## **REVIEW**



## Psychotropic effects of

# antimicrobials and immune modulation by psychotropics: implications for neuroimmune disorders

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### **Practice points**

- Antimicrobial and psychotropic medications can display pleiotropic psychotropic and immunomodulatory properties beyond their primary effect.
- Immune modulation may be an important final common pathway underpinning certain mechanisms of action of observed pleiotropy for these agents.
- Modulation of neuroimmune function can affect neuropsychiatric conditions.
- The understanding of these processes may lead to new therapeutic targets for neuropsychiatric conditions and reduce misattributions in clinical studies or treatment.

**SUMMARY** Antimicrobial compounds and psychotropic medications often share overlapping mechanisms of actions and pharmacological effects. The immune system appears to be an important site of interaction as several antimicrobials display neurological and, at times, direct psychotropic effects, while psychotropics have shown significant immunomodulatory properties. The isoniazid class of antibiotics for example has been shown to possess monoamine oxidase activity, while selective serotonin reuptake inhibitors have shown significant effects on leukocyte populations. As the importance of the immune system's role in CNS homeostasis and disease continues to move to the forefront of neuropsychiatric research, these shared pharmacological effects may provide an important insight, elucidating the complexities in neuroimmune pathophysiology and guiding the development of potential treatments.

Immunologic dysfunction has been implicated in the etiologies of diverse subpopulations of major neuropsychiatric conditions including developmental, psychotic, anxiety, mood and cognitive disorders. Although somewhat controversial, conditions including subsets of autism spectrum disorders (ASDs), schizophrenia, obsessive–compulsive disorder (OCD), Tourette syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's chorea (SC) have all been associated with observations

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of immune dysfunction [1-5]. In addition, epidemiology, clinical studies and animal models have all highlighted observations of immune irregularities, including disruptions in regulatory T-cell populations and altered cytokine expression, as well as evidence of immune activation, predominantly by pathogen exposure or stress [6,7]. In SC, PANDAS and Tourette syndrome for example, immunological cascades following group A streptococcal (GAS) pharyngitis, specifically the production of antistreptococcal antibodies, have been implicated as an integral component of the pathological mechanism in these disorders with observations of antigenic mimicry between these antibodies and proteins in the CNS leading to autoimmune-type reactions [8]. In schizophrenia and neurodevelopmental disorders such as ASD, prenatal exposure to maternal proinflammatory cytokines, commonly the result of prenatal infection, has been shown to be a key mechanism, disrupting early developmental events through the disruption of shared signaling pathways [9,10]. Other neurological disorders, such as multiple sclerosis, have also shown a strong immunological component with findings of regulatory T-cell abnormalities and cytokine disruptions, which seem to be key components of disease pathology [11]. Interestingly, the converse has also been true as individuals affected by autoimmune disease often display neuropsychiatric symptoms. In Grave's disease for example, increased anxiety, depression, OCD and, in rare cases, psychosis-like symptoms have all been noted as a consequence of the disorder [12]. Given the complex and enmeshed relationship between CNS neuroimmune components, it is not surprising that a number of classical psychotropic compounds have been found to have immunomodulatory properties likely to be directly responsible for components of their psychotropic effects nor for antimicrobial agents to display psychotropic effects.

Although the psychotropic effects of antibiotics are not commonly utilized therapeutically, the commonly associated side effects confirm their potential to influence CNS function. Several antibiotic medications have been known to cause confusion, anxiety and depression and in some instances, psychosis [13]. Although unfavorable in a therapeutic context, these effects are often influenced by age, dosage, blood-brain barrier (BBB) permeability and drug interactions. Research into the mechanisms behind these effects may help to elucidate a therapeutic

application. Penicillin for example was known to act on GABA receptors, a mechanism thought to be responsible for many of the side effects [14]. Other classes of antimicrobial compounds, particularly the antimalaria treatment methylene blue and several antituberculosis drugs, have been shown to have monoamine oxidase (MAO) inhibitor (MAOI) properties. Similarly, many psychotropic drugs are known to have significant immunomodulatory effects, particularly agranulocytosis. While these effects are not considered therapeutically useful, it is important to understand, especially in light of recent knowledge of immune CNS interactions, how this interplay affects therapeutic efficacy and how it can be manipulated pharmacologically. Among those compounds with actual psychotropic activity, teasing out whether this activity is due to CNS neuroimmune modulation or resulting from direct effects on neurochemical function is often difficult. Despite these significant limitations, in this review some of the investigations attempting to characterize the dynamics of these compounds with multimodal effects in an effort to better understand their possible roles as preventatives, therapeutics and confounders are explored. From a clinical perspective the understanding of 'off-target' effects of antimicrobial agents can be critically important in the case of drug interactions and adverse reactions; however, also important, are mechanistic insights gleaned from existing compounds, whether formally antimicrobial or psychotropic, these can altogether aid in the discovery and development of new therapeutic targets and potentially new future preventatives and treatments.

## Infection, immune dysregulation & neuropsychiatric disorders

Although the evidence supporting the role of infection and immune dysregulation in the pathogenesis of neuropsychiatric disorders seems significant, conflicting reports and a lack of clinical research has resulted in some reluctance to accept this as an etiological factor particularly in disorders such as PANDAS. Evidence from other disorders, however, point to a role for infection and potentially more importantly, the resulting immune disruptions in precipitating neuropsychiatric symptoms. In schizophrenia there is increasing evidence to support the role of specific pathogen exposure and resulting immune activation in precipitating the neuropsychiatric symptoms observed clinically. Several studies have alluded to a possible role for Toxoplasma gondii, a parasite commonly found in cat feces and of immense concern for pregnant women and is thought to infer increased risk for the disorder, possibly precipitating clinical symptoms. There have been findings of increased seroprevalence of toxoplasma antibodies in schizophrenic patients as well as observations that the parasite may affect dopamine signaling, a pathway commonly disrupted in schizophrenia [15,16]. The strong association of neuropsychiatric symptoms in autoimmune disorders and the mounting evidence to suggest antigenic mimicry as a central mechanism in infection-mediated neuropsychiatric symptoms strengthens the hypothesis of immune involvement, mediated by infection, in the appearance and progression of some neuropsychiatric disorders. In Grave's disease - an autoimmune disorder characterized by the production of excess thyroid hormones due to thyroid receptor autoantibody - anxiety, panic disorders and OCD are often associated and, in some rare cases, psychosis-like symptoms have also been reported [12,17].

#### Antimicrobial agents with psychotropic effects

The role of the immune system and, more importantly, its dysregulation in neuropsychiatric disorders has not only hinted at a potential pathological mechanism but may also provide new therapeutic alternatives. Antimicrobial agents are an appealing class of compounds owing to their inherent immunomodulatory properties. In addition, several of these compounds have been shown to have direct CNS effects, which may further hint to their efficacy in the treatment of some neuropsychiatric disorders, particularly those with an established or proposed immunological component.

#### **β**-lactams: penicillin

 $\beta$ -lactams are a class of antibiotic compounds with a cyclic amide ring, a  $\beta$ -lactam, as a core component of their molecular structure. While penicillin, named after the genus of the original producing mold, is the most prominent derivative, other members include cephalosporins, monobactams and carbapenems.  $\beta$ -lactams' antimicrobial activity is attributed to the structure and activity of the  $\beta$ -lactam ring connected to a thiazolidine ring that binds and inhibits bacterial transpeptidase, thereby disrupting peptidoglycan synthesis necessary for the formation of the bacterial cell wall and, thus, preventing cell division. Other penicillin target proteins include holing-like proteins in the cell membrane of certain bacteria [18].

While primarily utilized for their antimicrobial activity, B-lactam antibiotics were found to promote the expression of the glutamate transporter GLT1 and have a neuroprotective role in vivo and in vitro when used in models of ischemic injury and motor neuron degeneration, suggesting significant neuroprotective properties [19]. Azithromycin (AZM) and penicillin have been utilized in the treatment of PANDAS, with observations of improvement in neuropsychiatric symptoms after 2-6 weeks of antibiotic treatment [20]. Although eradication of chronic latent, undetected GAS may be responsible for these observations via lowering antigenic load and immune activation, the potential for pleotrophic effects is possible given the effects on glutamate, immunomodulation and neuroprotection outside its antimicrobial actions. Given the potential role of glutamatergic therapies in OCD, depression, TBI, neurodegenerative disorders and schizophrenia, CNS-permeable β-lactams could be expected to exhibit efficacy in these neuropsychiatric disorders but further study is needed. In a recent study investigating the effects of cephalosporin in a mouse model of major depressive disorder, ceftriaxone, of the cephalosporin family, was shown to exhibit antidepressant properties increasing glutamate uptake, thought to be impaired in major depressive disorder [21].

#### Clavulanic acid

Clavulanate is a  $\beta$ -lactamase inhibitor commonly used in conjunction with amoxicillin to overcome antibiotic resistance provisioned by  $\beta$ -lactamase production by some bacteria, but has no significant antibacterial activity when used alone, despite containing a  $\beta$ -lactam ring. This structural similarity, however, is integral to its inhibitory mechanism allowing it to irreversibly bind to and inactivate bacterial  $\beta$ -lactamase [22].

Clavulanate readily crosses the BBB and has demonstrated anxiolytic properties in rodents and nonhuman primates [22]; a mechanism possibly due to increased dopamine release [23] or due to its possible effects on glutamate transmission through *N*-acetyl-L-aspartyl-L-glutamate (NAAG) peptidase inhibition. Specifically, clavulanate through NAAG-peptidase inhibition may decrease glutamate, enhance NAAG stability and consequently lead to greater metabotropic glutamate (mGlu)3 receptor (mGlu3R) activation. Known agonists of mGlu3R appear to display anxiolytic, antidepressant and neuroprotective properties in animals [24]. Moreover, mGlu3R activation is associated with reductions in glutamate release from the presynaptic neurons and decreased excitotoxic glutamate-mediated neuron damage [25]. Further, NAAG-mediated mGlu3R activation on glial cells appears to lead to release of trophic factors [26,27]. In accord, clavulanate enhances TGF-B release from glial cells possibly due to it's ability to inhibit NAAG peptidase [28]. Through reductions in glutamate, enhancements in dopamine and trophic factors, clavulanate displays significant potential as an antidepressant and anxiolytic agent. Phase IIb clinical trials for major depressive disorder are pending [23].

#### The tetracyclines

Tetracyclines represent a class of broad-spectrum antibiotics from the *Streptomyces* genus displaying antimicrobial, antifungal, antibacterial and antiparasitic properties [29]. This broad therapeutic characteristic has led to their utilization in a wide range of infections, both therapeutically and prophylactically. They exert their antibiotic effects through inhibition of protein translation; specifically they act as an allosteric inhibitor preventing the assembly of translational machinery by preventing the association of the t-RNA subunit to the ribosomal complex [30].

While first-generation tetracyclines have seen declining use in recent years due to bacterial resistance, second-generation compounds, such as minocycline, have not only improved on antimicrobial efficacy, but increased lipid solubility and longer half-lives have led to broader therapeutic applications [31]. Minocycline has been shown to exhibit immunomodulatory and psychotropic properties unrelated to the antibiotic mechanism of action. These properties have been attributed to inhibition of oxidative stress through attenuation of the expression of inducible nitric oxide synthase (iNOS), COX2, and matrix metalloproteinase (MMP) [32]. In fragile X syndrome (FXS), where MMPs have been thought to play a major role in the pathological mechanism, minocycline has been shown to lower MMP9 levels, which are high in FXS and it also strengthens brain connections in animal models of FXS [32,33]. MMPs have been implicated in axonal guidance, synaptogenesis, neurotransmission, synaptic plasticity and behavioral learning [34,35]. These studies point to a potential role in these disorders and highlight the need for more research into their potential clinical applications. While these animal data are very exciting, further studies in humans are needed in order to guide clinical management.

Minocycline has also been shown to have psychotropic effects in disorders such as schizophrenia, although this may be related to these immunomodulatory activities. In clinical studies investigating the use of minocycline as an adjunct therapy in schizophrenia, minocycline was shown to improve associated negative symptoms and deficits in executive functioning [36]. The contribution of immune dysfunction has been implied with reported associations of prenatal viral and bacterial infections and an increased occurrence of schizophrenia in resultant offspring, as well as observations of viral nucleotide fragments in the cerebrospinal fluid of schizophrenic individuals [37-39]. In addition, unlike most classical antibiotics, minocycline has been shown to have antiviral capabilities. In an experimental model of HIV using simian immunodeficiency virus, minocycline reduced the severity of encephalitis, suppressed viral load in the brain and decreased the expression of inflammatory markers in the CNS [40]. These antiviral effects may be mediated by inhibiting the integration of viral DNA with host DNA as well as by inhibiting the activation of CD4<sup>+</sup> T cells [41]. The immunological component of psychiatric disorders such as schizophrenia may account for minocycline's therapeutic efficacy when coupled with its BBB permeability and its immunomodulatory potential.

#### Linezolid

The parent class of linezolid, the oxazolidinones, were found to display broad-spectrum antibacterial activity through inhibiting bacterial protein synthesis via a unique mechanism whereby the peptidyl transferase center active site of the 50S rRNA subunit is bound by the compound and protein synthesis is inhibited [42]. Several agents in this class are currently under evaluation including eperezolid, posizolid, radezolid, ranbezolid and torezolid.

The therapeutic activity of oxazolidinones, such as linezolid, have been shown to extend beyond their antimicrobial actions. These compounds were among the first selective-reversible inhibitors of MAO-A. Initially developed as antidepressants, oxazolidinones are still used as psychotropics outside the USA [43]. Linezolid's ability to also act as a potent antidepressant has been well demonstrated in animals through its ability to inhibit the breakdown of monoamines including dopamine, serotonin, norepinephrine and epinephrine as well as its favorable CNS penetration [44,45]. Likely neuroimmune function is also impacted given that immune components, including lymphocytes, natural killer cells, microglia and astrocytes express monoamine receptors [46–48]. Despite these data, direct evidence of neuroimmune modulation, as a component of linezolid's psychotropic effect, has not been demonstrated to date.

#### Vancomycin

First isolated in 1953, vancomycin is often utilized for the treatment of infections stemming from antibiotic-resistant Gram-positive bacteria. Its antibiotic effects are mediated through inhibition of cell-wall synthesis although its use is somewhat limited, often being utilized in antibiotic-resistant cases owing to unpleasant side effects including localized pain and vein inflammation resulting from blood clots.

The use of vancomycin has been investigated as a potential treatment for autism [49]. A subset of children with autism show normal development followed by a sudden regression with a loss of language skills and the appearance of abnormal social behaviors. In these children, this sudden regression has been hypothesized to be related to an imbalance of intestinal bacteria [49,50]. When children with regressive autism were treated with oral vancomycin in a small open-label trial there was a decrease in autistic symptoms, especially communication and behavior improvements, although it was reported as being transient and was not observed at follow-up [49]. Although further research is needed, these studies highlight the possibility of the role of intestinal bacteria in the progression of autistic symptoms in a subset of individuals and the potential role for antibiotics that target intestinal dysbiosis in the treatment of ASD or in other disorders such as restless legs syndrome [51].

#### Macrolides

The first macrolide erythromycin was discovered by a group at Eli Lilly led by J McGuire as an isolate from the bacteria *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) found in soil samples from the Philippines [18]. Clarithromycin soon followed in the 1970s followed by others including the other US FDA-approved macrolides: AZM, dirithromycin, roxithromycin and telithromycin. Interestingly, the nonantibiotic macrolides: tacrolimus, pimecrolimus and sirolimus also possess immunomodulatory properties. The antibiotic effects of macrolides are mediated by inhibition of bacterial protein synthesis, through inhibition of peptidyltransferase activity [52]. They have been frequently used in the past for treating many upper respiratory tract infections including GAS pharyngitis with adequate efficacy (>90%) [53]. Their effects on immunomodulation appear to extend beyond their antimicrobial actions as they have been shown to mitigate cytokine production in animal studies and human trials [54].

While there is little data on the therapeutic application of macrolides in neuropsychiatric disorders, observations of neuropsychiatric side effects have been observed with clarithromycin suggesting a potential role in the modulation of the CNS and the need for more research [55].

#### Azithromycin

Derived from erythromycin, AZM differs from the parent erythromycin by the addition of a methyl-substituted nitrogen atom onto the lactone ring, a modification that appears to imbue stability, improve tissue penetration and broaden antimicrobial spectrum. Despite high intracellular penetration and extensive tissue distribution its CNS penetration is poor [18]. AZM has a longer duration of action and allows for once-a-day dosing. The main drawback has been reports of macrolide-resistant GAS [56] as well as an increased risk of selection for resistant endemic pathogens over a longer course of treatment [57].

While its antibiotic properties have been attributed to mechanisms shared by other macrolides, AZM has been shown to act primarily on the lymphokine CD4 Th1 cell line reducing the production of the proinflammatory cytokines IL-12 and IL-6, and increasing the production of the anti-inflammatory cytokine IL-10 in macrophage cell lines after stimulation with a combination of lipopolysaccharide (LPS) and IFN-y [58]. The immunomodulatory potential of AZM is not limited to suppression of production and secretion of proinflammatory cytokines, it also suppresses iNOS-mediated nitric oxide production. These agents also work at a molecular level, decreasing mRNA expression thereby promoting apoptosis of inflammatory cells and a decrease in nuclear transcription factors [59]. Consistent with this hypothesis, a few in vitro studies point to

AZM's actions to downregulate NF- $\kappa$ B signaling, costimulatory molecules and alter function of antigen-presenting cells.

Innate immunity is thus impacted as well. TLR4 and IL-12 are reduced after AZM treatment; both of these signaling pathways are involved in streptococcal infections. A recent clinical study investigating the occurrence of polymorphisms in TLR4 and TLR2 in susceptibility to GAS infections suggested mutations in TLR4 (D299G, T399I) were associated with vulnerability to recurrent GAS infection [60]. Furthermore, soluble immune-activating factors, such as IL-12, IL-6 and TNF- $\alpha$ , released during GAS infection [61], and possibly during postinfection exacerbations seen in PANDAS, may contribute to autoantibody production or through transport across the BBB directly affect neuroimmune activity [62].

In a study designed to decrease GAS infections, researchers at the National Institute of Mental Health conducted a 12-month parallel investigation comparing prophylactic doses of penicillin and AZM. Eleven subjects were maintained on penicillin and 12 were maintained on AZM during the 12-month study [20]. During the study year the mean number of neuropsychiatric exacerbations was reduced to 0.9 (0.5 standard deviation) and the mean number of streptococcal infections was reduced to 0.1 (0.3 standard deviation; p < 0.01). No side effects or reports of any adverse effects from the medications were reported. The authors suggest that both antibiotics may be safe and effective in preventing GAS infection and in decreasing the number of neuropsychiatric exacerbations in these children without any significant differences between groups. This study was limited by the comparison of retrospective data for the baseline year to prospective data of the treatment year using an active comparator. However, this study lends support to the feasibility of pursuing a similar design but comparing the efficacy of an antibiotic to a placebo. AZM is currently under study as a possible treatment for acute onset of OCD in children and to examine it's influence on immune function [201].

#### Methylene blue

The thiazine dye methylene blue was medicinally discovered in the 1890s as a successful malaria treatment by Ehrlich and Guttmann [63] and, currently, interest in the use of the agent is renewed for malaria [64]. From an antiparasitic perspective, its effect appears to comprise the disruption of parasitic hemoglobin degradation and heme metabolism in cellular organelles as well as inhibition of glutathione reductase of *Plasmodium falciparum* [65].

Methylene blue has also been shown to exert significant effects on the CNS through a similar mechanism. Its redox capabilities, particularly its ability to modulate glutathione reductase or NADPH modulation, have been implicated in its neuroprotective actions against oxidative damage, tau and amyloid aggregation, and mitochondrial dysregulation in neurodegenerative disorders [66]. The implications of mitochondrial stabilization and resulting neuroprotection are broad given the plethora of psychiatric disorders that appear to involve mitochondrial dysfunction including: neurodegenerative processes, affective disorders [67], schizophrenia [68,69] and development disorders. Importantly, while genetic variants affecting mitochondrial function are likely to play a role in a subset of autism, more work needs to be done in this area prior to implementation of agents targeting mitochondrial function in patient care. Despite this, these data provide intriguing evidence supporting the hypothesis that neuroprotection through immunomodulation is a significant mechanism of psychotropic action for this agent. The MAOI properties of methylene blue have also been attributed to its oxidation/reduction characteristics as kinetic studies investigating these properties show its inhibition of MAO were mediated by its action as both an oxidizing substrate and as a oneelectron reductant at the active site of MAO-A [70]. Insights into the mechanism by which this is accomplished may elucidate possible therapeutic applications of methylene blue. Despite its association with serotonin syndrome, several clinical trials, conducted primarily in the late 1980s have investigated the use of methylene blue in the treatment of bipolar disorder [71,72]. Recent work in animal models may represent a renewed interest in the CNS properties of methylene blue. Rat models of methylene blue administrations have shown anxiolytic and antidepressant properties, which have been shown to be mediated through its regulation of nitrergic system, specifically inhibition of nitric oxide synthase and soluble guanylyl synthase [73].

#### D-cycloserine

Cycloserine's discovery led to a new treatment option for tuberculosis [74,75]. Now used as a second-line bacteriostatic agent for the treatment of Mycobacterium tuberculosis and some urinary tract infections, cycloserine also demonstrates activity against susceptible Gram-negative and Gram-positive bacteria including Chlamydia, Staphylococcus aureus, Escherichia coli, Enterococci and Mycobacterium avium complex microorganisms. Its mechanism of antimicrobial action involves the incorporation of D-alanine into the bacterial cell-wall components through inhibition of alanine racemase and D-alanine ligase [18]. In a different fashion, through partial agonism at the glycine site of NMDA receptors in the CNS, the D-isomer of cycloserine, D-cycloserine, has been extensively evaluated for a variety of uses, particularly the treatment of anxiety disorder including post-traumatic stress disorder and OCD as well as chronic pain and depression, at doses considered subtherapeutic for antimicrobial purposes [76,77]. It is well characterized as a cognitive enhancer and has been in trial for efficacy in adjunctive treatment of Alzheimer's disease [78], Parkinson's disease and schizophrenia [79] with mixed results. As various peripheral immune and neuroimmune cells also express NMDA receptors, effects on neuroimmune activity could be expected [80]. Despite these reports of psychotropic effects, which appear to be mediated through immune modulation, a clear immunomodulatory mechanism has not been established.

#### The isoniazid family

The first oral mycobactericidal drug, isoniazid, was discovered in 1912 by Meyer and Malley [81]. Much later it was found to have activity against M. tuberculosis in the 1940s concurrently by three pharmaceutical companies and is still used as part of chemoprophylaxis. Isoniazid is bacteriocidal through its conversion by katG catalaseperoxidase within M. tuberculosis thereby forming isonicotinyl radicals. These radicals in turn react with NAD and NADPH to produce various compounds capable of inhibiting enzymes critical for bacterial cell-wall synthesis and nucleic acid synthesis [18]. During its use as an antituberculosis agent it was found to exhibit moodenhancing properties through MAOI activity. This serendipitous discovery led to the development of the entire MAOI antidepressant class of compounds. In a similar fashion the relative of isoniazid, iproniazid, shares similar MAOI properties. The isoniazid derivatives including isocarboxazid, phenelzine, tranylcypromine and the reversible MAO-A inhibitor, moclobemide, are

still in use in the present day owing to their profound efficacy for treatment-resistant depression. In spite of its many effects, very limited, mostly *ex vivo* studies, have directly investigated isoniazid's potential to modulate immune functioning [82,83]. Based on these data, this agent appears to boost T- and B-cell populations under proliferative conditions mimicked by phorbal esters whereas in other studies isoniazid decreased IL-1 and IL-2 signaling in immune cells. Notably an autoimmune lupus-like syndrome is observed after treatment in some individuals.

# Psychotropic agents with notable immunomodulatory effects

While the use of psychotropic drugs in the treatment of infection may not be of therapeutic relevance, the immunomodulatory properties of psychotropic drugs is increasingly relevant in light of the increasing role of infection in neuropsychiatric disorders. The effects of several psychotropic medications have been documented in the context of their adverse effects on the immune system, however, the utilization of these effects in the treatment of the neuropsychiatric components of infection in autoimmune disorders requires more research. Increased research may not only give a broader understanding of the role immune dysregulation may play in neuropsychiatric disorders, but also new strategies for the management of conditions with both an infectious and a neuropsychiatric component.

#### Antidepressants

Antidepressants is the term used to encompass the class of compounds used to treat symptoms of depression, although anxiety, eating disorders and other neuropsychiatric conditions are commonly treated with these agents. Although selective serotonin reuptake inhibitors (SSRIs) are currently the pharmacologic treatment of choice for depressive and anxiety disorders, other antidepressants, including tetracyclic antidepressants, tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors, are also commonly used. These agents exert their therapeutic effects through modulation of neurotransmitter signaling. Since reduced availability of neurotransmitters such as serotonin, dopamine and noradrenaline have been implicated in the pathology of depression and other disorders, most of these agents act as inhibitors of reuptake or MAO. They also have the potential to exert their neuropsychiatric benefits via



immunomodulation and support of neurogenesis and repair mechanisms, processes in which neuroimmune cells intimately participate [84,85]. Some studies suggest that patients with major depressive disorder have elevated IL-6 and that antidepressant therapy leads to decreased IL-6 levels [86,87]. Furthermore these agents have been found to exert anti-inflammatory effects through suppression of IFN- $\gamma$  [88] as well as suppression of IL-1β, IL-2, TNF-α, natural killer cell cytotoxicity and T-cell proliferation [89-91]. SSRIs, tricyclic antidepressants and the heterocyclic antidepressant trazodone all decrease peripheral inflammation in rats [92,93]. The dopamine and noradrenaline reuptake inhibitor buproprion mitigated TNF- $\alpha$  and IFN- $\gamma$  in mice subjected to LPS-induced inflammation [94], an observation thought to be due to activity at adrenergic receptors. Microglia subjected to treatment with antidepressant agents including reboxetine, fluvoxamine and imipramine all exhibited decreased production of IL-6 stimulated by IFN-y pretreatment [95]. In human studies, strong evidence exists showing neuroprotective effects of the SSRI paroxetine as prophylaxis against IFN- $\alpha$ -induced depression [96]. However, results of other studies on this subject have been mixed [97]. Associated with PANDAS, GAS infections have also been reported to lead to degradation of the serotonin precursor tryptophan [98], hypothetically exacerbating neuroinflammation. Evidence that polymorphisms in cytokine genes may predict antidepressant treatment responsiveness supports a neuroimmune role in the therapeutic effects of these agents [99-101].

#### Antipsychotics

Similar to antidepressants, the therapeutic effects of antipsychotic agents are mediated through neurotransmitter receptor modulation. Unlike antidepressants, antipsychotics largely target the dopamine system, blocking dopamine receptors to minimize the effects of dopamine. Antipsychotic agents have been known to possess significant immunomodulatory properties, particularly on leukocyte cell populations. Antipsychotics have been shown to modulate immune function, primarily cytokine expression and T-cell activation, although the exact mechanism is still not clear. In complement to their possible antimicrobial effects, certain antipsychotics appear to boost the production of memory T cells, and soluble IL-2 receptor. Whereas enhanced TNF- $\alpha$  production has been

associated with clozapine therapy [102], IL-6 may be decreased with antipsychotic therapy [103,104]. Other studies have alluded to anti-inflammatory effects of these agents. Phenothiazine agents, such as chlorpromazine for example, has been shown to inhibit endotoxin-induced sepsis shock in murine models and the growth of *M. tuberculosis* in humans [105,106]. Chlorpromazine also demonstrates mycoplasmal activity possibly by inhibition of transport of the substrates through the membrane of the organisms [107].

Common side effects induced by psychotropic agents, particularly their ability to modulate granulocyte populations, and their antiinflammatory and apparent antibiotic activity confirm an ability to alter immune function and highlights the need for further research.

#### Psychostimulants

Used therapeutically in the treatment of attention deficit disorder/ADHD psychostimulants represent a class of psychoactive drugs that act through facilitation of catecholamine activity. The most accepted mechanism, in relation to their therapeutic effects is the facilitation of noradrenaline and/or dopamine activity through adenosine, nicotinic and adrenergic receptor antagonism. Catecholamines have been shown to play an important role in disorders such as attention deficit disorder/ADHD and depression as disruptions in dopamine and noradrenaline signaling have been implicated in both disorders. Consequent drugs known to target this neurotransmitter network, particular antagonist of adrenergic receptors, have been utilized in the treatment of these disorders.

While psychostimulants have been thought to have less of an impact on the immune system, there is research to suggest that they may exert significant effects on inflammatory mediators, acting as anti-inflammatory agents, an action mediated by their facilitation of noradrenaline activity. Increased inflammation has already been implicated as a potential pathological mechanism in disorders, such as depression, with the finding of cytokine irregularities and other immune irregularities in animal and human studies. Produced primarily in response to stress, catecholamines, such as noradrenaline, exert tonic sympathetic regulation of cytokine production and have been implicated in the maintenance of immunological homoestasis in the CNS. In a rat model utilizing systemic administration of LPS-enhancement of noradrenaline signaling,

achieved by administration of noradrenaline reuptake inhibitor, reboxetine, and  $\alpha$ -2 adenergic receptor antagonist, idazoxan, induced expression of anti-inflammatory cytokine IL-10 [108]. In studies involving the expression of inflammatory cytokines TNF- $\alpha$  and IL-6 from human whole blood administration of reboxetine was shown not only to promote expression of anti-inflammatory cytokines but also inhibit proinflammatory cytokine signaling [109].

#### Atomoxetine

Also used in the treatment of ADHD, atomoxetine differs from traditional psychostimulants by selectively targeting noradrenaline reuptake. Despite the differing mechanism, noradrenaline reuptake inhibitors such as atomoxetine have also been shown to possess significant anti-inflammatory properties through modulation of noradrenaline signaling. In rat models utilizing LPS to induce inflammation, atomoxetine was shown to reduce cortical gene expression of proinflammatory mediators TNF- $\alpha$ , iNOS and IL-1 $\beta$  as well as CD40 and CD11b, markers of migroglial activity. Interestingly when this study was repeated in vitro, these results were not replicated suggesting that the actions of atomoxentine, are mediated by the enhancement of noradrenaline signaling. In another study, atomoxetine not only reduced the expression of proinflammatory cytokines but also downregulated cell-adhesion molecules, important in leukocyte infiltration [110]. Although this has not been implicated in neuropsychitric disorders, infiltration of leukocyte populations often represent compromise of the BBB and may be an important mechanism in disorders such as multiple sclerosis, SC and PANDAS where autoantibody binding to CNS proteins is thought to play a significant role in disease pathology. In addition, the ability of these compounds to regulate TNF- $\alpha$  and iNOS, known to affect BBB permeability, may prove important for future therapeutic interventions.

#### **Future perspective**

Here we have reviewed the pharmacodynamic crossover of antimicrobial agents and psychotropic agents, properties which at times have common pathways of action involving immune modulation. Increasingly, it is becoming evident that neuropsychiatric syndromes represent heterogenous collections of disorders with some overlapping pathologic mechanisms involving dysregulated immune responses. As microbes often affect innate and adaptive immune responses throughout the host, at times inflammatory 'spillover' to CNS immune players leads to cross-activation of pathways responsive to the peripheral signals, but involved in very different processes compared with their peripheral immune counterparts. Further aberrant production of autoreactive antibodies of the IgG subclass that can cross the BBB, allows for yet another avenue of reactive neuroimmunomodulation after microbial infections. Elucidation and characterization of agents with multimodal effects against acute and chronic infections in combination with neuroprotective properties mediated by immune regulation are needed to more effectively treat neuroimmune-mediated disorders, likely represented in part by a variety of psychiatric syndromes and neurologic disorders. With developing advances in functional genomics and proteomics and a better understanding of the determinants of neural network functioning and pathology, pleiotrophic effects of existing agents will provide lead compounds for expanding the armamentarium of neuroprotective agents. These compounds may be discovered and/or rediscovered interventions for use in treating not only the acute, chronic and latent infections, but the immune sequelae of microbial infections. Furthermore, characterization of the immunomodulatory potentials of psychotropic agents may usher in new therapeutic targets for depression, anxiety and other neurocognitive disorders especially in relevant subsets of these syndromes.

Although it is evident that extensive research is needed in this area, the potential role of immune modulation as a therapeutic option for psychiatric disorders opens up a therapeutic avenue that may be a source of important therapeutic alternatives and increased mechanistic understanding of complex disorders with heterogeneous etiologies. The interplay between the immune system and the CNS makes antimicrobial agents potential therapeutic alternatives for some neuropsychiatric disorders. The overlap between immune and CNS pathways and signaling molecules suggest that disruption of the immune system may have secondary effects that extend beyond its localized actions. With this knowledge, there is the potential to characterize the mechanism driving the clinical pathologies in disorders that seem to have a clear immunological component, as many neuropsychiatric disorders have now been observed to have. Similarly, in autoimmune disorders with observed psychiatric presentations



and neuropsychiatric symptoms following infection, this area may be an opportunity to not only further understand the pathological mechanism but also to develop more targeted therapeutic alternatives. Characteristic markers of immune activation including increased expression of proinflammatory cytokines have been observed in psychiatric disorders and have been implicated in their pathological mechanism. In schizophrenia and depression, cytokine irregularities, particularly increased TNF- $\alpha$ , IL-6 and IL-1 $\beta$ expression have been observed, while in schizophrenia autoantibodies for CNS proteins have been observed in cerebrospinal fluid [111,112]. These findings, when coupled with the immunomodulatory and immunosuppressive properties of psychotropic medications strengthen the hypothesis of an immune component to the pathology of psychiatric disorders. Although promising, it must be noted that, like with any therapeutic intervention, the application of antibiotics for these disorders may rest heavily on clinician judgment and medical history and future research. In disorders such as PANDAS where onset is usually sudden and a clear connection has been delineated, the choice may be more obvious. Disorders such as schizophrenia may be more difficult to define, although there are clear immune aspects to this disorder, the efficacy of antibiotic treatment may not be as relevant as damage may be beyond antimicrobial or immunomodulatory interventions at the time of diagnosis. making the need for psychotropic medication necessary. Schizophrenia, thought to have developmental origins, may represent a class of disorders where chronic immunological irregularities have led to permanent and irreversible disruptions in brain function. This is

evidenced from dopamine disruption in these disorders. Nevertheless, this may be a relevant treatment option for exacerbations as stress and infection has been shown to exacerbate symptomology. This may suggest a continued role of the immune system in disease pathology. In addition, this may be a valuable alternative for special segments of the population presenting with nontraditional psychiatric symptoms. Persons who develop psychiatric disorders as a secondary effect due to immune disorders may also benefit from alternative treatment options. Although maintenance may still require psychotropic medications, antibiotics may be important options for treatment-resistant patients or those with frequent exacerbations.

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