- α , IL-1 β , and IL-6, which may contribute to neuronal dysfunction and tissue injury (Carruthers & Suzuki, 2007; Hwang *et al.*, 2018; Müller *et al.*, 2015). Psychotropic drugs may therefore improve infection-associated brain pathology through parasite-related effects, host-directed immunomodulation, or both.

Haloperidol and risperidone have been reported to suppress microglial activation and reduce inflammatory mediator release in experimental models, partly through pathways related to intracellular calcium signaling, oxidative stress, and NF- κ B-associated responses (Kato *et al.*, 2011; MacDowell *et al.*, 2013; Mizoguchi *et al.*, 2014; Patel *et al.*, 2023). Valproic acid also shows anti-inflammatory and neuroprotective properties, including modulation of cytokine production and glial responses

(Chen *et al.*, 2014; Monti *et al.*, 2009; Suh *et al.*, 2010; Ximenes *et al.*, 2012). These host-directed effects provide a plausible explanation for reduced neuroinflammatory markers in treated infection, but they should not be interpreted as equivalent to parasite elimination.

3.5. Dopamine-independent convergence

Although haloperidol and risperidone are primarily discussed through dopaminergic mechanisms, the possible anti-Toxoplasma and anti-inflammatory effects of psychotropic drugs may not depend directly on dopamine receptor blockade. Valproic acid is not a dopamine D2 receptor antagonist, while haloperidol and risperidone differ in D2 receptor affinity, yet overlapping reductions in parasite-associated and inflammatory endpoints have been reported under specific experimental conditions (Enshaeieh *et al.*, 2021).

Moreover, dopamine receptor antagonism did not prevent dopamine-stimulated tachyzoite proliferation in human fibroblast culture, suggesting that canonical dopamine signaling cannot fully explain the observed effects (Strobl *et al.*, 2012). A more coherent interpretation is that these drugs may converge on shared downstream processes, including calcium mobilization, cellular stress responses, microglial regulation, and inflammatory signaling. The mechanistic value of these pathways remains conditional and model-dependent. The proposed mechanistic links between the selected psychotropic drugs and downstream molecular or inflammatory outcomes are summarized in Figure 3.

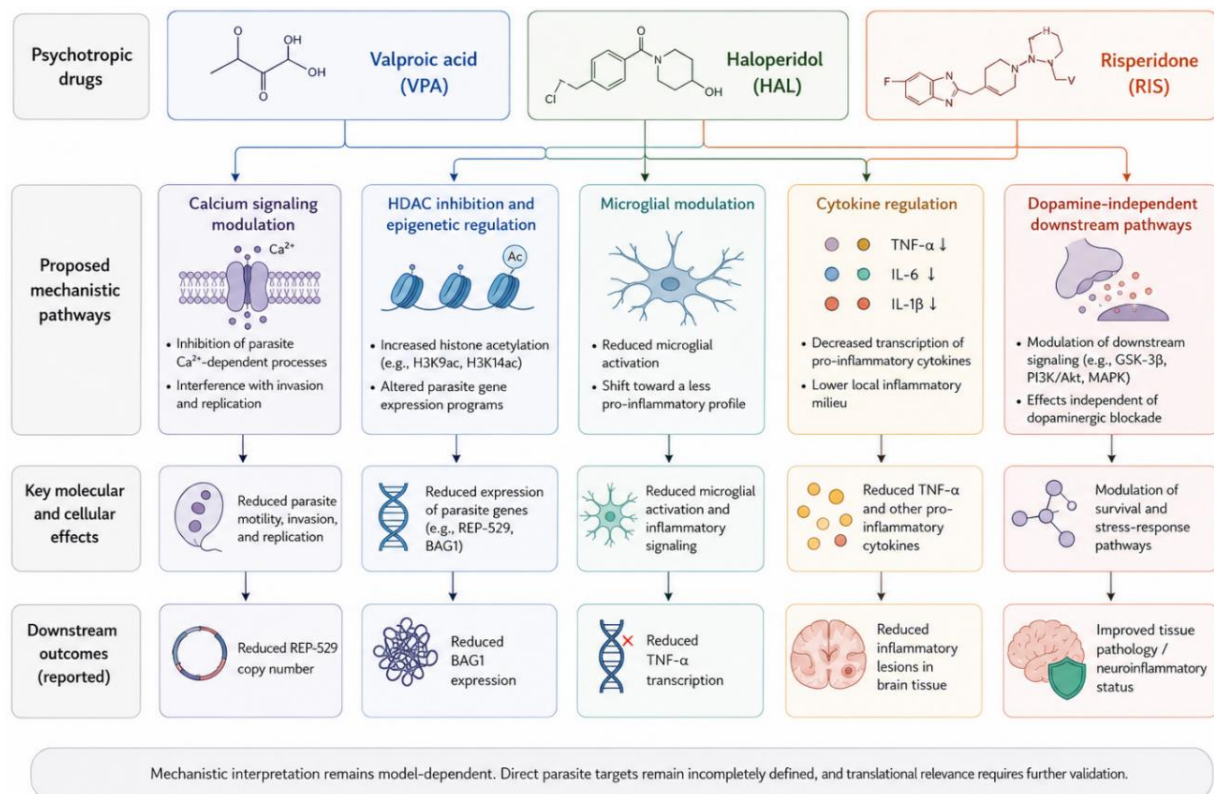


Figure 3. Proposed mechanistic links between valproic acid, haloperidol, and risperidone and their reported downstream effects during chronic *Toxoplasma gondii* infection. The scheme summarizes calcium-dependent processes, HDAC-related regulation, microglial modulation, cytokine regulation, and dopamine-independent pathways as model-dependent mechanisms connected to molecular and tissue-level outcomes (Enshaeieh *et al.*, 2021; Kato *et al.*, 2011; Lovett & Sibley, 2003; Mizoguchi *et al.*, 2014; Monti *et al.*, 2009; Pace *et al.*, 2014; Patel *et al.*, 2023; Pezzella *et al.*, 1997; Strobl *et al.*, 2012; Sullivan Jr & Hakimi, 2006).

4. Integrated Molecular and Neuroinflammatory Outcomes in Treated Infection

Molecular and inflammatory endpoints provide complementary information for evaluating psychotropic drugs in chronic *T. gondii* infection. REP-529 and BAG1 provide information on parasite-associated burden and cyst-stage activity, whereas TNF- α reflects infection-associated inflammatory activation in the brain. These markers should be interpreted together, because none of them alone defines drug mechanism, parasite viability, or clinical efficacy.

4.1. REP-529 and BAG1 as parasite-associated molecular readouts

REP-529 is a repetitive DNA element widely used for sensitive detection and quantification of *T. gondii*, while BAG1 is commonly used as a bradyzoite-associated marker linked to cyst-stage persistence (Berizi *et al.*, 2021; Homan *et al.*, 2000; Lyons *et al.*, 2002). These markers are particularly relevant in chronic infection because cyst number, intracystic parasite burden, and transcriptional activity may not be fully captured by direct microscopic counting.

Enshaeieh *et al.* reported that treatment with valproic acid, haloperidol, and risperidone significantly reduced REP-529 copy number and BAG1 expression in brain samples of chronically infected mice, with reductions comparable to cotrimoxazole under the same experimental design (2021). These results support a possible effect on parasite-associated molecular endpoints. However, lower REP-529 or BAG1 signals do not identify whether the effect reflects direct parasite killing, reduced bradyzoite burden, altered cyst-associated transcription, or changes in the infected tissue environment. Molecular markers should therefore be interpreted alongside inflammatory and histopathological findings.

4.2. TNF- α suppression as an inflammatory outcome

TNF- α is a major inflammatory mediator in the host response to *T. gondii* infection. In the central nervous system, chronic infection can activate microglia and astrocytes and increase pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6 (Carruthers & Suzuki, 2007; Hwang *et al.*, 2018; Müller *et al.*, 2015). These responses contribute to parasite restriction, but sustained activation may also promote neuronal dysfunction, gliosis, and tissue injury.

In chronically infected mice, valproic acid, haloperidol, and risperidone significantly reduced brain TNF- α transcript levels compared with infected untreated controls, and the reduction was comparable to cotrimoxazole under the tested conditions (Enshaeieh *et al.*, 2021). This result is consistent with the reported immunomodulatory properties of these drugs (Baumeister *et al.*, 2016; Kato *et al.*, 2011; MacDowell *et al.*, 2013; Patel *et al.*, 2023). However, TNF- α suppression does not determine whether the primary effect is antiparasitic, anti-inflammatory, or combined. This distinction is important because inflammatory signaling can contribute to both parasite control and tissue injury.

4.3. Interpreting concordance between parasite and inflammatory endpoints

The combined reduction of REP-529, BAG1, and TNF- α suggests a possible relationship between parasite-associated burden and neuroinflammatory response in treated infection. A lower parasite burden may reduce antigenic stimulation and thereby attenuate inflammatory signaling. Conversely, direct immunomodulatory effects of psychotropic drugs may reduce tissue inflammation without complete parasite elimination. Both interpretations are biologically plausible and may occur together.

The observation that valproic acid, haloperidol, and risperidone reduced molecular and inflammatory endpoints in the same experimental model supports a conditional model in which these drugs may affect chronic infection-associated pathology through both parasite-related and host-directed effects (Enshaeieh *et al.*, 2021). However, this concordance does not identify a single shared target or prove clinical anti-Toxoplasma efficacy. Stronger mechanistic conclusions will require parasite viability assays, stage-conversion analysis, parasite-specific transcriptional profiling, cytokine-modulation experiments, and dose-response studies. Until such evidence is available, reductions in REP-529, BAG1, and TNF- α should be viewed as coordinated molecular and inflammatory responses under defined experimental conditions.

5. Histopathological Evidence in the Infected Brain

Histopathological assessment provides tissue-level evidence for evaluating the biological relevance of molecular and inflammatory changes during chronic cerebral toxoplasmosis. In the infected brain, pathological alterations may include tissue cyst formation, perivascular inflammatory infiltration, glial nodules, meningitis, encephalitis, and disruption of normal tissue architecture. These changes are important because molecular reduction in parasite markers or cytokine transcripts does not necessarily indicate structural recovery. Therefore, histological findings should be used as a complementary level of evidence, linking parasite-associated burden and inflammatory response to the actual condition of brain tissue.

5.1. Cyst establishment and tissue-level pathology

Tissue cysts are a defining feature of chronic *T. gondii* infection in the central nervous system. In untreated infection, cysts may persist in different brain regions and are often associated with local inflammatory responses and tissue injury (Hermes *et al.*, 2008; Li *et al.*, 2019). Histological examination can therefore provide direct information on cyst establishment and the severity of infection-associated lesions. However, cyst visualization alone has limitations. The number of visible cysts may not fully represent intracystic parasite burden, parasite viability, or bradyzoite transcriptional activity. For this reason, histopathological assessment is most informative when interpreted together with molecular markers such as

REP-529 and BAG1. Enshaeieh *et al.* reported that brain sections from infected untreated mice and solvent-treated mice showed clear pathological features, including cyst presence and inflammatory lesions (2021). In contrast, mice treated with valproic acid, haloperidol, risperidone, or cotrimoxazole showed fewer visible cysts and milder pathological changes under the tested conditions (Enshaeieh *et al.*, 2021). These findings support the view that the tested psychotropic drugs may reduce tissue-level manifestations of chronic infection. Nevertheless, the result should be interpreted within the limits of the experimental model, including mouse strain, parasite strain, treatment timing, dose, route of administration, and histological sampling.

5.2. Perivascular infiltration, glial nodules, and encephalitis

Inflammatory lesions are a major component of brain pathology during chronic toxoplasmosis. Perivascular infiltration reflects recruitment of immune cells around blood vessels, while glial nodules indicate local activation and accumulation of glial cells in response to infection-associated injury. Encephalitis represents a more severe inflammatory condition involving brain parenchyma and can contribute to neuronal dysfunction and tissue disruption (Hermes *et al.*, 2008; Li *et al.*, 2019). These lesions are relevant to the neuropsychiatric dimension of chronic toxoplasmosis because persistent neuroinflammation may affect neural circuits, neurotransmitter regulation, and brain tissue integrity.

In the study by Enshaeieh *et al.*, infected untreated mice and solvent-treated controls showed heavy perivascular lymphocyte infiltration, glial nodules, meningitis, encephalitis, and cyst establishment (2021). In contrast, treatment with valproic acid, haloperidol, or risperidone was associated with fewer histopathological lesions, similar to the pattern observed in cotrimoxazole-treated mice (Enshaeieh *et al.*, 2021). This observation is consistent with the reported reduction in TNF- α transcription and parasite-associated molecular markers in the same experimental model. The histological data therefore strengthen the interpretation that these drugs may affect both infection-associated inflammation and tissue-level pathology. The improvement in histopathological appearance should not be interpreted as proof of complete parasite elimination. Reduced inflammatory infiltration may result from lower parasite burden, direct anti-inflammatory action of the drugs, or both. This distinction is particularly important for psychotropic drugs because they can modulate immune and glial responses independently of any direct effect on the parasite (Baumeister *et al.*, 2016; Kato *et al.*, 2011; MacDowell *et al.*, 2013; Mizoguchi *et al.*, 2014; Patel *et al.*, 2023). Therefore, histological improvement should be discussed as evidence of reduced tissue pathology rather than as definitive evidence of sterilizing antiparasitic activity.

5.3. Concordance between molecular and histological outcomes

A key strength of the available in vivo evidence is the concordance between molecular, inflammatory, and

histopathological outcomes. In the same experimental framework, treatment with valproic acid, haloperidol, and risperidone reduced REP-529 copy number, BAG1 expression, TNF- α transcription, and visible brain lesions (Enshaeieh *et al.*, 2021). This pattern suggests that parasite-associated burden, neuroinflammatory activity, and tissue-level pathology may be linked. However, concordance does not prove sequence or causality. It remains unclear whether reduced parasite burden led to lower inflammation, whether anti-inflammatory effects improved tissue pathology independently of parasite reduction, or whether both processes occurred together.

This distinction has direct translational relevance. A drug that reduces inflammatory lesions without eliminating cysts may still improve tissue pathology, but its long-term antiparasitic value would remain uncertain. Conversely, a drug that reduces parasite-associated markers but fails to improve tissue inflammation may have limited functional relevance for brain pathology. Therefore, future studies should combine histological scoring with molecular parasite quantification, cytokine profiling, parasite viability assays, and behavioral or neurological outcomes. Such integrated designs are needed to determine whether histopathological improvement reflects true parasite control, host-directed neuroprotection, or a combination of both.

Overall, the histopathological findings support the possibility that selected psychotropic drugs may attenuate brain pathology during chronic *T. gondii* infection under defined experimental conditions. The evidence is strongest when histological improvement is interpreted alongside reductions in REP-529, BAG1, and TNF- α . However, the current data remain insufficient to define the exact mechanism of tissue protection or to infer clinical efficacy. Histopathology should therefore be considered a critical supporting endpoint, not a standalone proof of therapeutic activity.

6. Translational Barriers and Safety Considerations

The available evidence suggests that selected psychotropic drugs may influence parasite-associated and inflammatory endpoints in experimental toxoplasmosis. However, translation of these findings to clinical use requires careful consideration. A reduction in parasite markers or inflammatory lesions in mice does not directly establish therapeutic value in humans. Differences in drug exposure, dose tolerance, treatment timing, infection stage, host immune status, and clinical outcome measurement may strongly affect the relevance of experimental findings. Therefore, the possible repositioning of antipsychotics and mood stabilizers against *T. gondii* should be discussed within a pharmacological and translational framework rather than only as a biological observation.

6.1. Dose, route of administration, and pharmacological relevance

Dose and route of administration are major limitations in interpreting animal studies. Experimental doses used in mice may not correspond directly to clinically acceptable exposure in humans, particularly for drugs with central

nervous system activity and narrow safety margins. In the study by Enshaeieh *et al.*, valproic acid was administered at a dose comparable to doses used in other psychiatric animal studies, whereas haloperidol and risperidone were administered at higher experimental doses relative to common psychiatric use in mice (2021). Although no marked weight loss or evident behavioral toxicity was reported under those conditions, the absence of overt toxicity in a short-term mouse experiment does not establish long-term safety or clinical feasibility.

This issue is particularly important for haloperidol and risperidone because dose-dependent neurological, metabolic, and endocrine effects may limit their application outside psychiatric indications. Valproic acid also has well-recognized safety concerns, including hepatic toxicity, teratogenicity, and drug interaction risks, which are relevant when considering any new infectious disease application (Perucca, 2002). Therefore, future studies should not only report efficacy endpoints, but should also include pharmacokinetic analysis, brain drug concentration, dose-response relationships, and safety monitoring. Without these data, it remains difficult to determine whether the observed anti-Toxoplasma effects occur at pharmacologically relevant and clinically tolerable exposures. A 2024 study by Sheikhshoae *et al.* provides a cautionary note regarding valproic acid in the context of *T. gondii* infection. In a mouse model of autism, valproic acid administration to *Toxoplasma*-infected mothers exacerbated cognitive impairments in their offspring, suggesting that the interaction between valproic acid and *T. gondii* may have adverse neurodevelopmental consequences under certain conditions (Sheikhshoae *et al.*, 2024). This finding underscores the importance of carefully evaluating the safety profile of psychotropic drugs in the context of toxoplasmosis, particularly in vulnerable populations.

Pharmacokinetic considerations represent a critical factor in interpreting the translational relevance of experimental findings. Clinically achievable plasma and central nervous system concentrations of psychotropic agents are influenced by absorption, distribution, protein binding, metabolic pathways, and blood–brain barrier permeability. Importantly, interspecies differences in drug metabolism and dosing regimens can result in exposure levels in experimental models that are not directly comparable to human therapeutic conditions. In several cases, concentrations required to achieve anti-Toxoplasma *gondii* effects in vitro or in vivo may exceed those safely attainable in clinical settings. Therefore, pharmacokinetic constraints should be considered alongside pharmacodynamic effects to avoid overestimation of clinical repurposing potential.

Pharmacokinetic and pharmacodynamic considerations are critical for evaluating the translational potential of psychotropic agents in *Toxoplasma gondii* infection. The central nervous system exposure of these compounds is determined by multiple factors, including absorption, systemic distribution, plasma protein binding, metabolic stability, and blood–brain barrier permeability. Importantly, effective concentrations observed in in vitro and in vivo experimental models may not correspond to clinically achievable plasma or brain levels under standard therapeutic dosing. This discrepancy underscores a

fundamental limitation in extrapolating antiparasitic effects from experimental systems to human clinical settings. Therefore, integration of PK/PD parameters is essential to accurately contextualize mechanistic and antiparasitic findings within a clinically relevant framework.

6.2. Treatment timing and chronic cyst establishment

Treatment timing is another key barrier to translation. Chronic toxoplasmosis is not a static condition. Bradyzoite replication, cyst maturation, and cyst-associated transcriptional activity change over time after infection (Ferguson & Hutchison, 1987; Watts *et al.*, 2015). Once cysts are established, pharmacological intervention may have reduced ability to affect parasite persistence, particularly if the drug mainly acts during active replication, stage conversion, or early cyst development. This may explain why some studies failed to detect meaningful reductions in cyst burden when treatment was initiated late during infection (Goodwin *et al.*, 2008; Saraei *et al.*, 2016).

Differences in treatment timing should therefore be considered when comparing positive and negative studies. Earlier treatment during the transition from acute to chronic infection may detect effects on cyst establishment or bradyzoite activity, whereas late treatment may test the more difficult question of whether established cysts can be reduced. These two questions are not equivalent. A drug that limits cyst development may not necessarily eliminate mature cysts. For this reason, future studies should define the infection stage at treatment initiation and distinguish prevention of cyst establishment from reduction of already established chronic infection.

The possibility of synergistic or additive effects among psychotropic agents in the context of *Toxoplasma gondii* infection remains largely theoretical. Several of the reviewed compounds share overlapping immunomodulatory and neurobiological mechanisms, including modulation of pro-inflammatory cytokines, microglial activation, and host-cell signaling pathways, which may suggest potential for additive biological effects. However, the current evidence base does not include systematic combination studies evaluating antiparasitic efficacy. From a clinical perspective, many patients with psychiatric disorders already receive these medications in combination, yet there is no evidence to support modification of therapeutic regimens for the purpose of influencing *Toxoplasma gondii* infection. Therefore, any proposed synergistic antiparasitic effect remains hypothetical and should be validated through controlled experimental and clinical studies before any translational conclusions can be drawn.

6.3. Distinguishing parasite suppression from clinical benefit

Another translational challenge is the difference between parasite suppression and clinical benefit. Molecular markers such as REP-529 and BAG1 provide important information on parasite-associated burden and cyst-stage activity, but they do not directly measure neurological function, psychiatric symptoms, or long-term

relapse risk (Berizi *et al.*, 2021; Homan *et al.*, 2000). Similarly, reduced TNF- α expression and improved histopathological appearance suggest lower inflammatory activity and tissue injury, but they do not necessarily predict clinical improvement in humans (Enshaeieh *et al.*, 2021).

This distinction is especially important because the proposed clinical context involves neuropsychiatric disorders, where outcomes are influenced by multiple biological and social factors. The association between *T. gondii* seropositivity and schizophrenia or bipolar disorder does not prove that parasite suppression will improve psychiatric symptoms (Burgdorf *et al.*, 2019; Torrey *et al.*, 2012; Tyebji *et al.*, 2019). Clinical studies suggesting better outcomes in seropositive patients receiving drugs with reported anti-Toxoplasma activity are relevant, but they remain indirect and cannot separate antiparasitic effects from psychiatric drug effects, immune modulation, or treatment selection bias (Fond *et al.*, 2015; Leweke *et al.*, 2004). Therefore, future clinical interpretation requires infection-specific endpoints, stratification by serological status, and direct assessment of parasitic and inflammatory markers.

6.4. Safety, toxicity, and uncertainty in human application

Safety considerations are central to any proposal for drug repurposing. Antipsychotics and mood stabilizers are pharmacologically active central nervous system drugs, and their use may be associated with adverse effects that limit long-term application. Haloperidol can produce extrapyramidal symptoms and other neurological adverse effects. Risperidone may be associated with metabolic, endocrine, and neurological complications. Valproic acid can cause hepatic, hematological, metabolic, and reproductive risks, and its teratogenic potential is a major concern (Perucca, 2002). These risks are particularly relevant in toxoplasmosis, where vulnerable populations may include pregnant women, immunocompromised patients, and individuals requiring prolonged treatment.

At the current stage, the evidence does not support replacing standard anti-Toxoplasma therapies with antipsychotics or mood stabilizers. A more defensible interpretation is that selected psychotropic drugs may serve as mechanistic leads or adjunctive candidates for further investigation. Any future translational strategy should determine whether the potential benefit is due to direct parasite suppression, host-directed immunomodulation, or combined effects. It should also define whether these drugs are useful only in selected patient groups, such as seropositive individuals already receiving psychiatric treatment, rather than in toxoplasmosis patients more broadly.

Overall, translational uncertainty remains substantial. The strongest current support comes from integrated animal data showing reductions in parasite-associated molecular markers, TNF- α expression, and histopathological lesions under defined experimental conditions (Enshaeieh *et al.*, 2021). However, clinical application requires evidence of efficacy at safe and achievable drug exposures, direct relevance to established chronic infection, and measurable benefit beyond

psychiatric symptom control. Until such evidence is available, antipsychotics and mood stabilizers should be considered investigational adjunctive candidates rather than established anti-Toxoplasma therapies.

7. Future Directions

Future studies should move beyond the simple classification of psychotropic drugs as active or inactive against *T. gondii*. The available evidence indicates that the outcome depends on parasite stage, treatment timing, drug exposure, and the endpoint used to define efficacy. Therefore, future experimental designs should distinguish direct parasite suppression from host-directed anti-inflammatory effects. This distinction is essential because reductions in REP-529, BAG1, TNF- α , and histopathological lesions may occur through related but not identical biological processes. Future studies should also consider the potential for drug-parasite interactions that may produce unexpected outcomes, as illustrated by the recent finding that valproic acid can exacerbate cognitive impairments in *T. gondii*-infected animal models under specific experimental conditions (Sheikhshoae *et al.*, 2024). Such findings highlight the need for comprehensive safety assessments alongside efficacy evaluations.

A first priority is to define stage-specific drug effects. Studies should separately evaluate tachyzoite replication, tachyzoite-to-bradyzoite conversion, cyst maturation, and established cyst persistence. This would clarify whether drugs such as valproic acid, haloperidol, and risperidone mainly prevent cyst establishment, reduce bradyzoite-associated activity, or affect mature tissue cysts. Molecular markers such as REP-529 and BAG1 should be combined with cyst viability assays, parasite-specific transcriptional profiling, and histological scoring to avoid reliance on a single endpoint (Berizi *et al.*, 2021; Enshaeieh *et al.*, 2021; Homan *et al.*, 2000).

A second priority is mechanistic validation. Calcium signaling, histone deacetylase inhibition, oxidative stress, and microglial regulation are plausible pathways, but their relative contribution to parasite control remains unresolved. Future studies should use dose-response experiments, parasite-stage assays, selective pathway inhibitors, and host-cell models to determine whether the observed effects result from direct action on the parasite, altered infected-cell physiology, or suppression of damaging neuroinflammation (Lovett & Sibley, 2003; Monti *et al.*, 2009; Pace *et al.*, 2014; Patel *et al.*, 2023). Such studies would also clarify whether dopamine receptor signaling is central to the observed effects or whether shared downstream pathways provide a more coherent explanation.

A third priority is pharmacological translation. Animal studies should include pharmacokinetic analysis, brain drug concentration, safety monitoring, and clinically relevant exposure ranges. This is particularly important for antipsychotics and mood stabilizers because their central nervous system activity and adverse effect profiles may limit repurposing outside established psychiatric indications. Future work should also compare monotherapy with adjunctive use alongside standard anti-Toxoplasma regimens, because adjunctive application is

more realistic than replacement of established chemotherapy at the current stage.

Clinical studies, if pursued, should be carefully stratified. Serological status, psychiatric diagnosis, medication history, immune condition, and infection-related markers should be defined before treatment effects are interpreted. In patients with schizophrenia or bipolar disorder, improvement in psychiatric symptoms cannot be assumed to reflect parasite suppression. Therefore, clinical studies should include infection-specific and inflammation-specific endpoints, rather than relying only on psychiatric outcome measures. This approach would help determine whether psychotropic drugs have genuine anti-Toxoplasma relevance, host-directed neuroprotective value, or only indirect clinical associations.

Future research should adopt more standardized and experimentally rigorous approaches to evaluate the anti-Toxoplasma gondii potential of psychotropic agents. Recommended strategies include quantitative assessment of parasite burden using stage-specific molecular markers such as REP-529 (parasite load) and BAG1 (bradyzoite differentiation), combined with validated histopathological scoring systems for brain and peripheral tissue cyst quantification. Longitudinal experimental designs are essential to evaluate treatment effects on chronic infection dynamics rather than acute responses alone. In addition, studies should incorporate stage-specific analyses to differentiate effects on tachyzoite replication versus bradyzoite persistence. Finally, integration of pharmacokinetic–pharmacodynamic modeling is necessary to ensure that observed antiparasitic effects occur within clinically relevant exposure ranges, thereby improving translational validity.

8. Conclusion

The available evidence indicates that selected psychotropic drugs may influence chronic Toxoplasma gondii infection through interconnected effects on parasite-associated burden, neuroinflammatory signaling, and tissue-level pathology. Valproic acid, haloperidol, and risperidone have received particular attention because experimental studies have linked them to reductions in REP-529 copy number, BAG1 expression, TNF- α transcription, and histopathological lesions in infected brain tissue (Enshaeieh *et al.*, 2021). These findings support the biological plausibility of psychotropic drugs as adjunctive candidates in chronic cerebral toxoplasmosis.

However, the evidence remains incomplete and model-dependent. In vitro studies have produced inconsistent results, animal studies differ in treatment timing and outcome measurement, and clinical observations remain indirect (Fond *et al.*, 2015; Fond *et al.*, 2014; Goodwin *et al.*, 2008; Goodwin *et al.*, 2011; Leweke *et al.*, 2004; Strobl *et al.*, 2007). Therefore, these drugs should not be considered established anti-Toxoplasma therapies at this stage. Their potential value lies in the mechanistic overlap between parasite-stage regulation, calcium-dependent processes, glial activation, cytokine modulation, and histopathological protection.

Future work should determine whether the observed effects reflect direct parasite suppression, host-directed neuroprotection, or combined activity. This requires stage-

specific infection models, pharmacologically relevant dosing, parasite viability assessment, inflammatory profiling, and clinically meaningful endpoints. Until such evidence is available, antipsychotics and mood stabilizers should be viewed as investigational adjunctive candidates rather than alternatives to standard anti-Toxoplasma chemotherapy.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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G.S. drafted the manuscript and critically revised the intellectual content. M.E. contributed to the literature search, the conception and design of the review, data synthesis, and preparation of figures. Both authors read and approved the final manuscript.

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