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THE PHARMACOLOGICAL ACTION OF ANTIDEPRESSANTS ON THE GASTROINTESTINAL TRACT AND THEIR IMPACT ON HUMAN MICROBIOTA

AÇÃO FARMACOLÓGICA DE ANTIDEPRESSIVOS NO TRATO GASTROINTESTINAL E SEU IMPACTO NA MICROBIOTA HUMANA

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ABSTRACT

Introduction: Antidepressant medications are frequently used in the treatment of Major Depressive Disorder. Currently, Selective Serotonin Reuptake Inhibitors are the most widely prescribed for its treatment. There is a strong connection between the human intestinal microbiota and the nervous system, with this communication being bidirectional. Therefore, bacteria play roles in processes related to brain physiology, psychology, and behavior. **Objective:** Thus, the aim of this review is to present the mechanism of action of Selective Serotonin Reuptake Inhibitors in the gastrointestinal tract and their impact on the microbiota. **Methods:** The review analyzed articles from PubMed, Elsevier, and Cochrane published between 2018 and 2023, using descriptors such as "pharmacology of Selective Serotonin Reuptake Inhibitors," "gut microbiome," and "antidepressants." The inclusion criterion was publications addressing the association between intestinal microbiota and antidepressants in adults. Duplicate articles and dissertations were excluded. A total of 13 articles were selected. **Results:** Selective Serotonin Reuptake Inhibitors affect the structure of intestinal communities. Sertraline, Fluoxetine, and Paroxetine exhibit greater intensity of antimicrobial action. Considering the impact of Selective Serotonin Reuptake Inhibitors on the intestinal microbiota, it is suggested that this environment has the potential to interfere with the efficacy of treatments by considering the potential for dysbiosis induced by prolonged use. **Conclusion:** Sertraline, Fluoxetine, and Paroxetine display greater intensity of antimicrobial action in the intestine, with different levels of absorption leading to variability in susceptibility to medications. Research suggests that the impact of Selective Serotonin Reuptake Inhibitors on the intestinal microbiota has the potential to interfere with pharmacological efficacy.

Keywords: Antimicrobial action; Psychopharmacology; Gut Microbiome; Probiotics; Selective Serotonin Reuptake Inhibitors.

RESUMO

Introdução: *Os medicamentos antidepressivos são utilizados no tratamento do Transtorno Depressivo Maior. Atualmente, os Inibidores Seletivos da Recaptação de Serotonina são os mais amplamente prescritos para esse tratamento. Existe uma forte conexão entre a microbiota intestinal humana e o sistema nervoso, sendo essa comunicação bidirecional. As bactérias desempenham papéis em processos relacionados à fisiologia cerebral, psicologia e comportamento.* ***Objetivo:*** *Revisar e apresentar o mecanismo de ação dos Inibidores Seletivos da Recaptação de Serotonina no trato gastrointestinal e seu impacto na microbiota.*

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Métodos: *A revisão analisou artigos das bases de dados PubMed, Elsevier e Cochrane, publicados entre 2018 e 2023, utilizando descritores: "farmacologia dos Inibidores Seletivos da Recaptação de Serotonina", "microbioma intestinal" e "antidepressivos". O critério de inclusão foi publicações que abordassem a associação entre microbiota intestinal e antidepressivos em adultos. Foram excluídos artigos duplicados e dissertações. Um total de 13 artigos foi selecionado.* ***Resultados:*** *Os Inibidores Seletivos da Recaptação de Serotonina afetam a estrutura das comunidades intestinais. Sertralina, Fluoxetina e Paroxetina apresentam maior intensidade de ação antimicrobiana. Considerando o impacto dos Inibidores Seletivos da Recaptação de Serotonina na microbiota intestinal, sugere-se que esse ambiente tenha potencial de interferir na eficácia dos tratamentos, levando em conta o risco de disbiose induzida pelo uso prolongado.* ***Conclusão:*** *Sertralina, Fluoxetina e Paroxetina apresentam maior intensidade de ação antimicrobiana no intestino, com diferentes níveis de absorção resultando em variabilidade na suscetibilidade aos medicamentos. As pesquisas sugerem que o impacto dos Inibidores Seletivos da Recaptação de Serotonina na microbiota intestinal tem potencial para interferir na eficácia farmacológica.*

Palavras-chave: *Ação antimicrobiana; Psicofarmacologia; Microbioma Intestinal; Probióticos; Inibidores Seletivos da Recaptação de Serotonina.*

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed as antidepressants, particularly for the treatment of major depressive disorder (MDD). Their proven effectiveness in conditions such as obsessive-compulsive disorder, generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD), combined with a lower incidence of anticholinergic side effects, has contributed to a significant 58% increase in the use of these medications in the Brazilian population between 2017 and 2021 (Sheffler, Patel, Abdijadid, 2023; Rocha, 2023).

Despite the popularity of SSRIs, their effectiveness in MDD remains limited: only 30-40% of patients achieve remission, while 20-40% experience recurrence, even with continuous treatment (Otte *et al.*, 2016; McGovern, Hamlin, Winter, 2019). MDD is a condition that profoundly impacts daily life and imposes a high social burden, requiring a broader understanding of the factors that interact with SSRIs to optimize treatment (Ahmadimanesh *et al.*, 2019; Czarny *et al.*, 2018; Bondarenko, Slominsky, 2018; McGovern, Hamlin, Winter, 2019).

The communication between the enteric mechanisms of the gut microbiota (GM) and the central nervous system (CNS) is bidirectional, with bacteria playing key roles in brain physiology, psychology, and human behavior (Colomer *et al.*, 2019). In recent years, the composition of the GM has been linked to various diseases, including psychiatric disorders (Moya and Ferrer, 2016; Rojo *et al.*, 2017). This occurs because GM components can cross the intestinal barrier, being transported through the bloodstream to other organs, where they directly affect their function (Winter *et al.*, 2018).

The gut microbiota plays a significant role in the pathogenesis of depression and in the response to antidepressant treatment. A study by Liu *et al.* (2023), conducted with MDD patients, showed that

inflammatory depression is associated with specific alterations in the composition of the GM, including reduced levels of short-chain fatty acids such as propionic and butyric acids. These changes were correlated with depressive behaviors in mouse models subjected to fecal microbiota transplantation (FMT). Supplementation with *Clostridium butyricum* was effective in normalizing the microbiota, reducing inflammation, and alleviating depressive symptoms.

The effects of *Bifidobacterium breve* supplementation in patients with MDD were investigated through a randomized, double-blind, placebo-controlled clinical trial over eight weeks. The study demonstrated that *Bifidobacterium breve* CCFM1025 significantly reduced depressive symptoms (assessed using the HAM-D and MADRS scales) and improved gastrointestinal symptoms. Additionally, the probiotic modulated the gut microbiota, increasing the abundance of *Bifidobacterium*, which altered tryptophan metabolism, potentially linking it to its antidepressant effects (Tian *et al.*, 2022).

The microbiota and its byproducts can influence the nervous system through various pathways, such as vagal signaling, the production of neuroactive metabolites (such as neurotransmitters and short-chain fatty acids), and immune system modulation (Bonaz *et al.*, 2018; Fung *et al.*, 2017; Kasubuchi *et al.*, 2015; Rooks and Garrett, 2016; Stilling *et al.*, 2016; Yano *et al.*, 2015). Although the results are promising, the mechanisms of action of these microorganisms vary depending on the host organism, which is determined by the presence and composition of specific microbial communities and their interaction with the environment (Moya and Ferrer, 2016). The goal of this review is to discuss the mechanisms of action of selective serotonin reuptake inhibitors (SSRIs) in the gastrointestinal tract and their impact on the microbiota.

METHODS

This is a qualitative narrative literature review, which is divided into stages of analysis without establishing a rigorous and replicable methodology in terms of data reproduction and responses to specific questions (Martins, 2018).

It serves as a means of updating knowledge on a specific topic, aiming to highlight ideas, methods, and themes that receive greater or lesser emphasis in the literature (Martins, 2018). Since this is a bibliographic analysis of the pharmacological action of antidepressants in the gastrointestinal tract and their impact on the microbiota, the following databases were selected: PubMed, Elsevier, and Cochrane. The search was conducted in September 2023, covering studies from the last five years.

The chosen search descriptors were “pharmacology of SSRIs,” “gut microbiome,” and “antidepressants,” which were used individually or in combination. The inclusion criteria required that the selected publications contain these terms in the title or keywords, or explicitly mention in the abstract the association between the intestinal microbiota and the pharmacological aspects of antidepressants in adult individuals.

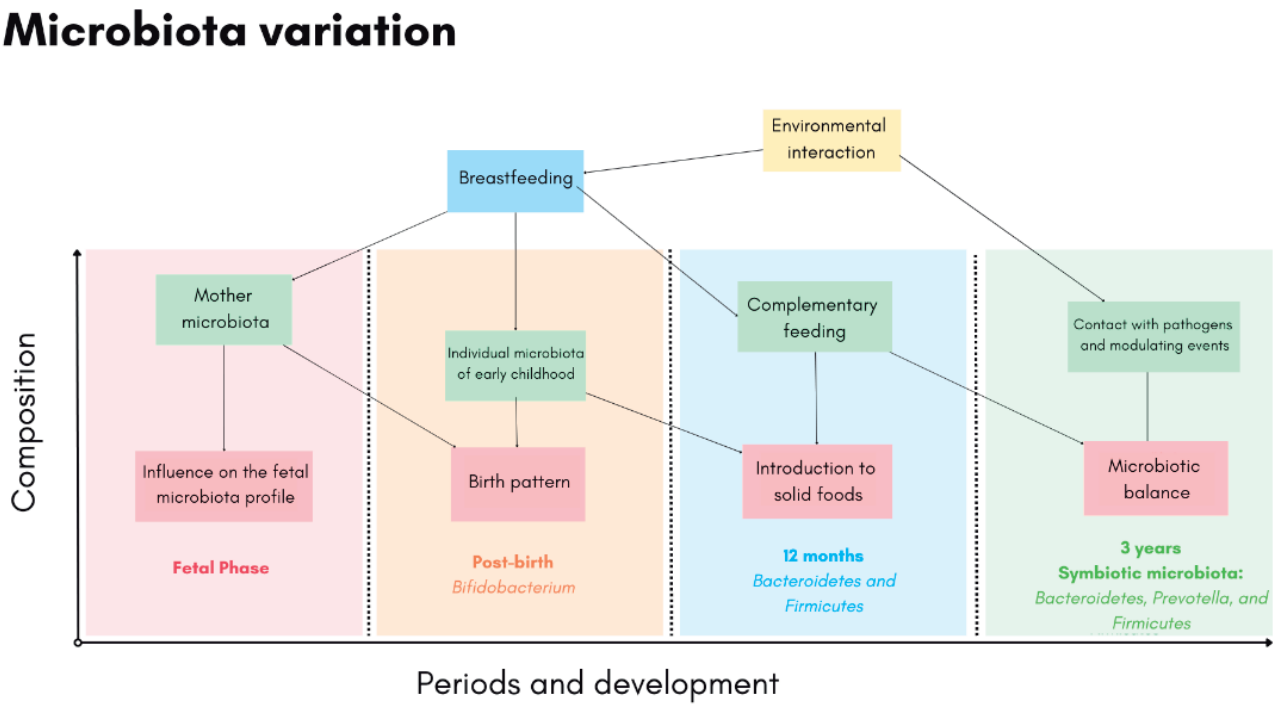
Duplicate articles - i.e., publications found in more than one database - along with dissertations and theses were excluded. Ultimately, 13 articles were selected for this review.

RESULTS AND DISCUSSION

MICROBIOME DYNAMICS AND DIVERSITY

The complexity of microbial communities arises from the intricate relationships between microbial species and their environments. The literature suggests that these communities are naturally inclined toward a balanced and stable composition, with this stability being either facilitated or hindered by host regulation and adequate nutrient intake - factors that begin influencing microbiota development even during gestation, as depicted in Figure 1 (Mehta *et al.*, 2018).

Figure 1 - Individual microbiota variation.



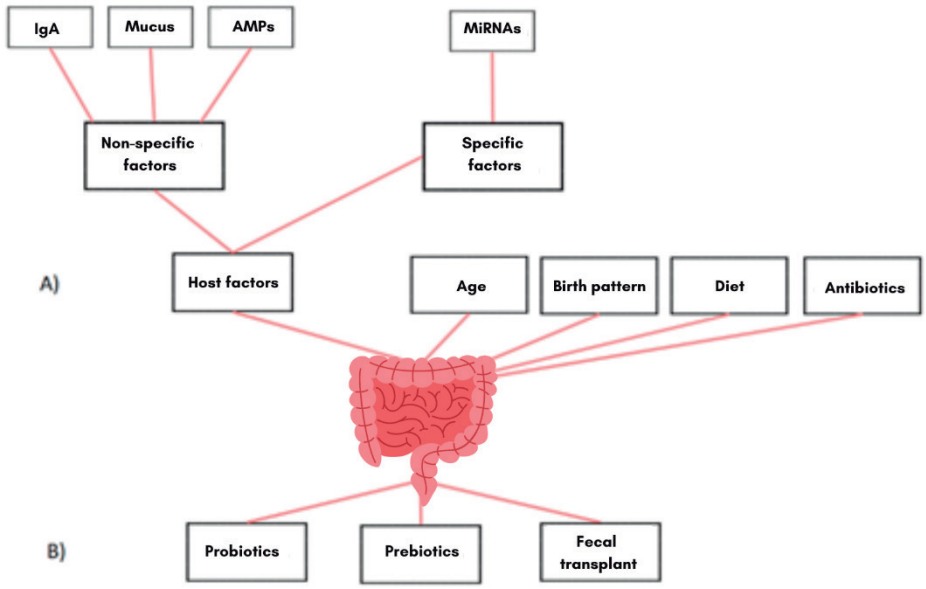
Author's production
Timeline of Human Microbiota Formation, Development, and Species Prevalence by Life Stage.

The balance of the microbial ecosystem is referred to as eubiosis, characterized by a predominance of beneficial species. Conversely, a predominantly negative composition leads to the condition of dysbiosis, which indicates a pattern where "beneficial bacteria" are no longer able to control "harmful bacteria," disrupting the harmony among species in the intestine (Al-Rashidi, 2021).

A variety of environmental and lifestyle-related factors, such as drug consumption and antibiotic use, can exacerbate the dysbiotic process, as illustrated in Figure 2 (Cryan and Dinan, 2019;

Kundu *et al.*, 2017; Rojo *et al.*, 2017). However, the tendency is for the gut microbiota to eventually return to its original balanced state over time (Rojo *et al.*, 2017). Pharmacological agents, even if not directly intended for intestinal purposes, have the ability to influence the diversity of the individual microbiota (Maier *et al.*, 2018; Zimmermann *et al.*, 2019). Given the diversity of the intestinal ecosystem, it is reasonable to assume that certain microorganisms may be capable of metabolizing specific types of drugs, and this action could either inhibit or promote growth, depending on the species (Zimmermann *et al.*, 2019), thereby affecting the entire microbial community by altering its overall diversity.

Figure 2 - Modifying Elements of the Intestinal Microbiota and Ways to Modulate.



(A) Factors affecting the gut/microbiota. (B) Ways to modulate the intestinal microbiota. Legend: AMPs - antimicrobial peptides; IgA - immunoglobulin A; miRNA - microRNA; FMT - fecal microbiota transplantation. Adapted from Hasan; Yang, 2019

Antidepressant medications, especially Selective Serotonin Reuptake Inhibitors (SSRIs), exhibit antimicrobial activity and can impact the gut microbiota during prolonged treatments. However, for these medications to exert a significant effect, they must be present in sufficient concentrations in the intestinal lumen. Therefore, this impact is dependent on the pharmacokinetic mechanism, only affecting the intestinal environment if the drug remains in the body for a sufficient period (McGovern, Hamlin, and Winter, 2019). Additionally, Maier *et al.* (2020) demonstrated that these antidepressants have antimicrobial activity against various intestinal bacteria, with minimum inhibitory concentrations ranging from 75 to 800 μg/mL, which may lead to adaptive changes in the microbiota. The study by Vasconcelos *et al.* (2022) compiles data on the antimicrobial activity of SSRIs such as sertraline, fluoxetine, and paroxetine, highlighting their synergistic action with antibacterial and antifungal agents, further reinforcing the clinical relevance of these interactions.

PHARMACOLOGICAL MECHANISMS OF SSRIs IN THE GASTROINTESTINAL TRACT

Selective serotonin reuptake inhibitors (SSRIs) are one of the medication classes available for psychotherapies, being the most commonly prescribed to treat depression due to their high efficacy and tolerability. The mechanisms of action and therapy of SSRIs are centered on reducing the reuptake of serotonin; these drugs exert inhibitory action on the neurotransmitter reuptake, thereby increasing the activity of serotonin in brain tissue (Chu; Waehwa, 2023). Currently, the six main drugs marketed within this class are fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine. Although the main mechanism of action is similar among these, each SSRI has its own pharmacokinetics and pharmacodynamics, as well as side effects (Edinoff *et al.*, 2021). In general, SSRIs inhibit the serotonin transporter (SERT) in the presynaptic terminal of the axon, resulting in an increase in the amount of serotonin in the synaptic cleft, which can stimulate postsynaptic receptors for an extended period (Chu; Wadhwa, 2023). The medications in this class differ in their degree of selectivity for binding to the serotonin transporter, as well as their potency of serotonin reuptake inhibition; however, there is no evidence that these factors lead to clinically relevant differences in treatment efficacy (Edinoff *et al.*, 2021).

The mechanism by which SSRIs affect the occupancy of serotonin transporters (SERT) is still not fully understood. Even at lower therapeutic doses, these medications achieve an average of 80% SERT occupancy. However, for some patients, higher doses of the drug are necessary for their symptoms to remit or be attenuated, suggesting that SERT inhibition may be the primary mechanism of action for this class of medications (Fries *et al.*, 2023). Furthermore, studies indicate that approximately 80% occupancy of the serotonin transporters is directly associated with the therapeutic efficacy of SSRIs, with this level typically achieved at minimal therapeutic doses. The fact that higher doses are needed in some cases to relieve symptoms further supports the hypothesis that SERT inhibition may be a central mechanism of action for these drugs. It is also important to note that the relationship between SSRI dose and SERT occupancy is nonlinear, with a plateau reached at higher doses (Meyer *et al.*, 2004; Sørensen, Ruhé, and Munkholm, 2021).

EXPOSURE OF THE INTESTINAL MICROBIOTA TO SSRIs

In addition to their therapeutic effects in the treatment of depression, some SSRIs exhibit direct antibacterial effects, such as on Staphylococci and Enterococci, which are vulnerable to sertraline, fluoxetine, and paroxetine (Shen *et al.*, 2021). To understand such a connection, it is necessary to recognize that SSRIs are lipophilic, dissolve slowly, and their passive absorption depends on drug concentration (McGovern; Hamlin; Winter, 2019).

The onset of action of antidepressant medications can vary significantly among different classes and types of drugs. In general, Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine (FLU), sertraline (SER), and fluvoxamine (FLX) may take several weeks for therapeutic effects to be fully perceived. This delay is due to the process of serotonin receptor regulation in the brain, which takes time to establish. On the other hand, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) such as venlafaxine and duloxetine may have a slightly faster onset of action, with therapeutic effects becoming noticeable within a few weeks. These medications act on multiple neurotransmitter systems, which may accelerate the onset of their efficacy (Pittenger and Bloch, 2014).

The estimation of SSRI concentration should be based on gastric emptying time and intestinal transit. Fluoxetine (FLU), sertraline (SER), and fluvoxamine (FLX) are not absorbed to the same extent when compared to escitalopram (ESC) and citalopram (CIT), which justifies why these drugs take less time to reach their peak plasma concentration (McGovern; Hamlin; Winter, 2019). It is estimated that due to the digestion mechanism, significant amounts of FLU, SER, PRX, and FVL remain in the colon for at least 4 hours, which is sufficient time for SSRIs to exert antimicrobial effects, as this region harbors the highest microbial abundance in the GI tract (McGovern; Hamlin; Winter, 2019).

Ramsteijn and colleagues (2020) demonstrated that treatment with SSRIs can alter the concentration of fecal amino acids during pregnancy and lactation. These amino acids are negatively related to the abundance of bacterial taxa such as *Prevotella* and *Bacteroides*. This supports the idea that intestinal exposure to SSRIs may be responsible for increasing the excitability of primary afferent neurons in the myenteric plexus, which, when altered in terms of velocity, can modify the diversity of the intestinal microbial flora (Shen *et al*., 2021).

Considering that antidepressant treatment occurs daily and for an indefinite period, it is estimated that bacterial communities present in the small intestine and colon are exposed to considerable concentrations of drugs for an average daily period of 4 hours. Drugs like SER and FLU exhibit stronger inhibitory effects on gram-positive bacteria due to the fact that different strains have varying susceptibility to each type of SSRI (McGovern; Hamlin; Winter, 2019). Given the uncertain effects of SSRIs on the composition of the gastrointestinal community, there is evidence that the antimicrobial effect may lead to consequences for the brain by inducing principles of dysbiosis, which can influence individual behavior (McGovern; Hamlin; Winter, 2019).

The interaction between antidepressants and the gut microbiota has become increasingly relevant in the context of psychopharmacological treatments, particularly regarding Selective Serotonin Reuptake Inhibitors (SSRIs). Studies have shown how psychotropic drugs, including antidepressants, antipsychotics, and benzodiazepines, alter the composition of the gut microbiota, highlighting the importance of using prebiotics and probiotics as potential interventions to address drug-induced dysbiosis (Silveira *et al.*, 2024).

Since dysbiotic conditions may impact the effectiveness of antidepressants, it suggests that modulating the gut microbiota could improve the response to treatment (Siopi *et al.*, 2020).

The connection between the gut microbiota and antidepressants extends beyond dysbiosis; it also involves the gut-brain axis, which has been shown to play a crucial role in regulating depressive symptoms. A 2020 review indicated that probiotic consumption could help alleviate depressive symptoms by influencing this axis (Souzedo *et al*., 2020). Additionally, the gut microbiota has been identified as a determinant factor in the success of SSRI treatment, playing a significant role in the response to antidepressant therapy by affecting host metabolic pathways, thereby influencing treatment efficacy (Jiang *et al*., 2024).

Furthermore, the antimicrobial activity of antidepressants, including SSRIs, has been demonstrated in various studies, highlighting their ability to inhibit the growth of normal gut microbiota bacterial strains (Rukavishnikov *et al*., 2023). This suggests that the complex interaction between antidepressants and the gut microbiota, both directly and indirectly, could become a valuable therapeutic strategy for optimizing the effects of antidepressant treatments and preventing microbiota-related side effects (Borgiani *et al*., 2024).

CONCLUSION

In conclusion, there is ample evidence that SSRIs affect the structure of intestinal communities. Although there are no direct investigations on the effect of this pharmacological class on human dysbiosis, there is considerable research investigating the antimicrobial properties of SSRIs. Sertraline, fluoxetine, and paroxetine exhibit higher intensity of antimicrobial action in the intestine, but there are differences in their absorption rates and gastrointestinal transit, which may eventually lead to variability in susceptibility to different drugs. Considering the impact of SSRIs on the GI tract, research suggests that this environment has the potential to interfere with treatment efficacy, particularly considering the potential for dysbiosis induced by prolonged drug use. Thus, there is a need for research to investigate the role of the gut-brain axis in the efficacy of pharmacological treatments, considering their antimicrobial activity in specific intestinal colonies both in vitro and in vivo to determine the effect this activity has on treatment efficacy, given that these microorganisms play a significant role in human physiology.

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