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DOI: https://doi.org/10.1016/j.brainresbull.2024.110883

Brain Research Bulletin 207 (2024) 110883

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

Potential effects of the most prescribed drugs on the microbiota-gut-brain-axis: A review

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ARTICLE INFO

Keywords:
Drug-induced
Dysbiosis
Bacterial metabolites
Metformin
PPIs
NSAIDs
Anti-depressants
Statins
Depression
Multiple sclerosis
Parkinson's
Alzheimer's

ABSTRACT

The link between drug-induced dysbiosis and its influence on brain diseases through gut-residing bacteria and their metabolites, named the microbiota-gut-brain axis (MGBA), remains largely unexplored. This review investigates the effects of commonly prescribed drugs (metformin, statins, proton-pump-inhibitors, NSAIDs, and anti-depressants) on the gut microbiota, comparing the findings with altered bacterial populations in major brain diseases (depression, multiple sclerosis, Parkinson's and Alzheimer's). The report aims to explore whether drugs can influence the development and progression of brain diseases via the MGBA. Central findings indicate that all explored drugs induce dysbiosis. These dysbiosis patterns were associated with brain disorders. The influence on brain diseases varied across different bacterial taxa, possibly mediated by direct effects or through bacterial metabolites. Each drug induced both positive and negative changes in the abundance of bacteria, indicating a counterbalancing effect. Moreover, the above-mentioned drugs exhibited similar effects, suggesting that they may counteract or enhance each other's effects on brain diseases when taken together by comorbid patients. In conclusion, the interplay of bacterial species and their abundances may have a greater impact on brain diseases than individual drugs or bacterial strains. Future research is needed to better understand drug-induced dysbiosis and the implications for brain disease pathogenesis, with the potential to develop more effective therapeutic options for patients with brain-related diseases.

Synonyms for the bacterial names

Names mentioned in this review	Their synonyms as per NCBI ((NCBI), 2023)
Firmicutes	Bacillota
Clostridium glycyrrhizinilyticum	*Mediterraneibacter glycyrrhizinilyticum*
Lactobacillus brevis	*Levilactobacillus brevis*
Bacteroidetes	Bacteroidota
Lawsonibacter phoceensis	*Lawsonibacter asaccharolyticus*
Clostridium coccoides	*Blautia coccoides*
Ruminococcus gnavus	*Meditarraneibacter gnavus*
Eubacterium	*Anaerobutyricum*
Eubactrium hallii	*Anaerobutyricum hallii*

1. Introduction

Humans host different microbial compositions in different body parts, the biggest being in the gastrointestinal tract. Microbial communities can produce metabolites, which help in different processes of the human body. Dysbiosis is characterized by a disruption of the microbiome resulting in an imbalance in the microbiota, changes in their functional composition and metabolic activities, or a shift in their local distribution. Dysbiosis can influence diseases varying from hepatic, cardiovascular, and neurological to cancerous and autoimmune diseases such as inflammatory bowel disorders (IBDs). Recent research emphasises the complex bidirectional communication between gut commensals and the brain, especially regarding their implications in

Abbreviations: AD, Alzheimer's disease; Bact2, Bacteroides enterotype 2; BBB, blood brain barrier; BMI, Body max index; CDI, *Clostridium difficile* infection; CNS, central nervous system; EECs, enteroendocrine cell; ENS, enteric nervous system; GABA, γ-Aminobutyric acid; GBA, gut-brain axis; GF, germ-free; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1; GM, gut microbiota; HPAA, hypothalamic - pituitary adrenal axis; IBDs, inflammatory bowel disorders; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MET, metformin; MGBA, microbiota-gut-brain-axis; MS, multiple sclerosis; NSAIDs, non-steroidal anti-inflammatory drugs; PD, Parkinson's disease; PPIs, proton-pump inhibitors; PYY, peptide YY; RCT, randomised control trial; SCFA, short chain fatty acid; SIBO, small intestinal bowel overgrowth; SSRIs, selective serotonin-reuptake inhibitors; TLR4, toll-like receptor 4.

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https://doi.org/10.1016/j.brainresbull.2024.110883
Received 12 October 2023; Received in revised form 12 January 2024; Accepted 16 January 2024
Available online 18 January 2024

neurological diseases (Agnihotri and Mohajeri, 2022; Knuesel and Mohajeri, 2021). Furthermore, preclinical studies with animal models have been able to reproduce findings of alterations in gut microbial composition to show the microbiota's influence on brain pathologies. This evidence suggests that human gut bacteria may contribute to brain physiology and pathology (Morais et al., 2021). New pharmaceutical products with live bacterial strains, i.e., probiotics, or a well-thought-out diet have been shown to restore the gut microbiota's (GM) integrity and improve these repercussions to some extent (Beam et al., 2021).

Almost 15'000 pharmaceutical drugs have been developed so far to treat a wide range of health concerns (Online, 2022). In 2021, 66% of the US population was on prescribed drugs. Canada had around 65% (2019) while more than 26% (2020) of UK citizens and over 35% (2018) Australians were prescribed drug users (SingleCare.com, 2022). Other OECD (Organisation for Economic Co-operation and Development) countries showed a rise in many commonly used medicines as well: between 2000 and 2019 anti-hypertensive drug consumption increased by 65%, anti-diabetic agents and anti-depressants doubled and lipid-modifying agents almost quadrupled (OECD iLibrary, 2021). Over-the-counter self-medication in India is around 52%, portraying an increasing health risk due to the potential unwanted side effects (Bindu Shajan Perappadan, 2015).

Some of these drugs are prescribed for chronic conditions such as diabetes, hypertension, cancer and arthritis. The most common drug classes used worldwide are antidiabetic and cardiovascular drugs, pain relievers, proton-pump inhibitors and antidepressants (ClinCalc.com, 2020). The WHO (World Health Organisation) highlights some of the drugs belonging to the aforementioned classes, essential for the basic healthcare system (Organisation, 2021). Many of these "essential" drugs, when taken together (e.g., by multimorbid patients), may counteract each other's effects and side-effects. Therefore, it is intuitive that the knowledge of both their effects and side-effects is of profound importance to optimally treat patients.

Antibiotics are important for human health. One major side effect of antibiotics, however, is a severe alteration of gut microbial compositions. Numerous studies, moreover, show a strong relationship between antibiotic-induced dysbiosis and the gut-brain axis (GBA). Other pharmaceutical drugs such as antidepressants, statins, non-steroidal anti-inflammatory drugs and many more, are reported to possess similar gut-microbiome-altering effects (Essmat et al., 2023; Lagadinou et al., 2020; Zádori et al., 2023). Therefore, we hypothesise a connection between the agents with "newly-found" antimicrobial properties and their mechanisms of affecting the microbiota-gut-brain axis (MGBA).

This review aims to gain knowledge about drug-induced dysbiosis, and the putative mechanisms involved, occurring due to medication being taken daily on the grounds of other morbidities such as diabetes or cardiovascular diseases. The discussed drug-induced dysbiosis is then extrapolated to seek future perspectives about its possible effects influencing the MGBA. Hence, this paper will summarise gut microbiota (GM) alterations generated by metformin (MET), proton-pump inhibitors (PPIs), statins, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-depressants. Sequentially, the mode of action for their influence on the microbiota-gut-brain axis will be postulated for major neurological and neurodegenerative diseases diagnosed in adults: depression, multiple sclerosis (MS), Parkinson's (PD) and Alzheimer's disease (AD). The mentioned bacterial names are summarised by taxonomical order in the section Supplementary Material under Figs. S1, S2, S3, S4, S5, S6, S7, S8, S9 and S10.

2. Materials and methods

PubMed was searched for articles under two different aspects. First, the search was for articles regarding the medication metformin, proton-pump-inhibitors, NSAIDs, statins, SSRIs and anti-depressants with gut microbiota. Excluded keywords were antibiotic, probiotic and prebiotic. The search results were until August 2022 (Fig. 1). For qualitative and quantitative analysis this review focuses more on human studies than animal studies.

Afterwards, the second search comprised articles with the keywords gut microbiota and gut-brain axis with the respective diseases: Depression, Alzheimer's, Parkinson's and Multiple Sclerosis. Here the search was limited span to the last 6 years (2017–2023) and to "humans". Excluded keywords using the advanced search in PubMed were: probiotics, antibiotics, prenatal, maternal, irritable bowel syndrome, diet,

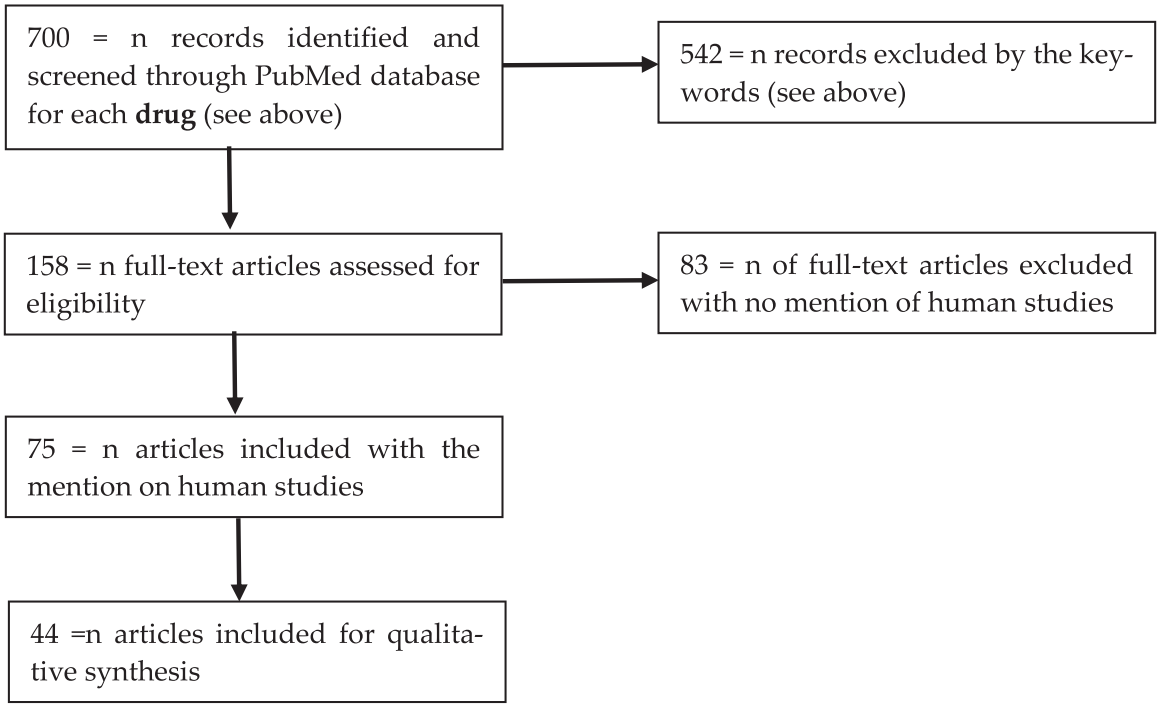

Fig. 1. Flow diagram for the systematic approach of the review (search for drugs) with PRISMA criteria (Statement, 2020) (This is a 2-column fitting image/figure.).

alcohol, infants, children, adolescent, cancer, chemotherapy, cirrhosis, and obesity (Fig. 2). These keywords were also used to eliminate articles for the abovementioned drugs during screening.

Articles that were redundant, not published in English, that had study cohorts concerning diseases not treated by the reviewed drugs, had no reliable control set, were only animal-based, or had no access granted through the institution articles were not taken into consideration. Reports mentioned in the references of the chosen articles were added as per the need.

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3. Gut microbiota

Different microbes inhabit various parts of the human body, giving each body part its unique flora. The microbiome in general consists of bacteria, viruses, archaea, parasites, fungi and eukaryotes (Adak and Khan, 2019; Beam et al., 2021; Liang et al., 2018; Sidhu and van der Poorten, 2017). They encode over 232 million genes, suggesting their essential role in human metabolisms (Eicher and Mohajeri, 2022; Morais et al., 2021). The gut inhabits the largest proportion of these microorganisms adding up to 100 trillion microbes with about 5000 species and weighing approximately 2 kg (Beam et al., 2021; Gomaa, 2020; Sidhu and van der Poorten, 2017). The focus of this article will remain on the bacterial composition of the gastrointestinal tract i.e., the stomach and intestines.

After the GM is acquired in the maternal womb and at birth, its interindividual compositional changes over the life's time span with age and different life experiences such as stress (Adak and Khan, 2019). The gut microbiota (GM) is influenced by environmental and lifestyle factors such as ageing, geographical location, ethnicity, diet, drugs, toxins and disease (Adak and Khan, 2019; Cryan et al., 2019; Koo et al., 2019). A study in the UK, based on twin pairs' faecal samples, also pointed to the role of the host's genetics influencing the GM (Adak and Khan, 2019).

A growing body of evidence discusses the possibility of GM being an important player in health and diseases such as neurodegenerative, cardiovascular, hepatic and autoimmune disorders. GM may also play an apparent role in the bioavailability of drugs and their efficacy, be it for lifestyle diseases such as diabetes mellitus type 2, hypertension, metabolic syndrome, or for life-threatening diseases such as neurological disorders or cancer (Weiss and Hennet, 2017). These findings ignited the idea of the human body and its microbiome living in a symbiotic relationship; the latter having its own-generated internal communication with the human body by direct or indirect mechanisms (Morais et al., 2021) (explained below in "Microbiota-Gut-Brain axis" section). These mechanisms involve metabolising nutrients, creating a strong host immune system and intestinal barrier integrity, producing enzymes, vitamins (e.g., vitamin K) and neurotransmitters (e.g., serotonin), and maintaining the homeostasis between beneficial and opportunistic bacterial species, i.e., eubiosis (Beam et al., 2021).

Eubiosis defines the homeostatic state in microbial compositions. The term 'dysbiosis' (first used by Bai in 1985; (Otani et al., 2017)) defines the upper hand of opportunistic and harmful bacteria over the beneficial ones, resulting in leaky gut, imbalance in the host immune system and pro-inflammatory responses. Dysbiosis leads to systemic inflammation and the onset of disorders such as metabolic syndrome, type 2 diabetes, neurological diseases or autoimmune diseases. Dysbiosis may be induced by environmental or lifestyle factors (Beam et al., 2021).

3.1. Gut flora composition and testing

Different bacterial populations proliferate in different parts of the digestive tract due to varying microenvironments. Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia and Cyanobacteria build the seven dominant phyla. In adults, the gut comprises 90% of Bacteroidetes (mostly gram-negative and mainly *Prevotella*) and Firmicutes (generally gram-positive and mainly *Clostridium, Ruminococcus*, and *Eubacterium*) (Adak and Khan, 2019; Gomaa, 2020; Liang et al., 2018; Pellegrini et al., 2018). Especially, the ratio of Bacteroidetes and Firmicutes plays a crucial role in the inflammation processes with a shift towards a pro-inflammatory microbiome (Adak and Khan, 2019; Gomaa, 2020; Liang et al., 2018; Pellegrini et al., 2018; Wang, Huang et al., 2021; Weiss and Hennet, 2017). A summary of gut bacterial composition residing in the stomach and intestines are explained in (Fig. 3). To distinguish these bacterial colonies based on their characteristics and area of habitancy, faecal samples, biopsies and aspirates are tested. Urine samples and blood samples are checked to

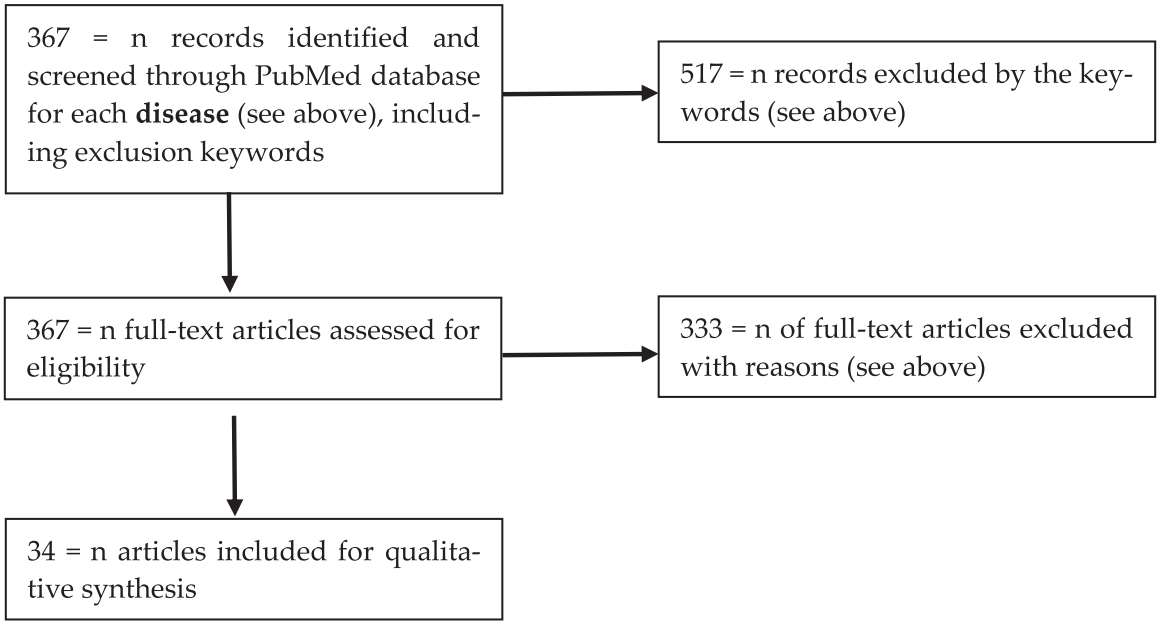

Fig. 2. Flow diagram for the systematic approach of the review (search for diseases) with PRISMA criteria (Statement, 2020) (This is a 2-column fitting image/figure.).

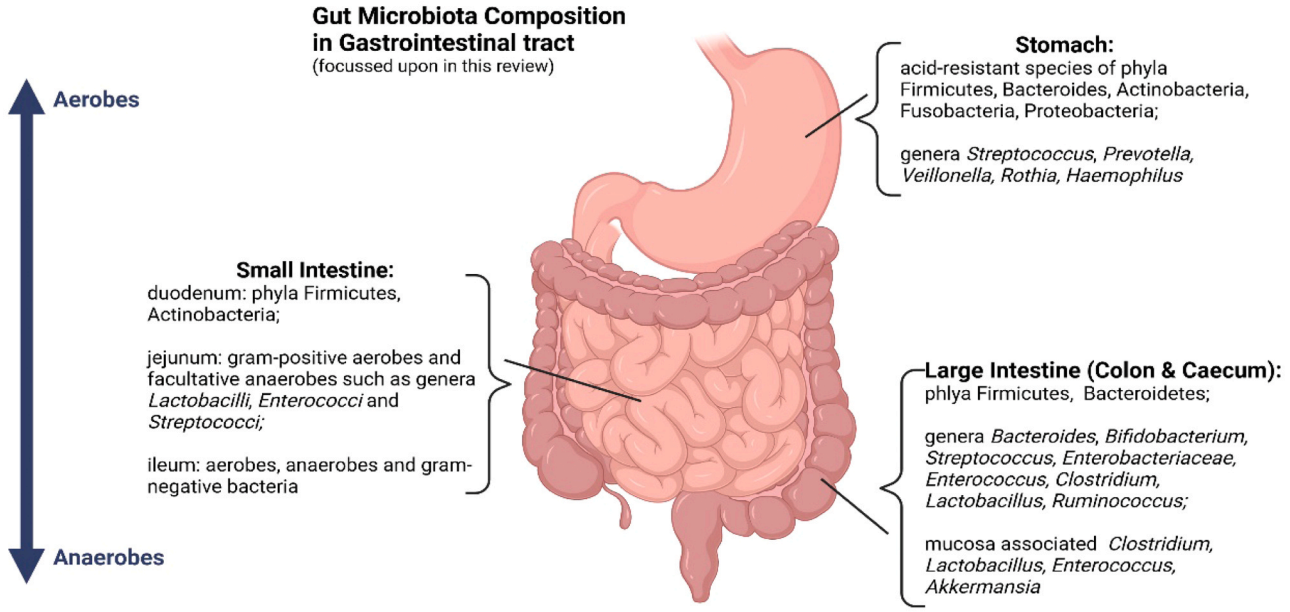

Fig. 3. Overview of gut microbiota composition in gastrointestinal tract i.e., stomach and intestines. In general, there is a transition from aerobes to anaerobes bacterial species from the upper gut to the lower. The first part of the gastrointestinal tract (GIT), the stomach, mainly holds acid-resistant bacterial species from the five major phyla Firmicutes, Bacteroides, Actinobacteria, Fusobacteria and Proteobacteria and bacterial genera Streptococcus, Prevotella, Veillonella, Rothia and Haemophilus. Next in line, the small intestine is made up of three parts, namely, the duodenum, jejunum and ileum. Starting from the duodenum to the ileum, the bacterial species and their abundancies alter. There is a transition from duodenal Firmicutes and Actinobacteria to jejunal gram-positive aerobes and facultative anaerobes. The ileum consists of aerobes and anaerobes and gram-negative bacteria. Caecum and colon reside with mainly Firmicutes and Bacteroidetes. (Illustration created with BioRender.com (Software, 2023); license agreement number 2023: OR25UMC72C) (This is a 2-column fitting image/figure.).

distinguish the bacterial colonies via their metabolites. The 16 s rRNA genomic sequencing and shotgun sequencing methods allow to identify culture-dependent and culture-independent genus' and species respectively (Adak and Khan, 2019).

4. Microbiota-gut-brain axis

The gut-brain axis defines the connection between the enteric nervous system (ENS) and the central nervous system (CNS). With growing research, it is now evident that the microbiota plays an essential role in this axis, extending the gut-brain axis to the microbiota-gut-brain axis (MGBA). MGBA is a bidirectional communication pathway between the GM and CNS, affecting physiological aspects of the gut and the brain. Different pathways have since been described to be involved in this communication (Fig. 4). GM may influence the brain via bacterial production of neurotransmitters and metabolites (so-called chemical signalling), the vagal nerve, the immune system, or the neuroendocrine system including the hypothalamic-pituitary-adrenal axis (HPAA) (Chakrabarti et al., 2022; Cussotto et al., 2018).

GM interacts with the brain either directly or indirectly through chemical cues (Chakrabarti et al., 2022). Chemical signalling mainly includes short-chain fatty acids (SCFAs), amino acids, neurotransmitters, gut hormones and neurotrophic factors. Chemical signalling interconnects all pathways with each other. Many of these chemicals are microbial products, which can affect the brain via neuronal pathways (Morais et al., 2021).

Acetate, propionate and butyrate are the most abundant SCFAs in the gut exerting anti-inflammatory responses (Dalile et al., 2019). SCFA are saturated fatty acids produced by the bacteria through the fermentation of host-indigestible dietary fibres. SCFAs can to some extent cross the blood-brain barrier (BBB) (Dalile et al., 2019) and exert their effects on the brain. Chemical signalling of SCFAs can also modulate the secretion of certain neurotransmitters and gut hormones such as glucagon-like peptide-1 (GLP1), peptide YY (PYY), leptin, ghrelin, and insulin (Chakrabarti et al., 2022; Dalile et al., 2019).

Along with SCFA gut bacteria also produce or metabolise various neuroactive molecules such as an amino acid tryptophan (Chakrabarti et al., 2022). Tryptophan can cross the BBB (Chakrabarti et al., 2022) and it is the precursor to serotonin synthesis. Thus, BBB-permeable SCFAs and tryptophan could affect the cerebral biosynthesis and availability of serotonin affecting brain circuits and influencing brain functions including mood and cognition (Chakrabarti et al., 2022; Liang et al., 2018). More than 90% of serotonin is synthesised in the enteric system through SCFAs-activated enteroendocrine cells (EECs) (Chakrabarti et al., 2022; Eicher and Mohajeri, 2022). Gastrointestinal serotonin is also produced by *Streptococcus spp. Candida spp., Enterococcus spp.* and *Escherichia spp.* (Eicher and Mohajeri, 2022). Furthermore, dopamine modulation is also associated with addiction, schizophrenia, and Parkinson's disease (Chakrabarti et al., 2022). Disruption of dopaminergic neurotransmissions is a possible consequence of dysbiosis (González-Arancibia et al., 2019), since research suggests that certain bacteria may be involved in dopamine production or modulation such as *Bacillus spp.* or *Bifidobacterium* (Eicher and Mohajeri, 2022; Strandwitz, 2018). Similar reportings have shown that perturbations in GM diversity and richness shape not only serotonergic and dopaminergic but also GABAergic, noradrenergic and glutamatergic neurotransmission (Chakrabarti et al., 2022; González-Arancibia et al., 2019).

The aforementioned diffusible metabolites, gut hormones and neurotransmitters also stimulate the parasympathetic vagal response, i.e. the vagus nerve (VN). For instance, diffusion of injected sodium butyrate evoked vagal afferent nerve action potential in male rats, which was discontinued following subdiaphragmatic vagotomy (Dalile et al., 2019). In addition, vagal afferents fibres are equipped with toll-like receptor 4 (TLR4) and can sense lipopolysaccharides (LPS) to activate the brain (Bonaz et al., 2018). These findings suggest a link between gut microbiota and vagal nerve stimulation.

The immune-triggering LPS found in the walls of gram-negative bacteria can also be detected by intestinal cells. In consequence, a local and systemic immune response cascade is activated (Eicher and Mohajeri, 2022; Weiss and Hennet, 2017). Dysregulation in systemic

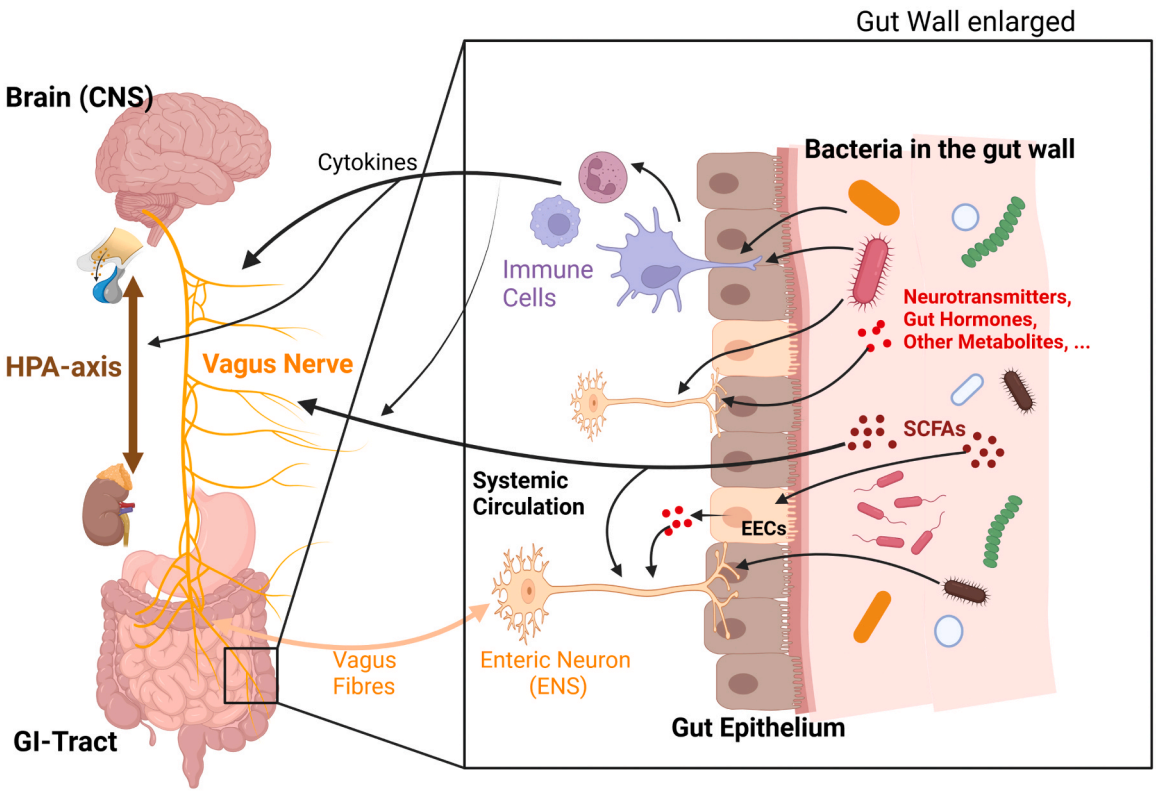

Fig. 4. Schematic overview on the bidirectional communication of the microbiota-gut-brain axis (MBGA). The gut inhabits many bacterial strains, which can communicate directly or indirectly with the brain. The arrows signify the signalling direction of the individual pathways between the different stations involved. Various neuronal, immune and endocrine mediators such as neurotransmitters, cytokines and gut hormones (mentioned in the order of the specified mediators) are communicators in the bidirectional pathways of MGBA. Released cytokines influence the brain directly after recognition of bacteria through immune cells. Cytokines and the vagus nerve can also influence the hypothalamic-pituitary adrenal axis (HPA-axis). Bacteria can also directly communicate with the enteric neurons via their lipopolysaccharides (LPS) triggering the toll-like receptors-4 (TLR4) on the enteric neurons. Indirect pathways include metabolites produced by the gut bacteria such as neurotransmitters and short-chain fatty acids (SCFAs). These metabolites can enter the systemic blood circulation and so influence the brain. In addition, the metabolites can stimulate enteroendocrine cells (EECs) in the gut, which then release gut hormones in the blood stream. The bacterial metabolites and the gut hormones can also send afferent signals via the enteric neurons belonging to the vagus nerve. On the other hand, the brain communicates via the efferent vagus nerve fibres and other enteric nervous system (ENS) cells. It so influences the gut physiology in important aspects such as mucous secretion and gut motility. (Illustration created with BioRender.com (Software, 2023); license agreement number 2023: DM25VBM0KY) (This is a 2-column fitting image/figure.).

immunity drives up systemic inflammation, disrupting different immune cascades and barriers such as the BBB. Consequently, less protection from toxins in the brain facilitates the development of various neurological disorders (Cryan et al., 2019). Compromised BBB integrity is a common feature in many neuropathological disorders (Eicher and Mohajeri, 2022; Morais et al., 2021). There is evidence in mice showing an increased BBB permeability, due to GM alterations (Morais et al., 2021). GF mice have exhibited increased permeability in BBB, which was directly inverted by butyrate treatment to the level of pathogen-free mice (Dalile et al., 2019). In addition, permeable BBB could modulate neuroinflammation via microglial dysfunction. The microbiota was found to influence the microglial structure and functional integrity in the CNS, since antibiotic-treated GF mice had severely compromised microglial functions (Morais et al., 2021). Microglial altered expression patterns have been reported in many psychiatric disorders like depression, autism-spectrum disorder, and obsessive-compulsive disorder (Eicher and Mohajeri, 2022). Moreover, SCFAs and microglia function may interrelate, because animals with a reduced or no microbiota showed positive correlation between inflammatory phenotype of microglia and perturbed circulating SCFAs amounts, proposing yet another indirect effect of SCFAs via MGBA (Cryan et al., 2019; Dalile et al., 2019). Other than microglial cells, astrocytes are also activated via neuroinflammation. Chronic inflammation or stress can maintain the astrocyte activation and therefore, the glutamatergic transmission as well. Activated astrocytes have been reported to reduce the internalisation of glutamate increasing the glutamate levels and consequently the glutamatergic excitatory transmission (Lee et al., 2022; Mahmoud et al., 2019; Troubat et al., 2021). Increased excitotoxic glutamatergic transmission has been regarded as neurotoxic, especially important in brain disorders such as depression (Troubat et al., 2021), Alzheimer's, Parkinson's, Huntington's and Epilepsy (Lee et al., 2022). This leads to the similar findings mentioned before, where perturbations in GM diversity and richness shape various kinds of neurotransmission (Chakrabarti et al., 2022; González-Arancibia et al., 2019) and that GM alterations can affect the immune system thereby altering the BBB.

Dysregulated stress responses have been seen in many neuropsychiatric disorders, where depression and autism spectre disorder are just two examples. A big communicator and regulator of stress and neuroendocrine pathways in the human body is the hypothalamus-pituitary-adrenal axis (HPAA). Evidence in GF mice exhibiting hyperresponsiveness of the HPAA, a reaction to stress, suggests HPAA regulation through GM, which in turn suggests GM's roleplay in stress regulation. Vagal nerve signalling circuits involved in sickness behaviour can also activate the HPAA through LPS and TLR4 (Agirman et al., 2021). Belda et al. discuss that dopamine also stimulates HPAA for a due stress response primary to the involvement of glucocorticoids (Belda and Armario, 2009). Hence, dysbiosis and different MGBA pathways alter the hypothalamus-pituitary-adrenal axis.

Altogether, the GM interacts in various ways with the MGBA and consequently has been reported to play an important role in altering or affecting the MGBA.

5. Results

The data presented in this review show that metformin, statins, proton-pump-inhibitors, NSAIDs, and anti-depressants, some of the most prescribed drugs, exhibit dysbiosis upon their intake. In this section, we will describe for each drug, the consequences of its intake on the composition of patients' microbiomes and outline the most prominent changes on bacterial abundances. We will then will discuss in chapter 6, the similarities between the drug-induced dysbiosis and brain-disorders related dysbiosis observed in selected brain-related diseases (depression, multiple sclerosis, Parkinson's, Alzheimer's) postulating potential correlations between the discussed drugs and diseases.

5.1. Metformin

Antidiabetic Drug Metformin (MET) is the first-line therapy for Type 2 Diabetes Mellitus (T2DM) and it is already being prescribed to patients with T2DM for over 60 years (C. B. Lee et al., 2021). In the USA alone 92.59 Million MET prescriptions have been reported in 2020 (Statista.com, 2022) for symptoms regarding prediabetics, diabetics, or insulin resistance. After oral administration, MET's bioavailability is around 40–60% after being absorbed in the small intestine (via medici, 2023). It is found at 30–300-fold higher concentrations in the human intestine than in plasma (Y. Lee et al., 2021). MET exerts its effects through modulating blood sugar levels by improving the effects of insulin, inhibiting hepatic gluconeogenesis, suppressing glucagon signalling in the liver, increasing glucose uptake in skeletal muscle and lowering body weight. New studies show its anti-cancer effects, by suppressing the onset or further growth of different tumour types (Kaneto et al., 2021). In addition, MET has been shown to decrease glucose levels through an interplay with GM (Zhang and Hu, 2020).

Growing evidence shows the gut-altering effects of anti-diabetic drugs like MET, Empagliflozin and GLP-1 receptor agonists and vice-versa, in mouse models as well as in humans (Deng et al., 2022; Y. Lee et al., 2021; Liu et al., 2022). MET changes the GM in diabetic and prediabetic patients (Wu et al., 2020), who are already reported to have an altered GM compared to healthy subjects (Liu et al., 2022). The gut-altering effects of MET may be due to direct action on the gut microbiomes and/or indirect action via other metabolites. Maniar et al.'s study suggests that hyperinsulinemia also changes the gut microbiota (Maniar et al., 2017). Therefore, lowering insulin through MET would induce an indirect change in the gut microbiota.

The main changes in the GM and their microbial metabolites through MET include an increased abundance of SCFAs-producing bacteria and elevated LPS (probably due to higher abundance of gram-negative bacteria) (Almugadam et al., 2020; Maniar et al., 2017). MET use increased the abundance of *Akkermansia muciniphila, Bifidobacterium, and B. adolescentis*, and decreased the ratio of abundance of phyla Firmicutes and Bacteroidetes (Bryrup et al., 2019; Forslund et al., 2015; Mueller et al., 2021; Vallianou et al., 2019; Wu et al., 2017). Increases in *Escherichia and Ruminococcus torques* with decreases in *Intestiniibacter barlettii* and genus *Roseburia* (with specific strains *of R. intestinalis* and *R. faecis*) were shown in randomised control trials (RCT) (Mueller et al., 2021). A trial conducted in healthy subjects showed a decrease in relative abundances in *Intestiniibacter, Clostridium* and *Romboutsia* and an increase in the *Escherichia* genus (Y. Lee et al., 2021; Liu et al., 2022). Bigger changes relative to other bacteria tested in the RCT were illustrated by an increase of *Blautia spp.* and *Faecalibacterium spp.* (Tong et al., 2018). *Megamonas* and *Klebsiella pneumoniae* were significantly decreased (He et al., 2022) in MET-treated patients compared to patients with Diabetes mellitus type 2 and in relatively higher abundance than in controls. An increased abundance of Lactobacillus spp. is also mentioned (Almugadam et al., 2020; Tong et al., 2018; Wu et al., 2017) in MET-treated patients. These data indicate that bacteria may help MET to achieve its effect of lowering blood glucose levels in type 2 Diabetes mellitus via their metabolites and/or their functional properties (Table 1).

Due to MET-induced GM alterations, this drug is also being studied for the treatment of autoimmune diseases like IBDs, and/or is used to revert the effects of other gut-altering drugs (Wang et al., 2021). Wang et al. discuss the possibility of MET ameliorating the antipsychotics-induced metabolic dysfunction, which mainly causes weight gain via various pathways such as insulin resistance and hyperglycaemia and affects neuro active substances (e.g., neurotransmitters and neuropeptides) (Wang et al., 2021). Mice treated with antipsychotics showed a larger weight gain than mice with a depleted microbiome, suggesting GM's role in weight management. In mice, under antipsychotic treatment, many bacterial populations were found to be reduced such as *Lactobacillus* and *Akkermansia* (Wang et al., 2021). On the other hand, *E. coli* and *Bifidobacterium* were increased. MET especially has been shown to decrease weight gain as also is shown for *A. muciniphila*. The latter has been proposed as a probiotic treatment for alleviating systemic inflammation. Thus, MET may ameliorate the side effects of antipsychotic use via gut microbiome (Wang et al., 2021).

Unpresented data are ambiguous, as the human studies are conducted in small cohort sizes (5–25 subjects) and do not yet exist in sufficient quantities. However, studies in mouse models abundantly confirmed the interplay between MET and GM. Wu et al. showed the same bacterial changes in mouse models as in human reports, receiving MET-treated faecal transplants from human patient's, suggesting MET-induced alterations in GM (Wu et al., 2017).

5.2. Statins

Statins are a widely used drug class to lower low-density lipoprotein (LDL) by inhibiting HGM CoA-reductase cholesterol-producing enzyme. Statins are one of the most used cardiovascular drugs to prevent heart disease and atherosclerosis. More than 200 million people take various types of statins alone or in combination (Medicine, 2022). Not many studies have been done in humans to identify statins' effects on the gut microbiota and the data are inconsistent. For instance, Rosuvastatin showed no significant changes in the under-powered human trials. On the other hand, it caused significant alterations in the functional potential of the GM, i.e., on the level of bacterial metabolites (Kummen et al., 2020). One meta-analysis study showed that statins have anti-inflammatory aspects by reducing Bact2 enterotype (Bacteroides 2) (Libby, 2020; Lim, 2020; Vieira-Silva et al., 2020), which arises from an increase in *Bacteroides* and a decrease in *Faecalibacterium*. Patients treated with statins were observed to have lower levels of Bact2 and decreased levels of *Bacteroides*. This result could be further interpreted, that *Faecalibacterium* may also be increased or the ratio of *Bacteroides* to *Faecalibacterium* is lower under statin treatment leading to lower Bact2. Statin therapy also seems to be associated with an increase in butyrate-producing microbiomes (Reichel and Knauf, 2021). Specifically, Atorvastatin treated hypercholesterolemic patients had an increased abundance of *Ruminococcaceae, Verrucomicrobiaceae, A. muciniphila, Ruminococcus sp., Oscillospira spp.,* and *Faecalibacterium spp.* compared to untreated hypercholesterolemic patients. Pro-inflammatory species such as *Bacteroides, Faecalibacterium prausnitzii and Akkermansia muciniphila*, were decreased. Genera *Oscillospira* (anti-inflammatory bacteria), Firmicutes, Proteobacteria, *Desulfovibrio sp.*, and opportunistic bacterial genera, including *Klebsiella, Streptococcus*, and *Collinsella* were also measured in decreased commensals compared to untreated hypercholesterolemic patients. In addition, a relative decrease in *Bilophila wadsworthia* and *Bifidobacterium bifidum* (bile acid-associated species) was observed in the same comparison. Increased abundance in different species of *Bacteroides* such as *B. dorei* and *B. uniformis*, with simultaneously lowered growth of *B. vulgatus* and *B. ovatus*, was also observed following statin treatment (Khan et al., 2018). These results indicate statin-induced changes in GM, which could further potentially influence the GBA via the GM (Table 2).

Table 1
Metformin (MET) – induced bacterial alterations found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients treated with MET. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. The sources with a higher significance level (e.g., $p < 0.01$) are shown in bold. Non-coloured cells with arrows depict only the relative change without any significance.

Bacteria altered with the use of Metformin	Direction of the Alterations	Source
Akkermansia muciniphila	↑↓	**(de la Cuesta-Zuluaga et al., 2017; Tong et al., 2018; Wu et al., 2017)**
Alistipes	↓	**(Tong et al., 2018)**
Bacteroides	↓	
Bifidobacterium adolescentis	↑	**(Wu et al., 2017)**
Bifidobacterium bifidum	↑	**(de la Cuesta-Zuluaga et al., 2017)**
Bifidocbacterium	↑	**(Wu et al., 2017)**
Bilophila wadsworthia	↑	**(Bryrup et al., 2019)**
Blautia spp	↑	**(Tong et al., 2018)**
Butyrivibrio	↑	**(de la Cuesta-Zuluaga et al., 2017)**
Clostridium	↓	**(Bryrup et al., 2019; de la Cuesta-Zuluaga et al., 2017; Y. Lee et al., 2021)**
Enterococcus	↓	**(Almugadam et al., 2020)**
Escherichia (Escherich-ia/Shigella) (most abundant strain of E.coli)	↑	**(Bryrup et al., 2019; Forslund et al., 2015; Y. Lee et al., 2021; Mueller et al., 2021; Wu et al., 2017)**
Faecalibacterium	↑↓	**(Almugadam et al., 2020; Tong et al., 2018)**
Intestinibacter barletti	↓	**(Forslund et al., 2015; Y. Lee et al., 2021; Mueller et al., 2021)**
Intestiniibacter	↓	**(Bryrup et al., 2019; Forslund et al., 2015; Wu et al., 2017)**
Klebsiella	↓	**(He et al., 2022)**
Klebsiella pneumoniae	↓	**(He et al., 2022; Tong et al., 2018)**
Lactobacillus spp.	↑	**(Almugadam et al., 2020; Tong et al., 2018; Wu et al., 2017)**
Megamonas	↓	**(He et al., 2022; Tong et al., 2018)**
Megasphaera	↓↑	**(Almugadam et al., 2020; de la Cuesta-Zuluaga et al., 2017; Tong et al., 2018)**
Methanobrevibacter	↑	**(Almugadam et al., 2020)**
Oscillibacter	↓	**(Tong et al., 2018)**
Oscillospira	↓	**(de la Cuesta-Zuluaga et al., 2017)**
Romboutsia	↓	**(Y. Lee et al., 2021)**
Roseburia	↓	**(Mueller et al., 2021)**
Roseburia faecis	↓	
Roseburia intestinalis	↓	
Ruminococcus torques	↑	**(Mueller et al., 2021; Wu et al., 2017)**

5.3. Proton-pump inhibitors

Proton-pump inhibitors (PPIs) are used to prevent gastric conditions in the GIT. Almost everyone, especially the elderly population, gets PPIs prescribed together with other medication such as painkillers or antidepressants to counteract the latter's side effects on the stomach. Even though PPI's effects are mainly targeted towards the stomach, many studies suggest an alteration in the gut microbiota. PPIs belong to the most researched medication in humans. Their effects on human metabolism induced by microbiome also include bacterial overgrowth in the oral cavity, stomach and small intestine (SIBO), an increase in enteric *Clostridium difficile* (Clooney et al., 2016; Freedberg et al., 2015; Koo et al., 2019) and *Salmonella* infections, hepatic encephalopathy, spontaneous bacterial peritonitis, community-acquired pneumonia, adverse consequences in inflammatory bowel diseases, and changes in functional pathways (Naito et al., 2018). Many of these diseases and alterations are said to be consequences of dysbiosis secondary to the use of PPIs. In general, a lower abundance of phyla Bacteroidetes and a higher abundance of Firmicutes are reported (Clooney et al., 2016; Freedberg et al., 2015; Jackson et al., 2016).

The specific dysbiosis in the GIT is as follows: A significant increase in the abundance of Bacilli class, Lactobacillales order, *Streptococcaceae* family, *Streptococcus* and *Veillonella* genera, *Streptococcus vestibularis* and *Veillonella dispar* (Koo et al., 2019). The family of Enterobacteriaceae was negatively correlated with PPIs use (Koo et al., 2019). Naito et al. summarised the relative increase in abundance of Bacteroidetes Bacteroidaceae, Odoribacteraceae, Streptococcus, Streptococcaceae, *Ruminococcus* (Lachnospiraceae), *Megasphaera*, *Actinomyces and Granulicatella*, with decreases in *Faecalibacterium, SMB53, Clostridium, Turicibacter,* Slackia, Defluviitalea, unclassified Dehalobacteriaceae, and *Oribacterium* (Naito et al., 2018). Another study concluded lower abundances of mucus-associated *Neisseria*, *Porphyromonas*, *Selenomonas*, *Haemophilus* and *Fusobacterium* in functional dyspepsia -starters vs. controls with a decrease in *Prevotella* in controls and functional dyspepsia after PPI use (Wauters et al., 2021). Neisseria was still increased after the withdrawal of PPI, suggesting that microbial changes persist after drug use (Wauters et al., 2021). Additionally, other bacterial groups such as *Holdemania* and *Blautia, Granulicatella, Rothia* and *Dorea*, as well as the *Clostridium cluster XIVa and XIVb* were enriched in PPI users (Clooney et al., 2016). At a species-level, *Holdemania filiformis* were increased. *Clostridium glycyrrhizinilyticum* (within *Clostridium cluster XIVa*), and *Rothia mucilaginosa* were significantly increased, while *Pseudoflavonifractor capillosus* (Clostridiales family) was decreased (Clooney et al., 2016). *Streptococcus parasanguinis* and *Streptococcus salivarius* were increased as well, however, not to a significant level (Clooney et al., 2016). Moreover, *Clostridium difficile* infections are associated with changes in the population of Streptococcaceae and Enterococcaceae (Freedberg et al., 2015).

Since PPIs are given to people having gastric or reflux issues, a study only examined the faecal microbiota composition of patients with reflux esophagitis before and after the PPI treatment. Therein, at different time intervals during treatment, *Lactobacillus* species (facultative anaerobes) such as subgroups of *L. gasseri, L. reuteri* and the *L. ruminis with L. fermentum* and *L. brevis* were significantly increased after the treatment (Hojo et al., 2018). The same goes for the genus *Streptococcus*, facultative anaerobic counts under Enterobacteriaceae and *Staphylococcus* (also facultative anaerobes) (Hojo et al., 2018). There are studies of oral administration of bacterial populations such as *C. jejuni or L. reuteri* showing changes in the vagal afferents signalling and reverted in vagotomised mice respectively (Cryan et al., 2019; Morais et al., 2021).

Many of the aforementioned bacterial groups are found in the oral cavity, throat and nasal cavity, suggesting the translocation of bacteria to lower gut areas due to reduced stomach acidity resulting from the use of PPIs (Hojo et al., 2018). Colonisation of distal gut parts with upper GIT parts was shown in faecal samples by PPI use through an increase in multiple taxa from the orders Bacillales (e.g., Staphylococcaceae), Lactobacillales (eg. Enterococcaceae, Lactobacillaceae, Streptococcaceae) and Actinomycetales (e.g., Actinomycetaceae, Micrococcaceae), the families Pasteurellaceae and Enterobacteriaceae and the genus *Veillonella.* Decreased taxa included Bifidobacteriaceae, Ruminococcaceae, Lachnospiraceae and Mollicutes (Macke et al., 2020). The same was observed in a healthy twins' study concluding that the dysbiosis was induced mostly due to the pharyngeal and oral microbiota colonisation into the lower gut (Jackson et al., 2016), resulting in the same bacterial alterations as in the aforementioned literatures.

PPIs-use induces further shifts in bacterial populations. For instance, the distal gut is shown to be colonised by the upper gut's microbiota following PPI treatment (Macke et al., 2020). Overall lower microbial diversity and decreased population sizes of bacterial species have been identified with a higher abundance of gut commensals in the upper GIT (Freedberg et al., 2015; Jackson et al., 2016). Small intestine bacterial overgrowth (SIBO) is an example of the latter condition, resulting in an increased abundance of *Streptococcus, Escherichia, Klebsiella, Bacteroides, Lactobacillus, Enterococcus, Veillonella*; and a decrease in *Bifidobacteria* and Actinobactericaceae (Fujimori, 2015). A reduction in the parasympathetic stimulation of the gut has been associated with bacterial translocation, such as small-intestinal bacterial overgrowth (SIBO). The change in bacterial populations is summarised in Table 3.

In addition, dysbiosis is observed in functional dyspepsia, with cirrhosis, haemodialysis, rheumatoid arthritis and cancer patients, who show specific increase in *Streptococcus* genus (Bajaj et al., 2018; Lin et al., 2021). PPIs are used to calm down dyspepsia, especially in infections with *Helicobacter pylori.* However, as it increases the abundance of *Streptococcus,* the dyspeptic symptoms may persist. Biopsies taken from antral gastritis patients show an overpopulation of *Streptococcus*, confirming the association of *Streptococcus* to dyspepsia (Minalyan et al., 2017).

In summary, PPIs use to prevent dyspepsia due to other medications such as NSAIDs does its work by reducing acid production. However, it changes the gut environment in a manner such that proximal gut bacterial populations translocate to the distal part of the gut. Simultaneously, it causes a few bacterial taxa to either increase or decrease in their abundances. Consequently, this dysbiosis leads to more enteric infections with opportunistic and or harmful bacteria such as *C. difficile* or *Salmonella*. Consumption of PPIs to treat dyspepsia, impacts the GM with alterations of bacterial abundancies and bacterial translocation. Main effects were detected on *Streptococcus* abundance and higher incidence in *Clostridium difficile* infection (CDI).

5.4. Non-steroidal anti-inflammatory drugs

As with other aforementioned medicinal groups, non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed on a daily basis for pain and anti-inflammation, or low-dose aspirin as a thrombocyte aggregation inhibitor for cardiovascular health. NSAIDs could also lead to dysbiosis and subsequent consequences like SIBO (Wang, Tang et al., 2021). Extensive NSAID induces intestinal enteropathy. The latter is a consequence of a compromised intestinal barrier due to enterocyte cell death and a disrupted immune system, which leads to the proliferation of gram-negative bacteria and a reduction in gram-positive bacteria (Wang, Tang et al., 2021). PPIs and NSAIDs play a combined role in gut enteropathy due to dysbiosis. NSAIDs can lead to gastropathy, and PPIs can reduce its initiation (Rogers and Aronoff, 2016; Utzeri and Usai, 2017; Wang, Tang et al., 2021). The combined intake of NSAIDs and PPIs leads to enteropathy, as PPIs shift the microbiome from the upper GIT to the distal tract (see above) (Rogers and Aronoff, 2016; Utzeri and Usai, 2017; Wang, Tang et al., 2021). For example, treatment with aspirin causes a shift in the composition of the gut microbiota, increasing *Prevotella, Bacteroides*, Ruminococcaceae, and *Barnesiella* (Rogers and Aronoff, 2016). Furthermore, celecoxib and ibuprofen increase the abundance of Acidaminococcaceae and Enterobacteriaceae (Rogers and Aronoff, 2016). In addition, ibuprofen causes enrichment in

Propionibacteriaceae, Pseudomonadaceae, Puniceicoccaceae, and Rikenellaceae species compared with either nonusers or naproxen users (Maseda and Ricciotti, 2020). Indomethacin induced an increase *in* Bacteroidetes, Prevotellaceae and a decrease in Proteobacteria, Alphaproteobacteria, Proteobacteria, Rhizobiales, Pseudomonadaceae (Maseda and Ricciotti, 2020). The same study showed a gender-specific effect since Firmicutes were lower in the female gut and higher in the male gut (Maseda and Ricciotti, 2020). A comparative study showed that various NSAIDs-induced dysbiosis increased taxa such as Enterobacteriaceae, Acidaminococcaceae, Propionibacteriaceae, Pseudomonadaceae, Puniceicoccaceae, Rikenellaceae, (Rogers and Aronoff, 2016). Concluding the above-mentioned results, there is an apparent shift noticed in diverse bacterial taxa and species leading to dysbiosis and NSAID enteropathy (Table 4).

5.5. Antidepressants

Antidepressants for instance selective serotonin-reuptake inhibitors (SSRIs) are the first-line therapy for depressive disorders. Serotonin is the target of selective serotonin-reuptake inhibitors (SSRIs), increasing its level of availability in the brain (Eicher and Mohajeri, 2022; Liang et al., 2018). Although a connection has been shown between the gut-brain axis and depression, only a few human studies research the effects of antidepressants on GM (Macedo et al., 2017). Shen et al. showed that escitalopram altered the GM with a significant increase in Christensenellaceae, *Eubacterium ruminantium* group and Fusobacterium, complemented by a respective decrease in the abundance of Lactobacillus with significant changes in Bacteroides (Shen et al., 2021). The article by Le Bastard et al. studying the effects of atypical antipsychotics- treatment in patients with bipolar disorder showed an increase in relative abundance of Lachnospiraceae ($p = 0.029$) and a decrease in relative abundance of *Akkermansia* ($p = 0.0006$) and *Sutterella* (Flowers et al., 2017; Le Bastard et al., 2018). In another study from a Dutch cohort, *B. dorei* ($p = 0.051$) and *Coprococcus eutactus* ($p = 0.041$) were positively associated with antidepressants, and *Eubacterium hallii* negatively ($p = 0.055$) (Le Bastard et al., 2018).

Many studies exist on SSRIs-induced gut alterations in mouse models (Sun et al., 2019; Zhang et al., 2021). The common selective serotonin reuptake inhibitors (SSRI) sertraline, fluoxetine, and paroxetine showed activity against gram-positive bacteria such as *Staphylococcus* and *Enterococcus* species. Other potentially toxigenic Enterobacteria, such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, Citrobacter spp.* and

Table 2
Statins – induced bacterial alterations were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Non-coloured cells with arrows depict only the relative change without any significance.

Bacteria altered with the use of Statins	Direction of the Alterations	Source
Akkermansia muciniphila	↑	**(Khan et al., 2018)**
Bacteroides	↑	**(Khan et al., 2018; Vieira-Silva et al., 2020)**
Bacteroides dorei	↑	**(Khan et al., 2018)**
Bacteroides ovatus	↓	
Bacteroides uniformis	↑	
Bacteroides vulgatus	↓	
Bifidobacterium bifidum	↓	
Bilophila wadsworthia	↓	
Collinsella	↓	
Desulfovibrio sp.	↓	
Faecalibacterium prausnitzii	↑	
Faecalibacterium spp.	↓	**(Khan et al., 2018; Vieira-Silva et al., 2020)**
Firmicutes	↓	**(Khan et al., 2018)**
Klebsiella	↓	
Oscillospira spp.	↑	
Proteobacteria	↓	
Ruminococcaceae	↑	
Ruminococcus sp.	↑	
Streptococcus	↓	
Verrucomicrobiaceae	↑	

M. morganii, Clostridium perfringens and *C. difficile* were also decreased to some extent with the use of SSRIs (Macedo et al., 2017). These results were found on the grounds of in vitro studies. Depressed adults taking certain anti-depressants, such as fluoxetine, were more prone to developing *Clostridium difficile* infections (CDI) (Rogers et al., 2013). In mice escitalopram and lithium were reported to increase serotonin levels in a similar extent (Bull-Larsen and Mohajeri, 2019). However, this study did not discuss dysbiosis as the underlying cause. While the mechanism of action of SSRI for depression is not related to any antimicrobial effect of these drugs, potential changes in microbial communities are still seen and may affect other inflammatory or physiological parameters linked to mood (Flowers et al., 2020).

6. Discussion

As mentioned above, many drugs may induce dysbiosis in addition to their intended pharmacological effect. Therefore, it is possible that other physiological pathways and diseases are influenced by these drugs as well. Dysbiosis is observed in many different diseases suggesting that there is a link between the alteration of the microbiome with the disease and its treatment, and that the microbiome may influence the disease development. Thus, we focused here on how drug-induced gut-alterations could influence brain-related diseases and compared these changes to the microbiome changes in such disorders,. In the tables below similarities have been highlighted between the drug-induced dysbiosis and brain-disorders related dysbiosis. Next, a potential link between the most prescribed medication and the diseases were discussed.

6.1. Depression

Depressive disorder or major depressive disorder is the most common neuropsychiatric disease. It is one of the leading causes of disability, morbidity and mortality leading to a low quality of life. Approximately every fifth person is diagnosed with it once in their lifetime. Depression is a complex disease with heterogeneous symptoms and pathophysiology. As per DSM-5 it is diagnosed with a cluster of the following symptoms persisting for more than 2 weeks: constant depressed mood, anhedonia, feeling of loneliness, reduced motivation, appetite and sleep disturbances, psychomotor agitation, trouble concentrating, fatigue, feelings of guilt or worthlessness and suicidal thoughts (Amboss, 2023d). The aetiology or pathophysiology is explained through many mechanisms, still unclear in their entirety, and are as follows: (1) low levels of serotonin, norepinephrine and dopamine and high levels of glutamate (Troubat et al., 2021); (2) alterations in the HPA-axis; (3) systemic inflammation due to imbalance in immune mediators leading to false communication to immune cells, esp. microglia; (4) and last but not the least the microbiota with MGBA.

To date, research has found that on the phylum level Bacteroidetes, Proteobacteria, Actinomycetes, Actinobacteria are increased, while Firmicutes are decreased in depressed patient's faecal matter (Eicher and Mohajeri, 2022; Liang et al., 2022; Liang et al., 2018; Winter et al., 2018; Yao et al., 2023). On the family and genus level, an increase is noted in Enterobacteriaceae, *Eggerthella, Holdemania, Gelria, Turicibacter, Paraprevotella, Anaerofilum,* Ruminococcaceae, Streptococceae, Lactobacillaceae, Clostridiales and Bifidobacteriaceae. A depletion is seen in Bacteriodaceae, Lachnospiraceae, Prevotellaceae, Sutterellaceae, Veillonellaceae (Chang et al., 2022; Eicher and Mohajeri, 2022; Knudsen et al., 2021; Skonieczna-Żydecka et al., 2018; Yao et al., 2023; Zhao et al., 2022). Further on the genus level a decrease in *Faecalibacterium, Ruminococcus, Dialister, Oscillospiraceae, Bacteroides plebeius, Roseburia, Gemmiger, Parasutterella, Coprococcus, Escherichia/Shigella* is mentioned, with an increase in *Desulfovibrio, Flavonifractor, Alistipes, Bacteroides, Parabacteroides, Barnesiella, Bacteroides vulgatus, Atopobium, Weissella, Halomonas, Blautia klebsiella, Anaerostipes, Clostridium, Phascolarctobacterium, Lachnospiraceae incertae sedis, Streptococcus* (Anand et al., 2022; Chang et al., 2022; Eicher and Mohajeri, 2022; Knudsen et al., 2021; Liang et al., 2022; Liang et al., 2018; Skonieczna-Żydecka et al., 2018; Valles-Colomer et al., 2019; Winter et al., 2018; Yao et al., 2023). In few bacterial populations such as Prevotellaceae, *Prevotella,* Bacteroides enterotype 2, *Bifidobacterium and Parasutterella* discrepancies were noticed in different studies (Anand et al., 2022; Eicher and Mohajeri, 2022; Liang et al., 2022; Liang et al., 2018; Skonieczna--Żydecka et al., 2018; Valles-Colomer et al., 2019; Winter et al., 2018; Yao et al., 2023; Zhao et al., 2022). .

Similarities can be observed in different bacterial taxa levels with one or more drugs while comparing depressed peoples' GM with the aforementioned drug-induced dysbiosis. *Bacteroides* are increased with statins and NSAIDs and within depressed guts. *Bacteroides* is a gram-negative GABA-producing bacteria with immune-triggering LPS and anti-inflammatory SCFAs (Eicher and Mohajeri, 2022; Knuesel and Mohajeri, 2021), thereby triggering an immune response. Depression is shown to be associated with both systemic and neuroinflammation (Eicher and Mohajeri, 2022) with depletion of serotonin (Knuesel and Mohajeri, 2021). However, elevated *Bacteroides* produced SCFAs and GABA, both of which are found in lower quantities in depressed patients, would help in alleviating depressive behaviour. *Ruminococcus*, an SCFA producer (Eicher and Mohajeri, 2022; Knuesel and Mohajeri, 2021), is increased in statins and PPIs, again counteracting the low quantity of SCFAs. The latter may also be a cause of low abundances of *Faecalibactierum* in depressed patients following oral application of statins or PPIs, where *Faecalibacterium* a known butyrate producer, is important for gut barrier homeostasis and an anti-inflammatory species (Eicher and Mohajeri, 2022; Knuesel and Mohajeri, 2021; Tran and Mohajeri, 2021; Valles-Colomer et al., 2019). Moreover, especially, statins have been shown to decrease bacteroides enterotype 2 (Bact2) arising from the ratio of increased Bacteroides and decreased *Faecalibacterium* (Vieira-Silva et al., 2020). This in turn could lead to depressive symptoms (Eicher and Mohajeri, 2022; Knuesel and Mohajeri, 2021). Depression may negatively correlate to the use of statins and PPIs due to low counts of *Ruminococcus* in depressed patients and higher counts in statins and PPIs users. *Clostridium* is decreased in metformin and PPIs but not in depression, therefore, metformin and PPIs might help in reducing *Clostridium*. Overgrowth of *Clostridia* might possess more unfavourable outcomes than favourable ones, for instance, *C. diffcile* is toxic and infectious, whereas *Clostridium clusters XIVa* produce beneficiary SCFAs (Clooney et al., 2016). Serotonin may influence humoral gut-brain pathways via the vagus nerves (González-Arancibia et al., 2019). *Escherichia* and *Streptococcus* with species of Enterobacteriocaceae are involved in serotonin synthesis (Eicher and Mohajeri, 2022). They are found in low and high abundancy in the gut of depressed patients respectively. Metformin may alleviate low levels of *Escherichia,* since increased abundance of *Escherichia* is observed following MET use. Furthermore, NSAIDs and PPIs may induce the same effect with Enterobacteriocaceae and *Streptococcus* respectively, while statins may counteract effects of PPIs with positive correlation in reduced amounts of *Streptococcus. Bacteroides*, *Lactobacillus, Bifidobacterium and Streptococcus* may also be involved in glutamate pathways. Therefore, their drug-induced influence may play a role in elevating the glutamatergic neurotransmission individually or with each other's interactions (Eicher and Mohajeri, 2022; McGuinness et al., 2022).

Thus, metformin, statins, PPIs, and NSAIDs drugs-induced dysbiosis may each affect depression development and progression and their effects may counteract or intensify each other.

6.2. Multiple sclerosis

Multiple Sclerosis is the most abundant autoimmune disease of the CNS. More than 2.5 million people worldwide are affected, mostly young adults. It is a chronic inflammatory disease characterised by demyelination of nerve fibres and secondary destruction of axons, signified by tissue lesions in white matter. The symptoms vary

Table 3
Proton-pump-inhibitors (PPIs) – induced bacterial alterations were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients treated with PPIs. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. The sources with a higher significance level (e.g., $p < 0.01$) are shown in bold format. Non-coloured cells with arrows depict only the relative change without any significance.

Bacteria altered with the use of PPIs	Direction of the Alterations	Source
Actinomyces	↓	**(Naito et al., 2018)**
Bacteroidaceae	↑	
Blautia	↑	**(Clooney et al., 2016)**
Clostridium	↓	**(Naito et al., 2018)**
Clostridium glycyrrhizinilyticum	↑	**(Clooney et al., 2016)**
Defluviitalea	↓	**(Naito et al., 2018)**
Dorea	↑	**(Clooney et al., 2016)**
Enterobacteriaceae	↓↑	**(Hojo et al., 2018; Koo et al., 2019)**
Faecalibacterium	↓	**(Naito et al., 2018)**
Fusobacterium	↓	**(Wauters et al., 2021)**
Granulicatella	↓	**(Clooney et al., 2016; Naito et al., 2018)**
Haemophilus	↓	**(Wauters et al., 2021)**
Holdemania	↑	**(Clooney et al., 2016)**
Holdemania filiformis	↑	
Lactobacillus brevis	↑	**(Hojo et al., 2018)**
Lactobacillus fermentum	↑	
Lactobacillus gasseri	↑	
Lactobacillus reuteri	↑	
Lactobacillus ruminis	↑	
Megasphaera	↑	**(Naito et al., 2018)**
Neisseria	↓	**(Wauters et al., 2021)**
Odoribacteraceae	↑	**(Naito et al., 2018)**
Oribacterium	↓	
Porphyromonas	↓	**(Wauters et al., 2021)**
Prevotella	↓	
Pseudoflavonifractor capillosus	↓	**(Clooney et al., 2016)**
Rothia	↑	
Rothia mucilaginosa	↑	
Ruminococcus	↑	**(Naito et al., 2018)**
Selenomonas	↓	**(Wauters et al., 2021)**
Slackia	↓	**(Naito et al., 2018)**
Staphylococcus	↑	**(Hojo et al., 2018)**
Streptococcaceae	↑	**(Koo et al., 2019; Naito et al., 2018)**
Streptococcus	↑	**(Hojo et al., 2018; Koo et al., 2019; Naito et al., 2018)**
Streptococcus vestibularis	↑	**(Koo et al., 2019)**
Turicibacter	↓	**(Naito et al., 2018)**
unclassified Dehalobacteriaceae	↓	
Veillonella	↑	**(Koo et al., 2019)**
Veillonella dispar	↑	

Table 4
Non-steroidal anti-inflammatory drugs (NSAIDs) – induced bacterial alterations were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients treated with NSAIDs. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned.

Bacteria altered with the use of NSAIDs	Direction of the Alterations	Source
Acidaminococcaceae	↑	**(Rogers & Aronoff, 2016)**
Alphaproteobacteria	↓	**(Maseda & Ricciotti, 2020)**
Bacteroides	↑	**(Rogers & Aronoff, 2016)**
Bacteroidetes	↑	**(Maseda & Ricciotti, 2020)**
Barnesiella	↑	**(Rogers & Aronoff, 2016)**
Enterobacteriaceae	↑	
Prevotella	↑	
Prevotellaceae	↑	**(Maseda & Ricciotti, 2020)**
Propionibacteriaceae	↑	**(Maseda & Ricciotti, 2020)**
Proteobacteria	↓	
Pseudomonadaceae	↑	
Puniceicoccaceae	↑	
Rhizobiales	↓	
Rikenellaceae	↑	
Ruminococcaceae	↑	**(Rogers & Aronoff, 2016)**

depending on the affected tissue area. The first most common symptom is visual disturbances due to opticus neuritis together with sensory disturbances and fatigue. Intermittent symptoms are movement disorders, pain, cognitive, psychological and vegetative impairments giving the disease either a progressive or relapsing character. The inflammatory process is explained through autoreactive peripheral T-lymphocytes invading CNS (Amboss, 2023b). However, the emergence of this autoimmune reaction is unclear. A genetic, imbalance between adipokine and cytokine levels (Bonnechère, 2022), autoreactivity due to Epstein-Barr-Virus -Infection, Vitamin-D deficiency, smoking, and bacterial and viral gut dysbiosis altering the MGBA are all described to be implicated in the pathophysiology of MS (Thirion et al., 2023).

It has been shown that MS patients have a divergent microbiota than healthy controls. GF mice with transplanted MS patients' faecal matter replicated the phenotype of resonated the autoimmune encephalomyelitis, a demyelinating disease found in animals. These results contrasted with GF mice with faecal matter of healthy controls (Doroszkiewicz et al., 2021). Even the disease severity and or activity appears to associate with different microbial composition (Thirion et al., 2023). In general, lower abundance of anti-inflammatory species has been observed (Tyler Patterson and Grandhi, 2020). Thirion et al. discovered that clinically active cases (i.e., with relapsing episodes) had a richer microbiome compared with clinically not-active, all among treatment-naïve patients. While comparing bacterial species, clinically not-active MS patients had significantly higher abundance in *Faecalibacterium prausnitzii* and *Gordonibacter urolithinfaciens* than the clinically active. The same study resulted in 61 species varying in microbial composition. The enriched species in MS are as follows: *Ruminococcus torques*, *Dysosmobacter welbionis*, *Flavonifractor plautii*, *Lawsonibacter phoceensis*, *Hungatella effluvia*, *Bilophila wadsworthia*, *Gordonibacter urolithinfaciens*, *Anaerobutyricum hallii*, *Pseudoflavonifractor capillosus*, *Blautia wexlerae*, *Blautia massiliensis*, *Anaerotruncus colihominis*, *Erysipelatoclostridium ramosum*, *Ruminococcus gnavus*, *Sellimonas intestinalis*, *Coprobacillus cateniformis*, and *Clostridium innocuum*. The depleted bacterial species, in comparison with healthy controls, included *Haemophilus parainfluenzae*, *Veillonella rogosae*, *Victivallis vadensis*, *Bifidobacterium angulatum*, and *Streptococcus australis* (Thirion et al., 2023). Overall, MS patients showed lower richness in microbial composition than the healthy controls. This was also associated with a higher abundance in specific inflammatory biomarkers in correlation to MS-related bacterial species (Thirion et al., 2023).

Other studies produced similar results: a significant increase in genus *Actinomyces, Akkermansia, Bifiodbacterium, Coprococcus, Dialister, Dorea, Haemophilus, Megasphaera, Paraprevotella, Pseudomonas, Mycoplana, Blautia, Ruminococcus*, and *Streptococcus* (Bonnechère, 2022; Bonnechère et al., 2022; Chen et al., 2021; Doroszkiewicz et al., 2021; Erturk-Hasdemir et al., 2021; Pellegrini et al., 2018; Tran and Mohajeri, 2021; Tyler Patterson and Grandhi, 2020); with a decrease in *Butyricicoccus, Gemmiger, Parabacteroides, Phascoarctobacterium, Prevotella, Collinsella, Lactobacillus, Adlercreutzia* and *Anearostipes* (Bell et al., 2019; Bonnechère, 2022; Bonnechère et al., 2022; Chen et al., 2021; Doroszkiewicz et al., 2021; Erturk-Hasdemir et al., 2021; Tran and Mohajeri, 2021; Tyler Patterson and Grandhi, 2020). Overall, a decrease in phylum Bacteroides was seen (Chen et al., 2021; Doroszkiewicz et al., 2021; Erturk-Hasdemir et al., 2021; Pellegrini et al., 2018) with the respective decrease in species such as *B. coprocola, B. coprophilus,* and *B. stercoris* (Pellegrini et al., 2018). Inconsistent results were seen in *Faecalibacterium, Slackia, Clostridium, Methanobrevibacter* and *Butyricimonas* (Bell et al., 2019; Bonnechère, 2022; Chen et al., 2021; Doroszkiewicz et al., 2021; Erturk-Hasdemir et al., 2021; Tyler Patterson and Grandhi, 2020).

An increase in *Akkermansia* and a decrease in *Prevotella* have been one of the consistent altered bacterial populations in all the cited literature about MS. .

Bacteroides, a gram-negative bacterial genus and SCFA- and GABA producer (Eicher and Mohajeri, 2022), is increased in statins and

Table 5
Altered bacterial abundancies in patients with depression (with its respective sources) in relation to altered bacterial abundancies in metformin, statins, PPIs and NSAIDs users. Bacteria that were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients with depression. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. Non-coloured cells with arrows depict only the relative change without any significance.
In the left 4 rows gut-bacterial alterations caused by drugs metformin (MET), statins, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are set in comparison to the altered gut bacteria populations found in patients with depression.

Source	Depression	Bacteria	MET	Statins	PPIs	NSAIDs
(Anand et al., 2022; Eicher & Mohajeri, 2022; Skonieczna-Żydecka et al., 2018; Yao et al., 2023)	↑	Alistipes	↓			
(Skonieczna-Żydecka et al., 2018)	↑	*Anaerofilum*				
(Anand et al., 2022)	↑	*Anaerostipes*				
(Eicher & Mohajeri, 2022)	↑	*Atopobium*				
(Knudsen et al., 2021; Zhao et al., 2022)	↓	Bacteriodeaceae			↑	
(Eicher & Mohajeri, 2022; Yao et al., 2023)	↑	*Bacteroides*	↓	↑		↑
(Valles-Colomer et al., 2019)	↑↓	Bacteroides enterotype 2		↓		
(Liang et al., 2022)	↑	*Barnesiella*				↑
(Eicher & Mohajeri, 2022; Knudsen et al., 2021; Liang et al., 2022; Liang et al., 2018); (Anand et al., 2022)	↑↓	*Bifidobacterium*	↑			
(Anand et al., 2022; Eicher & Mohajeri, 2022)	↑	*Blautia klebsiella*				
	↑	*Clostridium*	↓		↓	
(Chang et al., 2022; Eicher & Mohajeri, 2022; Liang et al., 2022; Valles-Colomer et al., 2019; Yao et al., 2023)	↓	*Coprococcus*				
(Liang et al., 2022)	↑	*Desulfovibrio*		↓		
(Anand et al., 2022; Eicher & Mohajeri, 2022; Liang et al., 2022; Skonieczna-Żydecka et al., 2018; Valles-Colomer et al., 2019)	↓	*Dialister*				
(Eicher & Mohajeri, 2022; Knudsen et al., 2021; Liang et al., 2022; Skonieczna-Żydecka et al.,	↑	*Eggerthella*				

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NSAIDs users in contrast to MS patients. Another gram-negative species *Bilophila wadsworthia* (Eicher and Mohajeri, 2022) is increased in MS and MET but decreased in statins, suggesting that MET may be disadvantageous and statins advantageous for MS patients. Gram-negative bacteria induce the host immune response because of the presence of LPS in their cell walls. The same goes for the genus *Streptococcus*, which is found in increased amounts in MS patients and PPI users and decreased in statin users. *Streptococcus* being an opportunistic bacteria can produce neurotoxins, acetate and serotonin (5-HT) (Eicher and Mohajeri, 2022). *Blautia spp*., on the other hand, is increased in MS, MET and PPIs. *Blautia spp.* are butyrate producers (Eicher and Mohajeri, 2022; Tong et al., 2018; Tran and Mohajeri, 2021), which is important for barrier integrities such as gut and BBB and for microglia maturation and activation (Eicher and Mohajeri, 2022). *Clostridium* is reduced in MET and PPIs user, however, is in ambiguous abundances in multiple sclerosis patients. *Clostridium* produces SCFA, which might influence Treg cells (Doroszkiewicz et al., 2021; Tran and Mohajeri, 2021) affecting autoimmunity in MS patients. *Ruminococcus* an SCFA producer is increased in MS and following Statins and PPI use. *Prevotella*, an LPS-bearer and GABA-producer (Eicher and Mohajeri, 2022) and propionate producer (Chen et al., 2021; Doroszkiewicz et al., 2021), is increased in NSAIDs and decreased in MS and after PPIs. *Bifidobacterium* and *Lactobacillus*, both GABA and acetate producers (Eicher and Mohajeri, 2022) are increased and decreased respectively in MS and after MET intake, proposing that the two genus may influence MS disease and progression.

Looking at the results, there could be many associations between MS and drug-induced dysbiosis. Nevertheless, more unambiguous research results are needed to prove these hypothesized associations.

6.3. Parkinson`s disease

In the field of MGBA, Parkinson's disease (PD) is the most intensively researched neurodegenerative disease. The main symptoms are motor symptoms with akinesia, rigor, resting tremor and postural instability, which come from dopamine-deficiency, mostly in Substantia nigra.

Table 5 (*continued*)

2018)						
(Liang et al., 2022)	↑	*Enterobacter*				
(Skonieczna-Żydecka et al., 2018; Yao et al., 2023)	↑	Enterobacteriaceae			↑↓	↑
(Anand et al., 2022; Eicher & Mohajeri, 2022; Liang et al., 2022)	↓	*Escherich-ia/Shigella*	↑			
(Anand et al., 2022; Chang et al., 2022; Eicher & Mohajeri, 2022; Knudsen et al., 2021; Liang et al., 2022; Skonieczna-Żydecka et al., 2018; Yao et al., 2023)	↓	*Faecalibacterium*	↑↓	↓	↓	
(Eicher & Mohajeri, 2022; Valles-Colomer et al., 2019)	↑	*Flavonifractor*				
(Skonieczna-Żydecka et al., 2018)	↑	*Gelria*				
(Yao et al., 2023)	↓	*Gemmiger*				
	↑	*Halomonas*				
(Liang et al., 2022; Skonieczna-Żydecka et al., 2018)	↑	*Holdemania*			↑	
(Zhao et al., 2022)	↓	Lachnospiraceae				
(Anand et al., 2022)	↑	*Lachnospiraceae incertae sedis*				
(Liang et al., 2018)	↓	*Lactobacillus*	↑		↑	
(Anand et al., 2022)	↑	*Megamonas*				
(Liang et al., 2022)	↓	Oscillospiraceae				
(Anand et al., 2022)	↑	Parabacteroides				
(Eicher & Mohajeri, 2022; Skonieczna-Żydecka et al., 2018)	↑	*Paraprevotella*				
(Anand et al., 2022);(Yao et al., 2023)	↑↓	*Parasutterella*				
(Eicher & Mohajeri, 2022; Liang et al., 2018);(Skonieczna-Żydeck a et al., 2018)	↑↓	*Prevotella*			↓	↑
(Eicher & Mohajeri, 2022; Liang et al., 2018;	↑↓	Prevotellaceae				↑
Skonieczna-Żydecka et al., 2018);(Zhao et al., 2022)						
(Yao et al., 2023)	↓	*Roseburia*	↓			
(Liang et al., 2022)	↑	*Rothia*				
(Zhao et al., 2022); (Valles-Colomer et al., 2019)	↑↓	Ruminococcaceae		↑		↑
(Anand et al., 2022; Eicher & Mohajeri, 2022; Liang et al., 2018; Yao et al., 2023)	↓	*Ruminococcus*		↑	↑	
(Liang et al., 2022)	↑	*Selenomonas*			↓	
(Anand et al., 2022; Liang	↑	Streptococcaceae			↑	
et al., 2022)	↑	*Streptococcus*		↓	↑	
(Eicher & Mohajeri, 2022)	↓	Sutterellaceae				
(Skonieczna-Żydecka et al., 2018)	↑	*Turicibacter*			↓	
(Eicher & Mohajeri, 2022)	↓	Veillonellaceae				
(Yao et al., 2023)	↑	*Weissella*				

Table 6
Altered bacterial abundancies in patients with multiple sclerosis (MS) (with its respective sources) in relation to altered bacterial abundancies in metformin, statins, PPIs and NSAIDs users. Bacteria that were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients with depression. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. Non-coloured cells with arrows depict only the relative change without any significance. In the left 4 rows gut-bacterial alterations caused by drugs metformin (MET), statins, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are set in comparison to the altered gut bacteria populations found in patients with multiple sclerosis.

Source	Multiple Sclerosis	Bacteria	MET	Statins	PPIs	NSAIDs
(Bonnechère et al., 2022)	↑	*Actinomyces*			↓	
(Chen et al., 2021)	↓	*Adlercreutzia*				
(Chen et al., 2021; Tyler Patterson & Grandhi, 2020); (Bell et al., 2019)	↑	*Akkermansia*				
(Doroszkiewicz et al., 2021)	↑	*Akkermansia muciniphila*	↑	↑		
(Thirion et al., 2023)	↑	*Anaerobutyricum hallii*				
	↑	*Anaerotruncus colihominis*				
(Tyler Patterson & Grandhi, 2020)	↓	*Anearostipes*				
(Pellegrini et al., 2018)	↓	*Bacteroides stercoris*				
(Chen et al., 2021; Pellegrini et al., 2018)	↓	*Bacteroides*	↓	↑		↑
(Pellegrini et al., 2018)	↓	*Bacteroides coprocola*				
	↓	*Bacteroides coprophilus*				
(Doroszkiewicz et al., 2021)	↓	*Bacteroidetes*				
(Thirion et al., 2023)	↓	*Bifidobacterium angulatum*				
(Bonnechère et al., 2022; Tyler Patterson & Grandhi, 2020)	↑	*Bifiodbacterium*	↑			
(Thirion et al., 2023)	↑	*Bilophila wadsworthia*	↑	↓		
(Pellegrini et al., 2018)	↑	*Blautia*	↑		↑	
(Thirion et al., 2023)	↑	*Blautia massiliensis*				
	↑	*Blautia wexlerae*				
(Bell et al., 2019)	↑↓	*Butyricimonas*				
(Bonnechère et al., 2022)	↓	*Butyricicoccus*				
(Bonnechère et al., 2022; Doroszkiewicz et al., 2021; Tyler Patterson & Grandhi, 2020)	↑↓	*Clostridium*	↓		↓	
(Thirion et al., 2023)	↑	*Clostridium innocuum*				
(Bell et al., 2019; Chen et al., 2021)	↓	*Collinsella*		↓		
(Thirion et al., 2023)	↑	*Coprobacillus cateniformis*				
(Bonnechère et al., 2022)	↑	*Coprococcus*				
	↑	*Dialister*				
(Bonnechère et al., 2022; Chen et al., 2021; Pellegrini et al., 2018)	↑	*Dorea*			↑	
(Thirion et al., 2023)	↑	*Dysosmobacter welbionis*				

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Lewy body aggregates, comprising of misfolded protein-aggregates i.e., amyloids, mostly alpha-synuclein amyloid, is the main cause of dopaminergic neuron destruction (Amboss, 2023c). Although, it is still unclear in detail as to how these aggregates are generated.

PD patients are vastly affected by non-motor symptoms, many of which precede decades before the onset of motor deficits. Gastrointestinal dysfunction, depressive mood, sleep disturbances, muscle and joint pain are a few of these prodromal symptoms (Amboss, 2023c). The former beholds most commonly obstipation or delayed gastric emptying, sialorrhea, dysphagia, gastroparesis and SIBO (Ryman et al., 2023). Patients with these prodromal gastrointestinal disturbances have more severe PD progression (Ryman et al., 2023). Amyloid

Table 6 (*continued*)

(Thirion et al., 2023)	↑	*Erysipelatoclostridium ramosum*				
(Bonnechère et al., 2022); (Doroszkiewicz et al., 2021; Tyler Patterson & Grandhi, 2020)	↑↓	*Faecalibacterium*	↑↓	↓	↓	
(Thirion et al., 2023)	↑	*Flavonifractor plautii*				
(Bonnechère et al., 2022)	↓	*Gemmiger*				
(Thirion et al., 2023)	↑	*Grodonibacter urothinfaciens*				
(Bonnechère et al., 2022; Pellegrini et al., 2018)	↑	*Haemophilus*			↓	
(Thirion et al., 2023)	↓	Haemophilus parainfluenzae				
	↑	Hungatella effluvii				
(Bonnechère, 2022; Tyler Patterson & Grandhi, 2020)	↓	Lactobacillus	↓			
(Thirion et al., 2023)	↑	Lawsonibacter phoceensis				
(Bonnechère et al., 2022)	↑	Megasphaera	↑↓		↓	
(Doroszkiewicz et al., 2021); (Bell et al., 2019)	↑↓	Methanobrevibacer	↑			
(Pellegrini et al., 2018)	↑	Mycoplana				
(Bonnechère et al., 2022; Chen et al., 2021)	↓	Parabacteroides				
(Bonnechère et al., 2022)	↑	Paraprevotella				
	↓	Phascolarctobacterium				
(Bell et al., 2019; Bonnechère et al., 2022; Chen et al., 2021; Doroszkiewicz et al., 2021; Tran & Mohajeri, 2021; Tyler Patterson & Grandhi, 2020)	↓	Prevotella			↓	↑
(Thirion et al., 2023)	↑	Pseudoflavonifractor capillosus			↓	
(Pellegrini et al., 2018)	↑	Pseudomonas				
(Knudsen et al., 2021)	↑	Ruminococcus		↑	↑	
(Thirion et al., 2023)	↑	Ruminococcus gnavus				
(Thirion et al., 2023)	↑	Ruminococcus torques	↑			
(Thirion et al., 2023)	↑	Sellimonas intestinalis				
(Bonnechère et al., 2022); (Bell et al., 2019; Chen et al., 2021)	↑↓	Slackia			↓	
(Tran & Mohajeri, 2021)	↑	Streptococcus		↓	↑	
(Thirion et al., 2023)	↓	Streptococcus australis				
	↓	Veillonella rogosae				
	↓	Victivallis vadensis				

Table 7
Altered bacterial abundancies in patients with Parkinson's disease (PD) (with its respective sources) in relation to altered bacterial abundancies in metformin, statins, PPIs and NSAIDs users. Bacteria that were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients with depression. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. Non-coloured cells with arrows depict only the relative change without any significance. In the left 4 rows gut-bacterial alterations caused by drugs metformin (MET), statins, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are set in comparison to the altered gut bacteria populations found in patients with Parkinson's disease.

Source	Parkinson's	Bacteria	MET	Statins	PPIs	NSAIDs
(Chen & Lin, 2022; Gerhardt & Mohajeri, 2018; Li et al., 2019; Ryman et al., 2023)	↑	*Akkermansia*				
(Nuzum et al., 2020; Pellegrini et al., 2018)	↑	*Akkermasia muciniphila*	↑			
(Chen & Lin, 2022)	↑	*Alistipes*	↓			
(Bell et al., 2019)	↓	*Anaerostipes*				
(Li et al., 2019; Pellegrini et al., 2018)	↓	*Bacteroides*				↑
(Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018)	↓	*Bacteroides fragilis*				
(Bell et al., 2019; Chen & Lin, 2022; Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018)	↑	*Bifidobacterium*	↑			
(Nuzum et al., 2020)	↑	*Bifidobacterium adolescentis*	↑			
(Bell et al., 2019; Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018; Ryman et al., 2023)	↓↑	*Blautia*	↑		↑	
(Nuzum et al., 2020; Pellegrini et al., 2018)	↓	*Clostridium coccoides*				
(Gerhardt & Mohajeri, 2018; Nuzum et al., 2020)	↓	*Coprococcus eutactus*				
(Chen & Lin, 2022)	↑	*Cornebacterium*				
(Bell et al., 2019; Chen & Lin, 2022; Gerhardt & Mohajeri, 2018; Pellegrini et al., 2018)	↑↓	*Corpococcus*				
(Chen & Lin, 2022; Ryman et al., 2023)	↑	*Desulfovibrio*		↓		
(Pellegrini et al., 2018)	↓	*Dorea*			↑	
(Bell et al., 2019; Gerhardt & Mohajeri, 2018; Pellegrini et al., 2018)	↑	Enterobacteriaceae				↑
(Chapelet et al., 2019)	↓	Enterococcaceae				
(Rajput et al., 2021)	↑	*Enterococcus*				

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formation has also been observed in ENS neurons, especially in the early stages of PD in mice and in PD patients (Wittung-Stafshede, 2022). Recent studies showed that Lewy-body formation in the brain was induced by amyloid fibres in the gastrointestinal tract of mice and a drastic risk reduction in those Lewy body formation via truncal vagotomy.

Amyloid formation does not have to be particular to one protein only. Amyloidogenic proteins can cross-seed each other to form amyloids. The molecular process is still unknown but can happen among human and between human and non-human amyloidogenic proteins. Several species in the GM produce biofilms containing amyloids. It is suggested that gut-amyloids could theoretically travel through the vagal route to the brain and cross-seed alpha-synuclein (Pellegrini et al., 2018). *E. coli*, *Pseudomonas, Streptococcus, Staphylococcus, Salmonella, Mycobacteria, Klebsiella, Citrobacter* and *Bacillus* are the bacterial candidates in the gut producing such extracellular amyloids (Wittung-Stafshede, 2022). Nuzum et al. also suggested an overall low abundance in SCFA-producing bacteria (Nuzum et al., 2020). Therefore, the gut microbiome could initiate as well as modulate PD-initiation.

When comparing microbial composition in PD patients with healthy controls, a predominance of Ruminococcaceae, Verrucomicrobiaceae, *Porphyromonas, Akkermansia* (incl. species *A. muciniphila*), Pasteurellaceae, Lachnospiraceae, *Desulfovibrio, Lactobacillus, Bifidobacterium* (incl. species *B. adolescentis*), *Ralstonia*, Enterobacteriaceae, *Flavonifractor, Cornebacterium, Alistipes, Escherichia* and *Megasphaera* is reported in PD patients (Bell et al., 2019; Chapelet et al., 2019; Chen and Lin, 2022; Gerhardt and Mohajeri, 2018; Li et al., 2019; Nuzum et al., 2020; Pellegrini et al., 2018; Rajput et al., 2021; Ryman et al., 2023; Zhang et al., 2022). Bacteroidetes, *Prevotella, Faecalibacterium* incl. *F. prausnitzii*, *Coprococcus, Blautia, Roseburia* (incl. *R. faecis*), *Eubacterium, Anaerostipes, Veillonella parvula,* Enterococcaceae and *Dorea* were found to exhibit depleted abundances (Bell et al., 2019; Chapelet et al.,

Table 7 (*continued*)

(Chen & Lin, 2022; Rajput et al., 2021)	↑	*Escherichia*	↑			
(Chapelet et al., 2019)	↓	*Eubacterium*				
(Bell et al., 2019; Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018; Ryman et al., 2023)	↓	*Faecalibacterium*	↑↓	↓	↓	
(Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018)	↓	*Faecalibacterium prausnitzii*		↑		
(Pellegrini et al., 2018)	↑	*Flavonifractor*				
(Zhang et al., 2022); (Chapelet et al., 2019; Chen & Lin, 2022; Pellegrini et al., 2018)	↑	Lachnospiraceae				
(Gerhardt & Mohajeri, 2018; Nuzum et al., 2020; Pellegrini et al., 2018; Ryman et al., 2023)	↑	*Lactobacillus*	↑			
(Chen & Lin, 2022; Nuzum et al., 2020)	↑	*Megasphaera*	↑↓		↑	
(Li et al., 2019)	↑	Pasteurellaceae				
(Chen & Lin, 2022; Li et al., 2019)	↑	*Porphyromonas*			↓	
(Gerhardt & Mohajeri, 2018; Pellegrini et al., 2018)	↓	*Prevotella*				↑
(Bell et al., 2019; Pellegrini et al., 2018)	↑	*Ralstonia*				
(Chen & Lin, 2022; Pellegrini et al., 2018; Ryman et al., 2023)	↓	*Roseburia*	↓			
(Li et al., 2019)	↑	Rumnicocaccaceae		↑		↑
(Rajput et al., 2021)	↑	*Streptococcus*		↓	↑	
(Nuzum et al., 2020)	↓	*Veillonella parvula*			↑	
(Gerhardt & Mohajeri, 2018; Li et al., 2019; Pellegrini et al., 2018)	↑	Verrucomicrobiaceae		↑		

Table 8
Altered bacterial abundancies in patients with Alzheimer's disease (AD) (with its respective sources) in relation to altered bacterial abundancies in metformin, statins, PPIs and NSAIDs users. Bacteria that were found in higher (↑, green coloured) or lower (↓, orange coloured) abundance in patients with depression. Coloured cells represent a significance level of at least $p < 0.05$, which are significant in at least one of the sources mentioned. Grey-coloured cells depicting both arrows (↑↓) have had significant changes in both higher and lower abundancies. Non-coloured cells with arrows depict only the relative change without any significance. In the left 4 rows gut-bacterial alterations caused by drugs metformin (MET), statins, proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) are set in comparison to the altered gut bacteria populations found in patients with Alzheimer's disease.

Source	Alz-heimer's	Bacteria	MET	Statins	PPIs	NSAIDs
(Chen et al., 2021; Zhou et al., 2022)	↑↓	Bacteroida-ceae			↑	
(Chen et al., 2021; Eicher & Mohajeri, 2022)	↓	*Bacteroides fragilis*				
(Chen et al., 2021; Zhou et al., 2022)	↑	Bacteroidetes				↑
(Eicher & Mohajeri, 2022)	↓	*Bifidobacte-rium*	↑			
(Chen et al., 2021)	↑	*Dorea*				
	↑	Enterococca-ceae				
(Chen et al., 2021; Choi et al., 2022; D'Argenio & Sarnataro, 2019; Doroszkiewicz et al., 2021; Wu et al., 2022)	↑	*Esche-richia/Shi-gella*	↑			
(Chen et al., 2021)	↓	*Eubacterium hallii*				
(Chen et al., 2021; Choi et al., 2022; D'Argenio & Sarnataro, 2019; Doroszkiewicz et al., 2021; Wu et al., 2022)	↑	*Eubacterium rectale*				
(Chen et al., 2021)	↓	*Faecalibacte-rium prausnitzii*		↑		
(Eicher & Mohajeri, 2022; Zhou et al., 2022)	↑↓	Firmicutes		↓		↑↓
(Chen et al., 2021)	↓	Fusobacteri-aceae			↓	
(Chen et al., 2021; Zhou et al., 2022)	↑↓	Lachnospi-raceae				
(Chen et al., 2021)	↑	Lactobacil-laceae				
(Chen et al., 2021; D'Argenio & Sarnataro, 2019; Zhou et al., 2022)	↑↓	*Lactobacillus*	↑			
(Chen et al., 2021)	↓	Negativicutes				
	↑	Prevotel-laceae				↑
(Chen et al., 2021; Zhou et al., 2022)	↑	Ruminococ-caceae		↑		↑
(Chen et al., 2021)	↑	*Streptococcus*		↓	↑	
	↓	Veillonel-laceae				

2019; Chen and Lin, 2022; Gerhardt and Mohajeri, 2018; Li et al., 2019; Nuzum et al., 2020; Pellegrini et al., 2018; Rajput et al., 2021; Ryman et al., 2023; Zhang et al., 2022). The family of Lactobacillaceae was observed inconsistently showing both higher and lower abundances. .

While comparing PD's dysbiosis and drug-induced dysbiosis, the postulations are as follows: PPIs induce SIBO (Koo et al., 2019) and increase the risk of *Salmonella* infections (Naito et al., 2018). Both could influence PD, since SIBO is also found in PD patients (Ryman et al., 2023) and *Salmonella* is a extracellular amyloid producer (Wittung--Stafshede, 2022). However, *Salmonella* is not observed as a common denominator in PPIs and PD. Similar to MS, the family of Ruminococcaceae is increased in PD, Statins and NSAIDs. However, SCFAs are known to strengthen BBB integrity (Eicher and Mohajeri, 2022), therefore, reducing the risk of inflammatory factors passing through the brain and thus, in formation of extracellular amyloid. On the other hand, *Faecalibacterium*, a known butyrate producer important for gut and BBB integrity and anti-inflammatory bacterial taxa (Eicher and Mohajeri, 2022; Tran and Mohajeri, 2021), is reduced in PD, statins and PPIs, suggesting that *Faecalibacterium* may be one of the reasons for the weakened barriers and heightened inflammatory processes in Parkinson's patients. MET and PPIs, however, may help to revert *Faecalibacterium's* disadvantages, since MET and PPIs increase the presence of *Blautia*, whereas it is reduced in PD patients. Similarly higher abundance in Ruminococcaceae due to statins and NSAIDs could also compensate *Faecalibacerium's* and other disadvantageous species effects. This also shows that no single medication exert all negative or positive effects, for instance, PPIs increase *Blautia* (an advantageous SCFA producer (Eicher and Mohajeri, 2022; Ryman et al., 2023; Tran and Mohajeri, 2021)) and simultaneously increase SIBO (Koo et al., 2019), which is a negative process in the human body.

Overall, MET consumption produces the most similar effects on microbiome to effects seen in Parkinson's disease than other drugs

mentioned in this article. Increased abundance of *Akk. muciniphila* (SCFA-producer and LPS-bearer (Eicher and Mohajeri, 2022; Tran and Mohajeri, 2021)), *B. adolescentis* (GABA-producer (Eicher and Mohajeri, 2022)), and *Escherichia* (LPS-bearer, 5-HT-metabolsier (Eicher and Mohajeri, 2022)) are observed in both PD patients and MET users, of which the first and the latter bacterial species are gram-negative with LPS in their cell walls, but also produce SCFA and 5-HT respectively. Again, they both convey advantageous and disadvantageous effects, suggesting that not one bacterium is the major determinant of the pathogenesis of a certain disease. Rather, their interplay and relative abundances seem to be important for the net-influence on disease onset and progression.

6.4. Alzheimer's disease

Alzheimer`s disease (AD) is the most common form of dementia of old age and makes up for around 50–70% of dementia cases worldwide. Since its prevalence grows with age and the world population is ageing, it is believed that AD's incidence will be higher in the next coming years. In most cases, it starts with the loss of newly formed memory with a further decline in neurocognitive and executive functioning such as in language and visuospatial orientation (Amboss, 2023a).

The pathophysiology is multi-faceted, yet unclear, leading to irreversible neuronal cell and synaptic loss. In addition to age, other hallmarks of AD are accumulation of insoluble amyloid beta plaques followed by neurofibrillary tangles of Tau protein, imbalance in neurotransmitters, and neuroinflammation (Amboss, 2023a). The gut microbiome undergoes substantial alterations as we age, therefore, it is suggested that age-related dysbiosis may contribute to the pathogenesis of AD as well. In the elderly a decrease in richness and compositional alterations are more prevalent with an increase in the ratio of pro-inflammatory to anti-inflammatory bacteria and a decrease in SCFA-producing bacteria leading to leaky gut, perturbed BBB, and microglial activation (Eicher and Mohajeri, 2022). The latter is important in clearing the Abeta plaques, and when its ability to do so is hindered by either greater production of Abeta or the loss in capability due to inflammatory structural changes, the amyloid plaques may accumulate in Alzheimer's patient's brains (Eicher and Mohajeri, 2022; Zhou et al., 2022). Amyloid proteins are postulated to also come from a bacterial source, which may, similar to PD, either cross-seed other amyloid structures in the brain or aggravate neuroinflammation rising from systemic inflammation due to the leaky gut (Eicher and Mohajeri, 2022). Moreover, translocation of bacteria through significantly positive SIBO breath tests ($p = 0.025$) was reported (Kowalski and Mulak, 2022). Bacterial translocation and increased levels of LPS in AD patients both heighten neuroinflammation (D'Argenio and Sarnataro, 2019; Doroszkiewicz et al., 2021; Epishina and Budanova, 2022).

The main findings point to increased levels of pro-inflammatory bacteria *Escherichia/Shigella* and decreased levels of anti-inflammatory *Eubacterium rectale* species (Chen et al., 2021; Choi et al., 2022; D'Argenio and Sarnataro, 2019; Doroszkiewicz et al., 2021; Wu et al., 2022). Their imbalance may be one of the main contributors to cognitive impairment and amyloid synthesis since respective correlation has been found between pro and anti-inflammatory cytokines (Choi et al., 2022) and also *Escherichia coli* belongs to amyloid-producing bacteria (Choi et al., 2022; Doroszkiewicz et al., 2021).

An increase in Bacteroidetes, Ruminococcaceae (Chen et al., 2021; Zhou et al., 2022), Prevotellaceae, Entereococcaceae, Lactobacillaceaea, *Dorea* and *Streptococcus* (Chen et al., 2021) were reported in AD patients. In contrast, a decrease in *Bifidobacteria, Bacillus/Bacteroides fragilis, Eubacterium hallii, Faecalibacterium prausnitzii* (Eicher and Mohajeri, 2022), Fusobacteriacaea, *Bacteroides fragilis*, Negativicutes and Veillonellaceae (Chen et al., 2021) were detected. Inconsistent results were found in Firmicutes (Eicher and Mohajeri, 2022; Zhou et al., 2022), *Lactobacillus* (Chen et al., 2021; D'Argenio and Sarnataro, 2019; Zhou et al., 2022), Lachnospiraceaea and Bacteroidaceae (Chen et al., 2021; Zhou et al., 2022). .

Among the drugs mentioned above and Alzheimer's patients, the association of statin-use showed the strongest association with the altered microbiota. Especially, *Faecalibacterium prausnitzii*, a butyrate producer (Eicher and Mohajeri, 2022; Knuesel and Mohajeri, 2021), is increased in statin-users, which could help maintain BBB, since butyrate plays a major role in anti-inflammatory processes and in microglia activation and maturation (Eicher and Mohajeri, 2022). Statins taken together with PPIs, may help to counterbalance the enrichment in *Streptococcus* due to PPIs use, since *Streptococcus* is suggested to produce extracellular amyloid. Ruminoccaceae, a SCFA-producer (Eicher and Mohajeri, 2022), is elevated in statins as well as NSAID users and in AD patients, possibly having the same compensating effects as in Parkinson's (PD), since lower abundance in SCFAs is observed in AD patients. As with PD, positive SIBO results are seen in AD patients, to which PPIs could be a major contributor, with or without oral application of NSAIDs.

7. Conclusion and future perspectives

The body of knowledge shows the great impact of dysbiosis on neurological diseases. Microbiota diversity and richness both are altered. Only few studies yet exist combining non-antibiotic drug-induced alterations to MGBA. Taking into account all relevant human data and supporting mechanistic data published in preclinical studies, we outlined here how and why metformin, statins, PPIs and NSAIDs may alter MGBA using depression, multiple sclerosis, Parkinson's and Alzheimer's as examples of neuronal diseases. Our data show that there are common bacterial strains in dysbiotic environments due to medication and in neuronal diseases. Few drugs could alleviate the dysbiosis under the specific conditions in one disease situation but also can give rise to it. On the other hand, there were drugs with both advantageous and disadvantageous effects. *Ruminococcus spp*., an advantageous SCFA-producer, is elevated in all the drug users and diseases mentioned above. *Prevotella* and *Akkermansia muciniphila* all have LPS in their cell walls and produce beneficial SCFAs. *Escherichia*, also an LPS carrier, can metabolise 5-HT and be a precursor for extracellular amyloids. Genus *Clostridia* has toxicogenic species such as *Clostridium difficile* and also SCFA-producer species. Depression has depleted levels of SCFAs and GABA, however, *Bacteroides spp*. are increased. They would be in abundance if the disease is correlated with the use of statins and NSAIDs. Bacteroides are GABA and SCFA producer and have LPS in their cell walls. These examples suggest that the relative abundances of the bacterial populations to each other and their interplay would influence the MGBA and not specific bacterial strains. In addition, the drugs discussed are frequently taken together in comorbid patients. Thus, their effects may counteract each other or intensify the respective changes in bacterial populations and associate positively or negatively with the dysbiosis in neurological diseases. In general, consistent results are debatable, since studies' diagnostic methods, gut or faecal microbiota detections, patients' exclusion/inclusion criteria, etc. vary considerably in most of the studies conducted (an e.g. is (Knudsen et al., 2021)). Depending upon the study, the bacterial specimens were either from the upper, middle, or lower GIT or stool samples. Not every article discussed in this review took all possible confounding factors (e.g., primary disease conditions, concomitant use of other medications, drug dose, drug exposure and duration of drug intake, age, sex, patients' diets, comorbidities and ethnicities) into account and or lacked appropriate controls and cohort sizes. Further, the control group represented patients already diagnosed with the diseases, rather than healthy patients. Wherever the case, the comparison to the respective control cohorts is mentioned. In addition, the authors transplanted the faecal bacterial samples from humans in antibiotic-treated mice (germ-free mice) to further support their clinical studies' results. Overall, these limitations may have led to some inconsistency in the results, as the varying differences made it difficult to compare the results for this review.

Even if not unequivocal, strong evidence suggests a link between

using medicinal drugs and MGBA and between MGBA and neuronal diseases, respectively. Future studies could focus on the implications of medicinal drugs, used to treat somatic diseases, and their gut-altering effects on MGBA influencing the onset or progression of brain-related disorders. Since the gut microbiome undergoes changes through various environmental and lifestyle factors, comorbid elderly people should be considered in such studies as well. Whilst ~~t~~aking more than one medication and with poor diet due to lack of appetite, one might expect different changes in the gut microbiota of elder people. However, the search for the correlation between daily prescribed drugs-induced dysbiosis and their implications on the brain related disorders via MGBA is still a new topic. Enough data on these correlations does not exist to draw suggestive conclusions. Closing this knowledge gap may result in new important perspectives in better understanding the bidirectional communication of the MBGA and in treating patients with the respective individualised treatment with novel therapies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Garg Kitri: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Mohajeri M. Hasan:** Writing – review & editing, Validation, Supervision, Project administration, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

Data Availability

Data will be made available on request.

Acknowledgements

We thank David P. Wolfer, Prof. MD, Julinka Waesche, Yogendra Garg and Luzi Brunner for their useful comments and the review of this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2024.110883.

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