Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness

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ABSTRACT

Objectives: The first drug repurposed for the treatment of depression was the tuberculostatic iproniazid. At present, drugs belonging to new classes of antidepressants still have antimicrobial effects. Dysbiosis of gut microbiota was implicated in the development or exacerbation of mental disorders, such as major depressive disorder (MDD). Based on the current interest in the gut-brain axis, the focus of this narrative review is to compile the available studies regarding the influences of gut microbiota in behavior and depression and to show the antimicrobial effect of antidepressant drugs. A discussion regarding the possible contribution of the antimicrobial effect of antidepressant drugs to its effectiveness/resistance is included.

Methods: The search included relevant articles from PubMed, SciELO, LILACS, PsycINFO, and ISI Web of Knowledge.

Results: MDD is associated with changes in gut permeability and microbiota composition. In this respect, antidepressant drugs present antimicrobial effects that could also be related to the effectiveness of these drugs for MDD treatment. Conversely, some antimicrobials present antidepressant effects.

Conclusion: Both antidepressants and antimicrobials present neuroprotective/antidepressant and antimicrobial effects. Further studies are needed to evaluate the participation of antimicrobial mechanisms of antidepressants in MDD treatment as well as to determine the contribution of this effect to antidepressant resistance.

Abbreviations: ACTH, adrenocorticotrophic hormone; BDNF, Brain-derived neurotrophic factor; CCL2, Chemokine (C-C Motif) Ligand 2; CMS, chronic mild stress; CNS, central nervous system; COX 2, cyclooxygenase 2; GABA, gamma-aminobutyric acid; GF, germ-free; GLT1, glutamate transporter 1; HC, healthy controls; HPA, hypothalamic-pituitary-adrenal; IFN- γ , gamma interferon; IgA, Immunoglobulin A; IgM, Immunoglobulin M; iNOS, inducible nitric oxide synthase (iNOS); JB-1, *Lactobacillus rhamnosus*; LPS, lipopolysaccharide; MAO, Monoamine-oxidase; MAOI, Monoamine-oxidase inhibitor; MDD, Major depressive disorder; MIC, minimum inhibitory concentrations; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; PGE2, prostaglandin 2; SPF, specific pathogen free; TCA, tricyclic antidepressants; TLR4, toll-like receptor 4; TNF- α , tumor necrosis factor alpha

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1. Introduction

Major depressive disorder (MDD) is a common and recurrent psychiatric illness associated with significant morbidity and social burden (Nemeroff, 2007). In 2010, the Global Burden Study (GBD) considered MDD the 19th most prevalent disease in the world and the second leading cause of disability (Ferrari et al., 2013; Vos et al., 2012). The major consequence of MDD is suicide, a public-health problem (Jenkins, 2002). Also, depression has been associated with increased risk of severe chronic diseases, such as atherosclerotic heart disease and stroke (Clarke and Currie, 2009). Therefore, these findings emphasize the relevance of depression as a public-health problem and the implementation of effective interventions to reduce its burden.

The first drug used for depression treatment was iproniazid in the 1950s. The choice of this drug was based on its euphoric effects in tuberculosis patients (López-Muñoz and Alamo, 2009). At that moment, the discovery of iproniazid antidepressant effects was especially important because it could relegate Ugo Cerletti's electroconvulsive therapy, the only antidepressant treatment available with significant rates of effectiveness, but used only in highly specific cases (López-Muñoz and Alamo, 2009). Subsequently, it was demonstrated that iproniazid was a monoamine-oxidase (MAO) inhibitor, particularly MAO-A. The role of MAO-A is to convert biogenic (e.g. serotonin and catecholamines) and sympathomimetic (e.g. tyramine and benzylamine) amines into deaminated products (Johnston, 1968). This discovery led to the development of the first class of antidepressants, the MAO inhibitors (MAOIs). Examples of this class include tranylcypromine and phenelzine. Subsequently, the prototype antidepressant molecule, desmethylinipramine, was developed (Ban and Lehmann, 1962). The development of imipramine gave rise to the tricyclic antidepressants (TCAs), a class of drugs whose mechanism of action involves the inhibition of noradrenaline and serotonin reuptake by neurons (Raisman et al., 1979). Later on, the monoamine serotonin was related to the pathophysiology of depression (Lapin and Oxenkrug, 1969). Based on this discovery, the first family of psychoactive drugs with a rational design, the serotonin-specific re-uptake inhibitors (SSRIs) was developed (Altamura et al., 1988). Fluoxetine was thus the first SSRI synthesized, quickly becoming one of the most prescribed antidepressants in the world (Altamura et al., 1988; López-Muñoz and Alamo, 2009). Therefore, thanks to the discovery and subsequent therapeutic use of TCAs and MAOIs, in the 1960s, the monoaminergic theories of depression were developed (López-Muñoz and Alamo, 2009).

Despite the development of different classes of antidepressant drugs, still today delayed onset of action and high rates of drug resistance are the major limitations of antidepressant therapy. These limitations may possibly be related to other mechanisms, than monoamines deficiency, involved in the pathophysiology of depression. Vis-a-vis, oxidative/nitrosative stress, neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis, neurogenesis/neurotrophins and ion channels have been important approaches for research in this field (Bakunina et al., 2015; Castrén and Rantamäki, 2010; Iijima et al., 2010; Maes, 2011; Moylan et al., 2014). More recently, on the basis of the important evidences about the role of gut microbiota in the regulation of behavior and in the pathophysiology of several mental disorders, among them depression, the gut-brain axis and its regulation has been subject of many studies (Foster and McVey Neufeld, 2013).

Dysbiosis refers to an altered balance of the gut microbiota. Indeed, dysbiosis is characterized by decreases in commensal bacteria, most notably the phyla Bacteroidetes and Firmicutes, including the clinically relevant *Faecalibacterium prausnitzii* and increases in adherent/invasive *Escherichia coli* (Jones et al., 2014). This gut microbiota imbalance is also observed in patients suffering from intestinal and extra-intestinal disorders, i.e. allergy, asthma, metabolic syndrome, cardiovascular disease, and obesity (Carding et al., 2015). Interestingly, both intestinal and extra-intestinal disorders are comorbidities of MDD

(Filipovic and Filipovic, 2014; Mayer et al., 2001).

Based on iproniazid antidepressant effects, it is not surprisingly that, at present, drugs belonging to new classes of antidepressants still have antimicrobial effects. In this regard, the antimicrobial effects of antidepressants range from weak to strong depending on the drug (Munoz-Bellido et al., 2000a). For instance, several new antidepressant drugs such as sertraline, fluoxetine, escitalopram and older drugs such as tranylcypromine and imipramine present antimicrobial effects (Lieb, 2004; Munoz-Bellido et al., 2000a). Conversely, β -lactams and tetracyclines also have potential antidepressant properties (Mello et al., 2013; Miyaoka et al., 2012). However, some antimicrobials, such as fluoroquinolones, have also been associated with neuropsychiatric adverse events and mood dysregulation, including depression (Ahmed et al., 2011; Grassi et al., 2001), manic (Bhalerao et al., 2006) and anxiety disorders (Kaur et al., 2016; Rollof and Vinge, 1993).

Thus, in the light of: i) the involvement of dysbiosis in depression and its comorbidities, ii) the antimicrobial effect of some antidepressant drugs and iii) the evidences for antidepressant effect of some antimicrobial agents; this review aims to compile the studies regarding the influences of gut microbiota in behavior and depression as well as to give evidences of antimicrobial effect of antidepressant drugs. We aim to further discuss the possible contribution of the antimicrobial effect of antidepressant drugs to its effectiveness/resistance.

2. Methods

For this narrative review, articles published in English from November 1984 to February 2016 were searched in relevant web datasets (PubMed, SciELO, LILACS, PsycINFO, and ISI Web of Knowledge). Search terms included combinations of the following: “MDD and gut microbiota”; “MDD and dysbiosis”; “behavior and germ-free animals”; “behavior and gut microbiota”; “antimicrobials and antidepressant activity”; “antidepressants and antimicrobial activity”. Two authors (AJMCF and DM) performed independent search of the articles. Four authors selected the relevant articles (DM, CNSS, AJMCF and JQ). Observational, experimental studies in humans and animal models and literature reviews were considered in the search. Inclusion criteria were pre-specified as the following: i) behavioral alterations induced by gut microbiota dysbiosis; ii) effects of stress and depression in gut microbiota, iii) original studies (in vitro and in vivo) and review papers presenting the antimicrobial effect of antidepressants and vice versa and iv) originality and the overall methodological quality of the studies. An exclusion criterion was being a conference abstract. The search retrieved 181 articles, 120 of which were selected.

3. Results

3.1. Gut microbiota and depression

3.1.1. Gut microbiota composition

The human gut contains a complex ecosystem, called intestinal microflora, consisting of a wide range of bacteria (Gerritsen et al., 2011). Studies have estimated that the intestinal microflora has at least 1800 bacterial genera and over 40,000 species of these microorganisms, which together possess about 100 times more genes than the human genome (Forsythe et al., 2010). Recently, the structure of the microbial flora has been better elucidated. Despite the presence of many phyla of bacteria in the gut, the most prominent are the Firmicutes and Bacteroidetes. These phyla comprise 70–75% of the gut microbiota with a Firmicutes/Bacteroidetes ratio of 10.9 in adult individuals (Mariat et al., 2009).

The composition of the gut microbiota varies among individuals (Gerritsen et al., 2011; Mariat et al., 2009). Indeed, the gut microbiota is an extremely dynamic entity, influenced by factors such as genetics, age, diet, metabolism, geography and stress (Mariat et al., 2009;

Yatsunen et al., 2012). In this regard, it was recently suggested that the gut microbiota could be considered a good representation of the genetic and environmental history of a person also contributing to the individual risks of acquiring diseases and response to therapy (Foster and McVey Neufeld, 2013).

Increasing studies points to the importance of gut microbiota to the function of the central nervous system (CNS) (Heijtz et al., 2011). The gut-brain communication involves multiple pathways, such as the autonomic nervous system, the enteric nervous system, the neuroendocrine system and the immune system. Despite the involvement of the aforementioned pathways in this communication, preclinical studies revealed that microbiota seems to present a central role in this function (Foster and McVey Neufeld, 2013).

3.1.2. Behavioral alterations induced by the manipulation of gut microbiota

The evidences of the role of gut microbiota in behavior regulation came from studies with germ-free (GF) animals (Neufeld et al., 2011; Sudo et al., 2004). Importantly, the behavioral alterations of GF animals were observed in several strains of rodents genetically distinct, strengthening the microbiota-behavior relationship (Clarke et al., 2013; Heijtz et al., 2011; Neufeld et al., 2011). Furthermore, GF animals when exposed to antibiotics, probiotics or pathogenic intestinal bacteria presents distinct behavioral alterations, indicating that the behavioral response and brain function of these animals are significantly impacted when the intestinal bacterial status changes (Collins and Bercik, 2009).

Studies have shown that GF animals have decreased anxiety-like behavior in validated tests such as elevated plus maze, light-dark test and open field tests. The overall reconstruction of the gut microbiota of these animals in early stages of life (up to 6 weeks) partially normalized their behavior, while its reconstitution in adult life, maintained the altered behavioral pattern (Neufeld et al., 2011). Deserves mention the fact that some brain alterations presented by GF animals are also observed in depressed patients. As examples of these alterations are reduced levels of the neurotrophin brain-derived neurotrophic factor (BDNF) (Bercik et al., 2011) and changes in the expression of 5-hydroxytryptamine (serotonin) receptor 1A (5HT_{1A}) (Neufeld et al., 2011). Accordingly, increases in BDNF levels, 5-HT_{1A} autoreceptor desensitization and increased 5-HT_{1A} receptor postsynaptic activation are related to the mechanism of action of some antidepressants (Czesak et al., 2012).

An increase in exploratory behavior and hippocampal levels of BDNF was observed in GF BALB/c mice colonized with microbiota from NIH Swiss mice, while the colonization of GF NIH Swiss mice with BALB/c microbiota reduced exploratory behavior (Bercik et al., 2011). In the same study the administration of oral antimicrobials to specific pathogen free (SPF) mice transiently altered the composition of the microbiota and increased exploratory behavior as well as hippocampal expression of BDNF. The changes observed in Bercik et al. (2011) study were independent of inflammatory activity, changes in levels of gastrointestinal neurotransmitters, and vagal or sympathetic integrity.

Taken together, these preclinical studies demonstrate that the intestinal bacterial status in early developmental periods is of great importance to the regulation of behavioral patterns.

3.1.3. Stress-induced alterations in gut microbiota

Early life stress is associated with several disorders ranging from depression to irritable bowel syndrome (Carr et al., 2013; Qin et al., 2014). In line with these studies, it was observed that rat pups when submitted to the model of depression by maternal separation combined with lipopolysaccharide (LPS) challenge, presented higher levels of plasma corticosterone, cytokines (e.g. TNF- α and IFN- γ), increased visceral sensitivity and alteration in the 16S ribosomal RNA gene profile of the fecal microbiota when compared to the control group

(O'Mahony et al., 2009).

Also, the exposition of GF animals to moderate restraint stress was associated with higher levels of adrenocorticotrophic hormone (ACTH) and corticosterone when compared to SPF animals (Sudo et al., 2004). This increase in ACTH and corticosterone release was completely reversed by GF colonization with *Bifidobacterium infantis*, a species of bifidobacteria commonly present in the gastrointestinal tract during childhood, while only partially reversed by nonspecific flora colonization (Collins and Bercik, 2009; Desbonnet et al., 2010). Noteworthy, this reversal of stress response was observed only in animals colonized during early stage of postnatal life. On the contrary, colonization of GF animals with enteropathogenic *Escherichia coli* during early postnatal life exacerbated the HPA axis response to stress. These studies points towards the important role of the gut microbiota in early stages of life to the development of an appropriate stress feedback mechanism during adulthood (Cryan and Dinan, 2012).

Stressful events during adulthood may also change the structure of gut microbiota (Bailey et al., 2011) and stimulate bacterial translocation (Nettelbladt et al., 2003). In this context, mice exposed to chronic restraint stress presented significant reduction of bacteria genus *Bacteriodes* spp. and increase of genus *Clostridium* spp. in cecum samples. These animals also presented higher levels of the pleiotropic cytokine interleukin (IL)-6 and of the chemokine C-C motif chemokine ligand-2 (CCL)-2 (Bailey et al., 2011). Other elegant study showed that adult rats subjected to chronic mild stress (CMS), an acknowledged animal model of depression, presented increased plasma levels of LPS, LPS-binding protein and increased brain levels of the LPS receptor, toll-like receptor 4 (TLR4). Also, CMS increased the levels of interleukin-1 beta (IL-1 β), prostaglandin-endoperoxide synthase 2 (COX-2), prostaglandin (PG)-E₂ and lipid peroxidation while reduced the levels of the anti-inflammatory prostaglandin 15-Deoxy-Delta-12, 14-prostaglandin J₂ (15D-PGJ₂) in brain tissue. Intestinal decontamination, by the use of gram-negative spectrum antibiotics, reduced brain levels of the pro-inflammatory parameters, decreased the systemic levels of corticosterone and LPS as well as increased the levels of the anti-inflammatory prostaglandin 15D-PGJ₂ (Gárate et al., 2011).

The suggested mechanisms underlying stress-induced alterations in gut microbiota are related to sympathetic neural activation and cortisol effects in gut permeability and microbiota composition. In this context, several studies suggest that the activation of noradrenergic fibers located close to intestinal lymphoid organs would facilitate the presentation of enteric bacteria to immune cells of the intestinal mucosa (Lyte, 2011). Indeed, injection of adrenaline in this intestinal epithelium has been shown to increase the capture of pathogenic bacteria in the lymphoid follicles. Also, norepinephrine release stimulates the growth of enteropathogenic bacteria, such as some strains of *E. coli* as well as influences bacterial adherence to the intestinal epithelium (Bailey et al., 2011; Chen et al., 2003; Collins et al., 2012). In relation to cortisol, the activation of HPA axis and the resulting increase in this hormone secretion can cause a local (in the gut) and systemically alteration in immune cells (including cytokine secretion). Cortisol can also alter gut permeability (by increasing gut permeability resulting in enhanced circulating levels of immunomodulatory bacterial components such as LPS) and barrier function as well as change gut microbiota composition towards a more endotoxigenic bacterial strains, such as *Coprococcus*, *Pseudobutyrvibrio* and *Dorea* (Bailey et al., 2011; Cryan and Dinan, 2012).

The traffic of information between the gut and brain involves vagal afferent fibers. This was demonstrated by studies showing that the beneficial effects of the ingestion of probiotics are abolished by vagotomy (Bravo et al., 2011; Perez-Burgos et al., 2013). Of note, Bravo and colleagues showed that the probiotic *Lactobacillus rhamnosus* (JB-1) reduced stress-induced behavioral (anxiety and depression) and corticosterone release, while non stressed animals fed with JB-1 presented region-dependent alterations in GABAA α 2 and GABAB1b mRNA in the brain. These neurochemical and behavioral

alterations were abolished in vagotomized mice (Bravo et al., 2011).

In conclusion, under conditions of stress the activation of HPA axis and sympathetic neural system can disrupt gut permeability and change gut microbiota composition, increasing the circulating levels of immunostimulant bacterial cell wall components such as LPS. These bacterial compounds could promote a local and systemic inflammation response with important consequences to brain biochemistry. Conversely, the gut microbiota and probiotic agents can alter the levels of circulating cytokines, and this can have a marked effect on brain function. Furthermore, vagus nerve is strongly implicated in the traffic of information from gut microbiota to the brain (Cryan and Dinan, 2012; Lyte, 2011).

3.1.4. Dysbiosis in depression

As previously mentioned the gut microbiota presents several beneficial functions to the host, such as: i) protection against pathogenic microorganisms, ii) supply of some essential nutrients to the body, iii) contribution to the metabolism of certain drugs and iv) participation in the absorption and storage of fatty acids (Arumugam et al., 2011). Taking into account the protective functions of gut microbiota, the disruption of the symbiotic relationship between the microbiota and the gastrointestinal tract, i.e. dysbiosis, compromises several functions of the host contributing to the weakening of the immune-intestinal epithelial barrier resulting in bacterial translocation. Of note, small intestinal exposure to bacteria is one powerful trigger of zonulin release, a protein related to intestinal permeability (Fasano, 2011). Zonulin signaling causes rearrangements of actin filaments and induces the displacement of proteins from the junctional complex, thereby increasing gut permeability (Tripathi et al., 2009). High levels of zonulin have been observed in autoimmune and inflammatory diseases (Fasano, 2011). Conversely, autoimmune diseases such as irritable bowel syndrome and pseudomembranous colitis present dysfunction of the intestinal epithelial barrier (Al-Asmakh et al.; Daneman and Rescigno, 2009), being also comorbidities of MDD (Mayer et al., 2001).

Regarding mental disorders, dysbiosis is being observed in patients suffering from schizophrenia, anxiety disorders and depression (Dinan et al., 2014; Foster and McVey Neufeld, 2013). Specifically in MDD patients, a recent study with 46 patients with depression, 29 with MDD (active-MDD), 17 in response to antidepressant treatment (responded-MDD) and 30 healthy controls (HCs) revealed increased levels of Bacteroidetes, Proteobacteria, and Actinobacteria, and reduction of Firmicutes in active-MDD and responded-MDD groups compared to the HC group. Also the MDD group had increased levels of *Enterobacteriaceae* and *Alistipes*, but reduced levels of *Faecalibacterium* (Jiang et al., 2015). Deserves mention the fact that *Alistipes* species are indole-positive microorganisms influencing thus tryptophan availability (Song et al., 2006). Knowing that tryptophan is the precursor of serotonin, increased abundance of *Alistipes* might therefore disrupt the balance of the intestinal serotonergic system. In this regard, Saulnier et al. (2011) found that higher levels of *Alistipes* were associated with a greater frequency of abdominal pain in patients with irritable bowel syndrome speculating thus that *Alistipes* are associated with gut inflammation. Furthermore, *Enterobacteriaceae* family seems to be better adapted for survival in the inflamed gut than are the anaerobic commensals dominant in healthy individuals (Lupp et al., 2007).

Using a large study group of 112 MDD patients and 28 normal controls Maes et al. (2012) demonstrated increased median values of serum IgM and IgA against LPS of the gut commensals Gram-negative *Enterobacteria*, *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae* in MDD patients when compared to controls. These findings indicate that translocated gut commensal bacteria activate immune cells eliciting IgA and IgM responses and that this phenomenon may play a role in the pathophysiology of chronic depression by

causing progressive amplifications of immune pathways. The authors concluded that bacterial translocation may occur secondary to systemic inflammation in depression intensifying and perpetuating the primary inflammatory response once the commensals are translocated or be a primary trigger factor associated with the onset of depression in some vulnerable individuals (Maes et al., 2012).

In summary, dysbiosis, increased gut permeability and bacterial translocation are observed in MDD triggering local and systemic immune response (Jiang et al., 2015; Maes et al., 2012, 2008). In line with this evidence, clinical studies with MDD patients have found increased bacterial translocation and a secondary immune response as a consequence of this translocation (Maes et al., 2012). Together, the weakening of the intestinal epithelial barrier and bacterial translocation influence the central nervous system maintaining the neuroinflammatory alterations in MDD (Cryan and Dinan, 2012; Walker et al., 2014a).

4. Antidepressant agents with antimicrobial effect

As previously mentioned, since its historical origin antidepressant drugs present antimicrobial effects (Chessin et al., 1957; Kristiansen, 1990; Munoz-Bellido et al., 2000b; Lieb, 2004). Currently, the treatment of depression by antidepressants is associated with mechanism unrelated to the antimicrobial effect of these drugs.

In this context, iproniazid shares similar properties with isoniazid. The mechanism of isoniazid bactericidal activity is through formation of isonicotinoyl radicals. These radicals react with the bacterial cofactors NAD and NADPH and produce various compounds capable of inhibiting bacterial cell-wall synthesis (Jena et al., 2014; Lei et al., 2000). Iproniazid is a MAOI. On the basis of its antimicrobial effect, MAOIs can remit infectious diseases such as aphthous ulcers, labial-genital herpes and respiratory infections (Liang et al., 2013). Despite the antimicrobial effects of MAOIs, as far as we know, there are no specific reference in the literature to the antimicrobial mechanism of action of isoniazid-iproniazid derivatives, i.e. isocarboxazid, phenelzine, tranylcypromine and moclobemide, drugs used for the management of treatment-resistant depression (Obregon et al., 2012; Thase, 2012).

Another class of antidepressant drugs, the TCAs, was reported to prevent the growth of intestinal pathogens such as *E. coli*, *Yersinia enterocolitica* (Csiszar and Molnar; Molnar, 1988) and *Giardia lamblia* (Weinbach et al., 1992). Furthermore, TCAs present antiparasitic activity (Molnar, 1988). Bacterial plasmids are extrachromosomal elements that carry genes conferring resistance to one or more antibiotics. The two potential targets for the action of TCAs against plasmids are the replicating plasmid DNA and the DNA gyrase enzyme, both essential for DNA structural conformation. Thus, given that bacterial conjugation is the major source of bacterial genetic advantage, this effect of TCAs opens perspectives for dealing with the major problem of multi resistant strains of bacteria (Csiszar and Molnar; Molnar et al., 1995). Besides this, TCAs presented in vitro activity against *Plasmodium falciparum* (Bitonti et al., 1988; Salama and Facer, 1990) and *Leishmania* spp. (Zilberstein and Dwyer, 1984).

The antimicrobial effect of the SSRIs sertraline, fluoxetine and paroxetine is especially against Gram-positive bacteria such as *Staphylococcus* and *Enterococcus* (Ayaz et al., 2015; Coban et al., 2009; Munoz-Bellido et al., 2000b). In addition, the SSRIs present good activity against potentially toxigenic *Enterobacteria*, such as *Citrobacter* spp., *P. aeruginosa*, *K. pneumoniae* and *M. morganii*, and anaerobic, such as *Clostridium perfringens* and *Clostridium difficile* (Kruszewska et al., 2012; Munoz-Bellido et al., 2000b).

The mechanisms underlying SSRIs antimicrobial effects are not fully understood. One proposed mechanism is inhibition of efflux pumps. This effect may explain the synergistic effect of SSRIs in combination with certain antibiotics, as well as its effects against some strains of bacteria resistant to antimicrobial agents (Bohnert et al.,

2011; Gjestad et al., 2015). This synergistic effect is confirmed by decreases in the minimum inhibitory concentrations (MICs) of antibiotics when combined with antidepressants (J. L. Muñoz-Bellido et al., 2000b; Muñoz-Bellido et al., 1996). In this regard, synergistic effects

were observed by the combination of some antidepressant drugs and antibiotics against resistant microorganisms such as *Corynebacterium urealyticum* (Kristiansen et al., 2007; Muñoz-Bellido et al., 2000b; Muñoz-Bellido et al., 1996).

Table 1

Chemical structure of some antidepressant drugs with their related antimicrobial action.
Source of the chemical structures: PubChem.

Chemical structure	Antimicrobial Action	Reference
Iproniazid	<i>M. tuberculosis</i>	López-Muñoz and Alamo (2009)
Sertraline	<i>S. aureus</i> , <i>Bacillus subtilis</i> , <i>E. coli</i> , <i>Shigella dysenteriae</i> , <i>Salmonella</i> spp., <i>Vibrio cholerae</i> , <i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>Aspergillus</i> spp., <i>Corynebacterium urealyticum</i>	Munoz-Bellido et al. (1996); Samanta (2015); Lass-Flörl (2001)
Fluoxetine	Gram positive bacteria, <i>H. influenzae</i> , <i>M. catarrhales</i> , <i>Campylobacter jejuni</i> , <i>Aspergillus</i> spp. and <i>C. parapsilosis</i>	Munoz-Bellido et al. (2000a); Lass-Flörl (2001)
Paroxetine	Gram positive bacteria, <i>H. influenzae</i> , <i>M. catarrhales</i> and <i>Campylobacter jejuni</i>	(Munoz-Bellido et al., 2000a); Lass-Flörl (2001)
Amitriptyline	<i>S. aureus</i> , <i>K. pneumoniae</i> , <i>Shigella</i> spp., <i>Bacillus</i> spp., <i>Salmonella</i> spp., <i>E. coli</i> , <i>Vibrio cholerae</i> , <i>Vibrio parahaemolyticus</i> , <i>P. aeruginosa</i> , <i>Lactobacillus sporogenes</i> , <i>Citrobacter</i> spp., <i>Cryptococcus</i> spp.	Mandal et al. (2010); (Muthukumar and Janakiraman, 2014)
Escitalopram	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>Proteus mirabilis</i> and <i>Enterobacter cloacae</i> .	Akilandeswari; Ruckmani; Ranjithmathan, 2013.

Ketamine also presents antimicrobial activity (Gocmen et al., 2008). This drug is an N-methyl-D-aspartate (NMDA) antagonist with a rapid onset of antidepressant action (Miller et al., 2014). Indeed, in the last decades, several studies have pointed out to the striking antidepressant effects of ketamine, which can emerge into hours and significantly improve the most of depressive symptoms, even in conditions of treatment-resistant depression (Berman et al., 2000; DiazGranados et al., 2010; Ibrahim et al., 2011). Ketamine was effective against some bacterial species, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes* and *P. aeruginosa* and fungal infections such as *Candida albicans* (Begec et al., 2013; Kruszewska et al., 2012; Gocmen et al., 2008).

Table 1 and Fig. 1 present the chemical structure, antimicrobial activity against microorganisms and antimicrobial mechanism of action of some antidepressant drugs..

5. Antimicrobial agents with antidepressant effects

In recent years antimicrobial compounds were studied for their neuroprotective properties and for their potential as psychotropic medications (Obregon et al., 2012). In this regard drugs like β -lactam antibiotics, for instance, ceftriaxone, were found to promote the expression of the glutamate transporter GLT1, thus presenting neuroprotective properties in animal models of depression (Mineur et al., 2007). Indeed, glutamatergic transmission has emerged as a potential therapeutic target for the development of antidepressant drugs (Medina et al., 2013; Mineur et al., 2007; Sapolsky, 2000) due to the excessive glutamatergic neurotransmission observed in MDD (For a review please read (Mathews et al., 2012)). The tetracycline, minocycline, has been shown to exhibit immunomodulatory and psychotropic properties possibly unrelated to its antibiotic mechanism of action. Minocycline's psychotropic properties, including the antidepressant activity (Miyaoka et al., 2012) have been attributed, for example, to inhibition of oxidative stress through attenuation of the expression of inducible nitric oxide synthase (iNOS), COX-2, and matrix metalloproteinase (MMP) and regulation in glutamatergic neurotransmission

(Chaves et al., 2009; González et al., 2007; Monte et al., 2013; Réus et al., 2014). Additionally our research group showed that doxycycline, a second-generation tetracycline, also presents antidepressant-like properties against LPS-induced depressive-like behavior in mice (Mello et al., 2013). The antidepressant-like effect of doxycycline was associated to a prevention and reversal of brain oxidative and neuroinflammatory alterations induced by LPS (Mello et al., 2013).

D-cycloserine is a second-line bacteriostatic agent for the treatment of *Mycobacterium tuberculosis* being also active against susceptible Gram-negative and Gram-positive bacteria including *Chlamydia*, *S. aureus*, *E. coli*, Enterococci and *Mycobacterium avium* complex microorganisms. This drug was evaluated for a variety of uses including the treatment of MDD displaying antidepressant properties at doses considered subtherapeutic for antimicrobial purposes (Crane, 1959). The isoniazid derivatives including isocarboxazid, phenelzine, tranlylcypromine and the reversible MAO-A inhibitor, moclobemide, present profound efficacy for treatment-resistant depression. Finally, among the macrolide antibiotics, rapamycin is an agent that inhibits the mammalian target of rapamycin (mTOR). mTOR is a key regulator of cell autophagy by controlling the intracellular levels of aggregated proteins and toxic substrates. The modulation of mTOR seems to be a promising target for neuroprotection and antidepressant therapy (Cleary et al., 2008; Ravikumar et al., 2004; Ravikumar and Rubinsztein, 2004; Tang et al., 2002). In this context, it was demonstrated that enhancement of autophagic process is involved in the mood stabilizing effects of lithium (Sarkar et al., 2005). Furthermore, the subchronic administration of rapamycin (10 mg/kg) resulted in antidepressant-like effect in rats and mice submitted to forced swim and tail suspension tests (Cleary et al., 2008).

Besides presenting antidepressant mechanisms, as mentioned above in this section, many antibiotics can have unintended and profound effects on the indigenous microbiota. Taking this into account, previous studies observed changes in gut microbiota induced by minocycline and their relation with MDD treatment (Miyaoka et al., 2012).

Overall, the studies regarding alterations in gut microbiota induced

Fig. 1. Possible mechanisms of antibacterial action of some classes of antidepressant drugs. Monoamine Oxidase Inhibitors (MAOIs) acts through the formation of radicals that react with the bacterial cofactors NAD and NADPH and produce various compounds capable of inhibiting bacterial cell-wall synthesis (Jena et al., 2014; Lei et al., 2000). Selective serotonin reuptake inhibitors (SSRIs) inhibit efflux pumps (Bohnert et al., 2011; Gjestad et al., 2015). Tricyclic antidepressants (TCAs) present antiparasitic activity (Molnár, 1988).

by antimicrobial drugs and its relation with the antidepressant effect of these drugs are still incipient. This calls our attention for the need of further studies evaluating the alterations in gut microbiota of MDD patients in clinical protocols designed to study the antidepressant effect of antimicrobials and vice versa.

Fig. 2 presents the chemical structure of some antimicrobial drugs already studied for their antidepressant effects..

6. Discussion

As previously mentioned, studies have associated dysbiosis, *increased gut permeability and bacterial translocation* with the pathophysiology of MDD (Dinan and Cryan, 2013; Jiang et al., 2015; Maes et al., 2012). Conversely, these alterations are also observed in extra-intestinal and intestinal comorbidities of MDD, for instance, irritable bowel syndrome (Carding et al., 2015; Fadgyas-Stanculete et al., 2014).

Cycloserine

(CRANE, 1959)

Minocycline

(ARAKAWA et al., 2012; MOLINA-HERNÁNDEZ et al., 2008; DEAN et al., 2014; ZHENG; KANEKO; SAWAMOTO, 2015).

Clavulanic acid

(KOST et al., 2011)

Ceftriaxone

(MINEUR; PICCIOTTO; SANACORA, 2007;

ROTHSTEIN et al., 2005)

Methylene blue

(EROGLU; CAGLAYAN, 1997)

Doxycycline

(MELO et al., 2013)

AMOXICILINA

Amoxicillin

(ROTHSTEIN et al., 2005)

Isoniazid

(SALZER; LURIE, 1953; BERMAN, 1955;

OLDHAM, 1955; JOSHI, 1976)

Fig. 2. Chemical structures of antimicrobial drugs and main references related to the antidepressant effect of each drug.

Intestinal microbial dysbiosis observed in depressed patients is associated with increased levels of gut Bacteroidetes, *Enterobacteriaceae*, Alistipes and decreased levels of Firmicutes and Faecalibacterium when compared to healthy subjects (Foster and McVey Neufeld, 2013; Maes et al., 2012), triggering local and systemic immune response (Cryan and Dinan, 2012). Intestinal dysbiosis compromises the gut-brain communication as well as triggers increased gut permeability and bacterial translocation. Bacterial translocation in turn leads to increased blood levels of the bacterial endotoxin LPS in MDD patients (Maes et al., 2012). LPS in turn sustains neuroinflammatory alterations induced by depression (Cryan and Dinan, 2012; Walker et al., 2014b).

Based on the alterations in gut microbiota observed in MDD we can suggest that the use of drugs presenting antimicrobial activity (i.e. some antidepressants, as aforementioned or antimicrobials) may present positive or negative effects that needs to be better evaluated in future preclinical and clinical studies. Thus, one possible positive issue related to the use of drugs with antimicrobial effect for the treatment of depression would be the restoration of gut microbiota balance and the reestablishment of homeostatic conditions, leading to an improvement of brain-gut communication. This homeostasis of brain-gut communication may be of relevance to the efficacy of antidepressant drugs. This hypothesis is reinforced by studies showing that sertraline was at least as cost-effective as or more cost-effective for MDD treatment than other antidepressant drugs (Kaplan and Zhang, 2012), being also a strong candidate as the initial choice of antidepressant in people with acute major depression (Cipriani et al., 2010). Deserves mention the fact that sertraline possesses strong intrinsic antibacterial and antifungal activities (Ayaz et al., 2015; Coban et al., 2009). Another point for reflection is that the MAOIs are drugs used for the management of treatment-resistant depression (Thase, 2012) also presenting important antimicrobial effects (Liang et al., 2013). Furthermore, antidepressants are effective for the treatment of irritable bowel syndrome (Clouse, 2003). Of note, patients with irritable bowel syndrome often have pathological gut microbiota (Whitehead et al., 2002).

On the other hand, one negative effect would be the induction of gut microbial alteration or resistance (Hu et al., 2013) due to the chronic use of antidepressants with antimicrobial activity. This is reinforced by the findings of a populational-based study showing that adults with depression and taking specific antidepressants seem to be more likely to develop *C. difficile* infections (Rogers et al., 2013). Noteworthy, *C. difficile* infection is the most commonly diagnosed cause of antibiotic-associated diarrhea, and has emerged as a major nosocomial infection, surpassing methicillin-resistant *S. aureus* in some hospitals (Miller et al., 2011). The significantly higher risk of *C. difficile* infection was observed in patients taking both the atypical antidepressants mirtazapine and trazodone together (Rogers et al., 2013).

Therefore, several implications, beneficial or deleterious, not fully understood may result from the chronic use of antidepressant drugs with antimicrobial properties and their effects on gut microbiota. In this context, we hypothesize that these antimicrobial properties of antidepressant drugs could also have some relevance for the development of tardive dysphoria. Tardive dysphoria occurs in treatment-resistant depression. Indeed, patients who develop tardive dysphoria present positive initial response to antidepressant drugs and invariably have received high doses of these agents for prolonged time periods (El-Mallakh et al., 2011). Several mechanisms have been classically implicated in the neurobiology of tardive dysphoria, such as desensitization of neurotransmitter receptors and their transporters (Lira et al., 2003; Meyer et al., 2004). Given the influence of gut microbiota in brain neurochemistry (Bravo et al., 2011; Clarke et al., 2013), we speculate that the chronic use of some antidepressant drugs could lead to adaptive alterations in gut microbiota, such as drug-induced resistance, which could contribute to the development of tardive dysphoria. However, further studies are needed to test this hypothesis.

7. Conclusion and future directions

Both antidepressants and antimicrobials present neuroprotective/antidepressant and antimicrobial effects. One proposition of this review is that the antimicrobial effect of antidepressants could be important for the correction of intestinal dysbiosis observed in MDD patients, restoring then the balance of gut microbiota. Contrary to this idea, the chronic use of drugs presenting antimicrobial effects may be related to the development of adaptive alterations in gut microbiota, which effects could be deleterious. This issue could be of great importance since some patients present treatment-resistant depression, although the association of treatment-resistant depression with gut microbiota has not been studied yet.

Finally, although accumulating evidences support the relevance of the microbiota–gut–brain axis for brain functioning and behavior in health and disease, some caveats need to be considered. First, the relative contributions of several components of microbiota–gut–brain axis, such as immune, neural and endocrine systems, to the development of pathological states, such as depression, need to be clarified. Second, it is fundamental to understand how the several microbial strains differentially affect CNS, for example, how the differences in bacterial cell components, metabolite production and genetic variability could interact with host factors, such as immune system. Third, caution need to be taken when translating animal microbiome studies to humans.

Therefore, future studies elucidating the mechanisms by which microbiota interacts with the gut–brain axis will be crucial to understand its involvement in the pathophysiology of depression and to the development of microbiota-derived therapeutic alternatives. Also, clarifying the real contribution of the antimicrobial effects of antidepressants for MDD treatment as well as determining the long-term consequences of these effects to gut microbiota composition and their implications to clinical outcomes could be a promise and future direction for research.

Authors contributions

AJMCF, DFL and DM performed the articles search. AJMCF wrote the first draft. DFL and DM wrote the final version of the review. CNS, JQ, HVNJ and TB designed the tables and figure and revised the final version of the manuscript.

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