

REVIEW

New findings: Depression, suicide, and *Toxoplasma gondii* infection

Pao-Chu Hsu, PhD, FNP-C (Family Nurse Practitioner, Clinic Provider/Clinic Director/Clinic Manager),
Maureen Groer, PhD, FAAN (Professor), & Theresa Beckie, PhD (Professor)

College of Nursing, University of South Florida, Tampa, Florida

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Correspondence

Pao-Chu Hsu, PhD, ARNP, FNP-C, College of
Nursing, University of South Florida, 12901
Bruce B. Downs Blvd., MDC22, Tampa, FL
33612. E-mail: phsu@health.usf.edu,
PaoC.hsu@gmail.com

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Abstract

Purpose: This article provides an overview of the evidence of a potential pathophysiological relationship between depression, suicide, and the *Toxoplasma gondii* (*T. gondii*) infection. It discusses the role of inflammatory processes in depressive illness and the infection theory of psychiatric disease. It also provides guidelines for the screening, diagnosis, and treatment of depression for nurse practitioners (NPs).

Data source: A narrative review was conducted of the literature from PubMed, PsycINFO, and Google Scholar. References of identified articles were also reviewed.

Conclusions: Seropositivity of the obligate intracellular protozoan parasite, *T. gondii* is related to various mental health disorders including schizophrenia, suicide attempt, depression, and other neuropsychiatric diseases. Depressive symptoms have been linked to interferon- γ (IFN- γ) blocking *T. gondii* growth by inducing indoleamine-2,3-dioxygenase (IDO) activation and tryptophan depletion, which results in a decrease of serotonin production in the brain. Although exposure to *T. gondii* was considered unlikely to reactivate in immune-competent individuals, new findings report that this reactivation may be triggered by immune imbalance.

Implications for practice: NPs caring for patients with psychiatric illness need to understand the potential mechanisms associated with depression and the *T. gondii* infection in order to provide effective screening, treatment, and disease prevention.

Introduction

Depression is the most common affective disorder and it is the leading cause of the chronic illness burden globally (Henriquez, Brett, Alexander, Pratt, & Roberts, 2009; World Health Organization [WHO], 2013). Depression is a mood disturbance characterized by changes in mood, and loss of interest, pleasure, cognitive function, sleep, appetite, or energy level (Pratt & Brody, 2008). According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV, American Psychiatric Association, 2000) criteria, "depressive disorder is a period of at least two weeks of feeling sadness, hopelessness, and discouragement. The individual should also experience at least four additional symptoms including: changes in appetite or weight, sleep and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking,

concentrating or making decisions, or recurrent thoughts of death or suicidal ideation or suicide attempt" (p. 349). Suicide is the 10th leading cause of death in the United States and over half of all individuals who attempt suicide have a depressive illness (Centers for Disease Control and Prevention [CDC], 2013a; Okusaga & Postolache, 2012).

Inflammation-associated depression models have been postulated in many animal and human studies. The hypothesis of such a model is that immune-mediated cytokines alter serotonin and glutamate biosynthesis leading to depression or suicidal behavior (Mann, 2003; Muller & Schwarz, 2007). Inflammation may occur in infectious illnesses that have been associated with mood disorders. Cases of actual psychoses caused by microbial pathogens such as herpes viruses, cytomegalovirus, and *Toxoplasma gondii* (*T. gondii*) support an infectious theory of psychosis (Yolken & Torrey, 2008).

The incidence rate of *T. gondii* infection is approximately 22.5% in the United States and approximately 33% of the population worldwide (CDC, 2013a). *Toxoplasma gondii* is an obligate intracellular protozoan. Felines are the only definitive host of *T. gondii*, in that sexual reproduction occurs only in the feline intestinal tract. Most humans are infected by *T. gondii* through ingestion of undercooked meat or food contaminated with the parasite (Dabey & Johns, 2008; Kim & Weiss, 2008).

Toxoplasma gondii tachyzoites have a tendency to form tissue cysts in the brain. The possibility of *T. gondii* altering human behavior may vary with genetic susceptibility, timing of infection, and the ingestion stage of the parasite (Henriquez et al., 2009). A number of studies have found that *T. gondii* seropositivity is related to personality changes and various mental disorders including development of schizophrenia, suicidal tendencies, obsessive compulsive disorder, bipolar disorder, and depression (Arling et al., 2009; Hinze-Selch, Daubener, Erdage, & Wilms, 2010; Ling, Lester, Mortensen, Langenberg, & Postolache, 2011; Okusaga et al., 2011; Tedla et al., 2011; Torrey, Barko, Lun, & Yolken, 2007). Recently this relationship has also been reported for other neuropsychiatric diseases such as migraine headaches, epilepsy, Alzheimer's, and Parkinson's disease (Dalimi & Abdoli, 2012; Fekadu, Shibre, & Cleare, 2010; Hurley & Taber, 2012).

Depression is a common disorder that is associated with significant morbidity and mortality. The prevalence of depression is high in patients with medical illnesses such as the *T. gondii* infection. It is important for nurse practitioners (NPs) to screen for depressive symptoms or risk factors and diagnose using tools and laboratory tests to differentiate causes of depression related to medical illnesses. They may then follow practice guidelines to treat patients with depression or refer patients with suicidal ideation to mental health specialists.

Review of literature

Depression and suicidal behavior link to inflammatory processes

Depression is a complex mood disorder that is influenced by inflammation, genetics, and psychosocial environmental interactions. Immune system proinflammatory cytokine production and liver production of C-reactive protein (CRP) are commonly correlated with behavioral disturbances (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Raison & Miller, 2011). Recently it has been reported that individual genetic factors such as 5-hydroxytryptophan (5-HT) transporter gene

polymorphisms influence depression development and suicidal behavior (Kenna et al., 2012).

The immune system communicates with the brain in a bidirectional scheme. The immune system responds to inflammatory stimuli and activates neuroendocrine pathways to induce behavior changes such as sickness behavior (fatigue, decreased appetite, sleep disorder, altered cognition). The brain regulates immune response through the hypothalamic–pituitary–adrenal axis, and the sympathetic nervous system acts as the immune function modulation in the depression model (Capuron & Miller, 2011; Dantzer et al., 2008).

Macrophages, dendritic cells, and microglia in the brain produce cytokines and other proinflammatory mediators after recognizing pathogen-associated molecular patterns through binding with specialized receptors called Toll-like receptors (Chaplin, 2010; Matzinger, 2002; Okusaga & Postolache, 2012). The cytokine signals access the brain in three ways: (a) infiltration leakage or impairment of the blood–brain barrier (BBB), (b) indirect signaling through cytokine-specific carrier proteins that transfer cytokines across the BBB and bind to cerebral vascular endothelial cells' cytokine receptors, or (c) transmission of immune messages from peripheral to the brain through afferent nerve neural pathways (Raison & Miller, 2011; Schiepers, Wichers, & Maes, 2005).

Infectious pathogens can trigger systemic innate and adaptive immune responses. Cytokines are secreted by various stimulated immune cells in response to different types of infectious pathogens. The innate immune response to infectious pathogens results in the production of proinflammatory cytokines that include interleukin (IL)-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α). The later response is adaptive immunity, which has two types. Type-1 immunity promotes cellular cytotoxicity to secretion type-1 cytokines (IFN- γ , IL-2). Type-2 immunity is considered anti-inflammatory and includes both the T helper 2 (Th2) and secretion of type-2 cytokines (IL-4, IL-5, IL-13) from multiple sources (Chaplin, 2010; Raison & Miller, 2011).

Many studies have reported elevated levels of inflammatory cytokines in depressed individuals (Alesci et al., 2005; Capuron et al., 2011; Kelly et al., 2003; Raison, Capuron, & Miller, 2006). In animal studies, feline defensive rage behaviors were related to IL-1 β and IL-2, which affect the hypothalamus and midbrain periaqueductal gray serotonin 5-HT 2 receptors and gamma-aminobutyric acid receptors (Zalcman & Siegel, 2006). In human studies, chronic exposure to inflammatory cytokines (IFN- α or IL-2) treatment in patients with the hepatitis C virus infection or cancer resulted in increased depression symptoms (Felger et al., 2013; Kelly et al., 2003). Chronic inflammatory diseases such as

cardiovascular disease, strokes, cancer, diabetes, and other infections increase inflammatory processes that have been reported to increase the risk of depression development (Capuron et al., 2011; Groer et al., 2011; Raison & Miller, 2011).

In a comparison of suicide attempters with nonsuicidal depression patients and healthy controls, suicidal behavior has been associated with increased plasma levels of IL-6 and TNF- α , and decreased IL-2. This altered cytokine level in the peripheral blood supports the hypothesis that inflammation may affect the central nervous system and lead to development of mood disorders (Janelidze, Mattei, Westrin, Traskman-Bendz, & Brundin, 2010; Okusaga & Postolache, 2012).

Neuroimmune pathways in depression and suicidal behavior

Research has shown depression and suicidal behavior is often associated with an imbalanced immune response and metabolism of monoamine neurotransmitters including serotonin, dopamine, epinephrine, and norepinephrine. Immunological pathways that activate neurotransmitters include (a) the serotonergic system: indoleamine 2,3-dioxygenase (IDO) activation and hence tryptophan depletion, and (b) the dopaminergic system: guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) activation of tetrahydrobiopterin (BH4) and hence tyrosine depletion (Capuron et al., 2011; Haroon, Raison, & Miller, 2012; Sperner-Unterweger, Kohl, & Fuchs, 2014).

Serotonergic system. IDO is an immune regulatory enzyme that provides a balance between immunity and tolerance to reduce harm from pathogens. Tryptophan is an important amino acid for serotonin and melatonin biosynthesis. T cells and natural killer cells secrete IFN- γ to induce IDO activity, catalyzing tryptophan to breakdown to kynurenine, which decreases serotonin synthesis (Haroon et al., 2012).

Tryptophan catabolizes through two pathways. One is through tryptophan 5-hydroxylase decarboxylation to form serotonin. The other pathway is the kynurenine pathway through tryptophan 2,3 dioxygenase (TDO) and IDO in which tryptophan is catabolized to kynurenine, leading to degradation into 3-hydroxykynurenine, then quinolinic acid. Kynurenine acid then crosses the BBB and acts on the glutaminergic receptor *N*-methyl-d-aspartate, which is associated with the functions of cognitive memory, learning, and attention (Capuron et al., 2011; Dantzer et al., 2008; Haroon et al., 2012).

Dopaminergic system. IFN- γ and other proinflammatory cytokines (IFN- α and IFN- β) induce GTP-CH1 activation, which enhances production of neopterin and increases nitrate concentration through production of BH4.

It also decreases phenylalanine and tyrosine levels (Capuron et al., 2011; Sperner-Unterweger et al., 2014). Phenylalanine is the precursor for norepinephrine and dopamine biosynthesis. Decreased dopamine synthesis is correlated with sleep disturbance, fatigue, and disturbances of the gastrointestinal and musculoskeletal systems (Capuron et al., 2011).

Depression, suicide, and the *T. gondii* infection

***Toxoplasma gondii* life cycle and global epidemiology.** *Toxoplasma gondii*, which is part of the phylum Apicomplexa and class Sporozoa, is an obligate intracellular protozoan that was first found in 1908 in rabbit tissue. *Toxoplasma gondii* can infect all warm-blooded animals including humans and livestock. It is estimated that one third of the human population is infected with *T. gondii* (CDC, 2013b; Kim & Weiss, 2008). Women of childbearing age (15–45 years) including those already pregnant, are at a high risk of infection, and other risk factors include hot, humid climates, low altitude regions, and low socioeconomic status. Traditionally, high prevalence areas included Latin America, Eastern and Central Europe, the Middle East, South-East Asia, and Africa (Pappas, Roussos, & Falagas, 2009). In Canada and South America, transmission rates of *T. gondii* oocysts through contaminated water and environmental sources are high (Dubey & Jones, 2008).

According to National Health and Examination Nutrition Study (NHANES) data, women aged 15–44 born in the United States had an 11% *T. gondii* incidence rate in 1999–2004, compared to foreign-born women who experienced a 28.1% incidence rate. Overall African and Mexican Americans have higher seroprevalence. The northeastern region of the United States had higher seroprevalence than all other regions at 29.2%, compared to the South at 22.8%, the Midwest at 20.5%, and the West at 17.5% (Dubey & Jones, 2008).

Toxoplasma gondii has genome types I, II, and III, and the most frequently isolated in human hosts are types I and II (Kim & Weiss, 2008). The *T. gondii* transmission cycle has two stages: asexual and sexual. Felines are the only species in which *T. gondii* can complete its reproductive cycle. Mammals or birds are the intermediate hosts in the asexual stage of the parasite life cycle. *Toxoplasma gondii* develops into three forms of cysts: the oocyst (which releases sporozoites), the tachyzoite, and the tissue cyst bradyzoites. Humans can be infected by *T. gondii* in various ways including ingestion of *T. gondii* oocysts by environmentally contaminated feline feces, undercooked foods, vertical transmission from an infected mother, and blood transfusion or organ transplants from infected donors (Dubey & Jones, 2008).

Oocysts invade the host cell, produce sporozoites, and differentiate into tachyzoites, which are highly immunogenic and rapidly divide within the host cell in the acute stage (Kim & Weiss, 2008). Tachyzoites differentiate into the chronic, latent, slower growing bradyzoite forms. Bradyzoites induce little to no immune response and establish a chronic infection in the host. Bradyzoite cysts usually remain in the brain, muscle, or eye. This type of tissue cyst can persist indefinitely for the duration of the life of the host.

Most immune-competent people with the primary infection are asymptomatic, and the infection is unrecognized (Dubey & Jones, 2008). *Toxoplasma gondii* reactivation after primary infection is rare, as it is believed to occur only in immune-compromised individuals such as patients with AIDS and those having received transplant. When an individual becomes immune-compromised, tissue cysts can reactivate into rapidly growing tachyzoites, which cause encephalitis, chorioretinitis, lymphadenopathy, or systemic infections (Kim & Weiss, 2008).

***Toxoplasma gondii* and behavioral manipulation.** After primary infection with *T. gondii*, the plasma antibody titers remain seropositive for life (Kim & Weiss, 2008). Latent chronic infections in immune-competent persons are usually asymptomatic. Acute *T. gondii* reactivation is common only in immune-compromised patients. Many recent reports show that in an immune-competent healthy population, *T. gondii* seropositivity is associated with mental and behavioral disorders such as schizophrenia, depression, and suicide attempts (Dalimi & Abdoli, 2012; Fekadu et al., 2010; Ling et al., 2011).

Animal studies suggested the *T. gondii* behavioral manipulation theory, in which *T. gondii* establishes cysts in the central nervous system and manipulates host behavior to enhance their transmission rates (Flegr, 2013a, 2013b; Hurley & Taber, 2012; Webster, Lamberton, Donnelly, & Torrey, 2006). These behaviors include delayed reaction time, increased novelty seeking, and attraction to the odors of predators. Behavioral changes associated with chronic latent *T. gondii* infection may act on neural and glial cysts, disruptions of neurotransmitters such as dopamine, serotonin, or norepinephrine, and local inflammatory processes in the brain (Hurley & Taber, 2012).

Human studies have revealed that the latent *T. gondii* infection is associated with personality changes and neuropsychiatric disorders. The first report of increased *T. gondii* antibody titer in schizophrenia patients was in 1953. Later, Torrey et al. (2007) reported high prevalence of the *T. gondii* infection in patients with schizophrenia. More recently, epidemiological studies have shown the relationship between the *T. gondii* infection and increased

incidence of schizophrenia (Telda et al., 2011; Yolken & Torrey, 2008).

Arling et al. (2009) first reported the relationship between *T. gondii* infection and suicidal behavior in a study of 218 participants. They found that depressed individuals who had a history of attempted suicide had higher levels of *T. gondii* immunoglobulin G (IgG) titer than non-suicide attempters. A series of *T. gondii* infection and suicide studies in China and European countries also found that countries with high *T. gondii* prevalence had higher suicide rates (Hurley & Taber, 2012). Ling et al. (2011) reported *T. gondii* seropositivity correlated with suicide rates in women aged 60 and older. Three additional studies reported that *T. gondii* IgG titers were higher in schizophrenic and suicidal patients (Okusaga et al., 2011; Telda et al., 2011; Zhang et al., 2012). A further interesting case (Kar & Misra, 2004) reported that depressive symptoms were successfully resolved after treatment of *T. gondii* infection despite the fact that antidepressant treatment did not resolve the patient's depression.

The pathophysiological mechanism by which *T. gondii* causes psychiatric behaviors remains unclear to date. Zhu (2009) suggested that psychosis might be associated with the *T. gondii* infection, and the potential mechanism of the *T. gondii* infection in behavioral change may be its direct effect on neuronal function and immune-mediated dopamine and serotonin synthesis. The host immune response in *T. gondii* infection produces proinflammatory cytokines such as IL-6 and TNF, and activates Th cells, which secrete IFN- γ , blocking *T. gondii* growth by inducing activation of an enzyme, IDO, which causes tryptophan depletion and ultimately results in a decrease of serotonin production in the brain (Caruthers & Suzuki, 2007; Dalimi & Abdoli, 2012; Mann, 2003; Webster & McConkey, 2003). Resultant tryptophan depletion leads to a decrease of serotonin production in the brain, which may contribute to depression (see Figure 1). Another finding shows two genes of *T. gondii* encode tyrosine and phenylalanine hydroxylases to catalyze phenylalanine to tyrosine and tyrosine to dopa (the precursor to dopamine), which may directly alter behavior (Gaskell, Smith, Pinney, Westhead, & McConkey, 2009).

***Toxoplasma gondii* and pregnancy.** *Toxoplasma gondii* can be transmitted to the fetus through the placenta. Pregnant women with the primary *T. gondii* infection have increased risk of miscarriage, fetal congenital toxoplasmosis, retinochoroiditis, and psychosis in their offspring (Lopes, Goncalves, Mitsuka-Bregano, Freire, & Navarro, 2007; Montoya & Remington, 2008; Pappas et al., 2009). During pregnancy it has been shown that the latent *T. gondii* infection is associated with symptoms of depression and anxiety. For example, Groer et al.

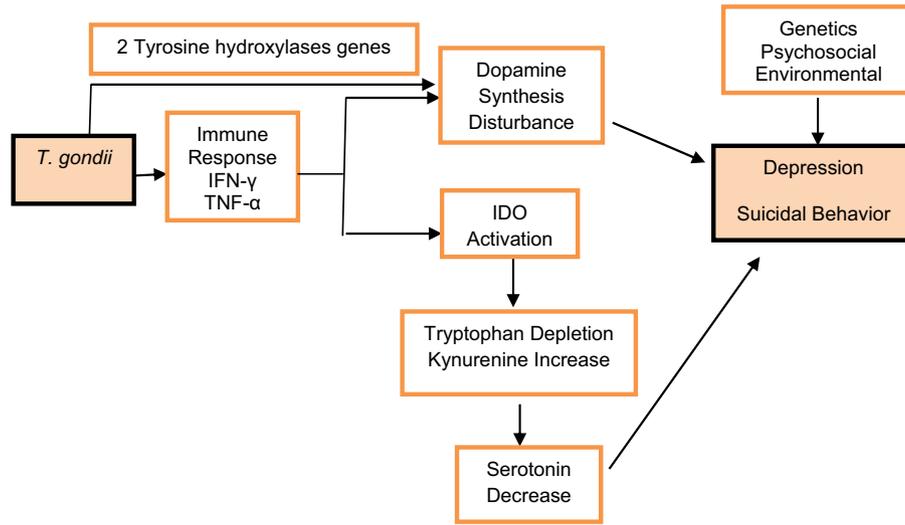


Figure 1 Relationship between *T. gondii* and depression/suicidal behavior and possible mechanisms.

(2011) reported that *T. gondii* IgG titers were associated with prenatal depressive symptoms. Brown et al. (2005) conducted a study of 63 mothers with positive *T. gondii* antibodies whose offspring later developed schizophrenia. Mortense et al. (2007) used filter paper blood from a Denmark biobank to analyze *T. gondii* IgG antibodies in 186 individuals with affective disorders and 71 with schizophrenia. Xiao et al. (2009) further investigated the relationship between maternal *T. gondii* antibodies and genotype, and risk of schizophrenia or other psychosis in their adult offspring. Mothers with positive *T. gondii* type I had a significantly increased risk of development of offspring with psychosis.

Exposure to *T. gondii* was considered unlikely to reactivate during pregnancy and affect the fetus; however, there are conflicting reports that may challenge this concept (Elbez-Rubenstein, 2009; Kodjikian et al., 2004). Elbez-Rubenstein reported a case of an immune-competent woman with previous exposure to *T. gondii* whose reactivated latent infection during pregnancy resulted in fetal infection. In a second case (Kodjikian et al., 2004) was an immune-competent Brazilian woman who had a chronic *T. gondii* infection. In the seventh week of her third pregnancy, long-standing immunity to *T. gondii* was confirmed without any recent evidence of infection, and at 35 weeks a preterm baby was born. Serology tests from the mother, umbilical cord, and the new born baby detected rises in anti-*T. gondii* IgG and IgA. Comparative immunoblot analysis confirmed congenital toxoplasmosis in the infant. These cases suggest that latency does not automatically protect from future infections with different strains or reactivation of *T. gondii*.

Clinical implications

Diagnostic evaluation depression and suicidal behavior

Depression is the leading cause of disability in the United States. The burden of depression and suicide is high, and the rates of diagnosis of depression are poor. The U.S. Department of Veterans Affairs (VA/DoD) Clinical Practice Guidelines (2009) outline the steps in depression evaluation; standard initial Patient Health Questionnaire-2 (PHQ-2) screening used for depression in routine primary care office visits (Kroenke, Spitzer, & Williams, 2003). The PHQ-2 should be completed annually in the primary care office.

Patient with a positive response to PHQ-2 questions implies the need to further evaluate depressive symptoms, which include medical history, physical examination, mental status examination, drug inventory, psychosocial history, and relevant laboratory tests. Evaluation should also include a suicidal thought questionnaire (Table 1; Soleimani, Kyle, Lapidus, & Losifescu, 2011).

Patients should be referred to mental health specialists if severe, dangerous, and unstable conditions appear to be

Table 1 Example of suicidal thought questionnaire

Suicidal thought questionnaire

1. This last week have you had any thoughts that life is not worth living?
2. What about thoughts of hurting or even killing yourself?
3. If yes, what have you thought about?
4. Have you actually made plans?
5. Have you told anyone about it?

present. If patients are not an immediate threat to themselves but have depressive symptoms, it is then possible to obtain PHQ-9 scores, risk factor assessments, and diagnose depression per DSM-IV criteria (American Psychiatric Association, 2000; Kroenke et al., 2001; Soleimani et al., 2011; VA/DoD, 2009).

PHQ-9 score of 5–14 indicates mild depression, which requires monitoring and support counseling. Antidepressant drug therapy should be considered if no improvement in symptoms is seen in 1 month. A PHQ-9 score of 15–19 indicates moderate depression; treatment should start with antidepressant monotherapy or psychotherapy, or a combination of both. A PHQ-9 score greater than 20 indicates severe depression, which requires a combination of antidepressant drugs and psychotherapy or multiple antidepressant drugs therapy (VA/DoD Depression Guideline, 2009).

Depression risk factors assessment include prior episodes of depression, family history of depression, prior suicide attempt, female gender, age of onset under 40, postpartum period, lack of social support, stressful life-event, current substance abuse, or medical comorbidity. Medical conditions that may cause depressive symptoms include autoimmune disorders, neurological disorders, endocrine disorders, cancers, and infectious diseases (hepatitis, human immunodeficiency virus, mononucleosis, and toxoplasmosis).

Laboratory findings relating to both infection and depression can help to improve the diagnosis and treatment of diseases. Laboratory tests include B12, folate level, and thyroid function tests. Clinical studies have identified several biomarkers that may help to diagnose and treat patients with depression. These biomarkers are as follows: cytokines (IL-1, IL-6, IFN- α , CRP), endocrine markers (cortisol, thyroid-stimulating hormone, T3), metabolic factors (insulin, blood glucose), growth factors (growth hormone), and *T. gondii* antibody titers (IgG, IgM, and IgA; Schmidt, Shelton, & Duman 2011). For the *T. gondii* infection, polymerase chain reaction (PCR) can also be used if patients have high risk factors (region, social economic factors, pregnancy, or immune compromise; CDC, 2013b; Hotop, Hlobil, & GroB, 2012) or are resistant to antidepressant medications. These biomarkers may be identified through peripheral blood tests.

Peripheral blood tryptophan, neopterin, and phenylalanine levels may also provide clinical tools for diagnosis, treatment decisions, and treatment outcome measurements for patients with depression or suicidal behavior. Sperner-Unterweger et al. (2014) proposed a personalized treatment approach that measures biomarkers kynurenine/tryptophan and phenylalanine/tyrosine metabolic pathways to improve therapy for depression; however, this is a recommendation only.

Pharmacotherapy antidepressant drugs and treatment guidelines

Options for clinical treatment of depression include monoaminergic neurotransmitter agents such as selective serotonergic reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), the monoamine oxidase inhibitors (MAOIs), noradrenergic dopamine reuptake inhibitors (NDRIs), serotonin 2A antagonist reuptake inhibitors (SARIs), and noradrenergic and specific serotonin antidepressant (NaSSAs; Soleimani et al., 2011; VA/DoD Guideline, 2009; Table 2).

The choice of medication is based on side effect profile, patients' history, and comorbidity. According to the VA/DoD depression treatment guidelines, first-line options are SSRIs along with SNRIs or bupropion and mirtazapine. SSRIs usually are the first-line antidepressants for patients in the primary care setting because of their low side effect profile. An appropriate dose titration and target dose range should be included in the treatment plan. Antidepressant agents may take 4–6 weeks to become effective, and full effectiveness can take 8–12 weeks. Patients may benefit from changing or combining different antidepressant agents if patients do not improve with single agent treatment. Discontinuation of therapy should be done using slowly tapering doses and monitoring withdrawal or depressive symptoms.

Antiparasitic/microbial drugs and dosages for the *T. gondii* infection

There are additional options for treatment of patients with suspected depression when the *T. gondii* infection is present (high anti-*T. gondii* IgG, IgM, or IgA antibody titers or PCR positive). Treatment of the *T. gondii* infection includes a combination of pyrimethamine/daraprim (100 mg for first day as a loading dose, then 25–50 mg/day) and sulfadiazine (1 g four times/day), plus folinic acid/leucovorin (5–25 mg/day) or pyrimethamine and clindamycin if patient has a hypersensitive reaction to sulfa drugs. Spiramycin is recommended for first and early second trimester pregnant women with *T. gondii* infection. Pyrimethamine, sulfadiazine plus folinic acid is recommended for late second and third trimesters pregnant women with acute *T. gondii* infection (CDC, 2013c; Hotop et al., 2012).

Other treatment options for depression

Tyring et al. (2006) conducted a double-blind placebo-controlled clinical trial in patients with psoriasis. The results showed that patients had minimal response to

Table 2 Commonly prescribed antidepressant drugs and dosages

Class of medication	Generic name	Brand name	Starting dose (mg/day)	Maximum dose (mg/day)
SSRIs	Citalopram	Celexa	20	20–60
	Escitalopram	Laxapro	5–10	10–20
	Fluoxetine	Prozac	10–20	10–60
	Paroxetine	Paxil and Paxil CR	10–20	10–50
	Sertraline	Zoloft	25–50	25–200
	Fluvoxamine	Luvox	25–50	50–300
SNRIs	Duloxetine	Cymbalta	20–40	40–120
	Venlafaxine	Effexor and Effexor XR	37.5	75–225
	Desvenlafaxine	Pristiq	50	50–100
TCAs	Amitriptyline	Elavil	10–50	100–300
	Imipramine	Tofranil	10–25	100–300
	Nortriptyline	Pamelor	10–25	50–150
	Desipramine	Norpramine	25–50	100–300
	Doxepin	Sinequan or Adapin	25–50	100–300
MAOIs	Phenelzine	Nardil	15	45–90
	Isocarboxazid	Maeplan	20	30–60
	Tranlcypromine	Parnate	10	30–40
NDRIs	Bupropion	Wellbutrin	75–150	300–450
SARIs	Trazodone	Desyrel	25–50	600
NaSSAs	Mirtazapine	Remeron	15	15–45

Note. SSRIs, selective serotonergic reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; NDRIs, noradrenergic dopamine reuptake inhibitors; SARIs, serotonin 2A antagonist reuptake inhibitors; NaSSAs, noradrenergic and specific serotonin antidepressant.

antidepressants therapy and significant improvement in depressive symptoms with TNF- α antagonist therapy.

There may be evidence that the anti-inflammatory agents beneficial in depression treatment are inflammatory signaling pathway inhibitor cyclooxygenase (COX-1, COX-2), TNF- α antagonist, IL-17 inhibitor, IDO inhibitors, and glutamate receptor antagonist (Capuron & Miller, 2011; Krishnadas & Cavanagh, 2012). Use of anti-inflammatory COX-2 inhibitors is another potential approach to depression therapy (Muller et al., 2004; Muller & Schwarz, 2007). However, this study only shows that when treating patients with depression and psoriasis as comorbidity, patients respond to anti-inflammatory medications. Further study would be needed to conclude if patients who are depressed without psoriasis also respond to anti-inflammatory treatment.

Studies also reported that the widely available prescription antipsychotics drug haloperidol and mood stabilizer drug valproic acid also inhibits *T. gondii* replication in vitro and animals (rats), which supports the hypothesis that *T. gondii* infection is linked to altered host behavior (Jones-Brando, Torrey, & Yolken, 2003; Webster et al., 2006). Jones-Brando et al. (2003) conducted an in vitro study to test 12 neuroleptic pharmacological compounds and found that the antipsychotic drug haloperidol and mood stabilizer valproic acid are the most effective drugs to inhibit *T. gondii* growth. Furthermore, Webster et al. (2006)

tested those two drugs compared to standard anti-*T. gondii* drugs pyrimethamine with dapsone treatment in a study of *T. gondii* infected rats. They found that antipsychotic drugs have the same efficiency as anti-*T. gondii* drugs in prevention of behavioral alteration in rats. Goodwin et al. (2011) found similar results in mice and human cell culture studies. Further research on clinical trials could provide more evidence of *T. gondii* treatment in *T. gondii* induced depression patients.

Conclusion

Brain and immune system interactions play an important role in neuropsychiatric disease development. Research shows that there is a positive relationship between the *T. gondii* infection and neuropsychiatric disorders. A growing number of studies support the hypothesis that *T. gondii* manipulates a host's behavior to increase transmission rates. However, further research is needed regarding mechanisms and treatment of *T. gondii* induced depression and suicidal behavior.

It is important for NPs to screen patients for depressive symptoms, particularly with medical comorbidity in the primary care office setting. Following clinical depression guidelines, assessing and evaluating patients with depressive symptoms should account for risk factors and laboratory biomarker test evaluations to differentiate

depression caused by a medical condition. NPs need to understand the potential mechanisms associated with depression development and the *T. gondii* infection in order to provide screening, efficient treatment, and suicide prevention.

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