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Review Article

Effect Of Antibiotics On Mental Health: A Review

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ABSTRACT

The review delves into the association between antibiotics and psychiatric side effects, such as depression and anxiety, highlighting the role of the brain-gut-microbiota axis. Through mechanisms like vagal nerve manipulation and short-chain fatty acid modulation, the gut microbiota significantly influences brain function. While certain antibiotics exhibit antidepressant properties, like isoniazid and minocycline, their broader impact warrants further exploration. Antibiotic-induced changes in gut barrier function, neurotransmitter levels, and blood-brain barrier integrity, coupled with reduced neurotrophic factors and vagal tone, present additional risks. Notably, fluoroquinolones and beta-lactams may stimulate the central nervous system, necessitating caution alongside antidepressants. Preclinical research on rifampicin for neurodegenerative diseases shows promise. Although psychiatric disorders from antibiotic use are rare, mitigating unintended impacts on brain-gut-microbiota interactions is crucial. Addressing antibiotic resistance in drug development underscores the importance of clinicians' awareness of these potential mental health effects. In conclusion, while antibiotics are crucial for treating infections, their association with psychiatric side effects underscores the importance of understanding their impact on mental health. Further research is needed to elucidate the mechanisms underlying these effects and to develop strategies for mitigating unintended impacts on brain-gut-microbiota interactions.

INTRODUCTION

The notion that mental health, antibiotics and bacteria are related might be whimsical [1]. There is no doubt that antibiotics have played a significant role in modern medicine in the 20th century [2]. The overuse of antibiotics is associated with detrimental effects on the gut microbiota, potentially leading to various disorders. Antibiotics, while crucial for treating infections, can have harmful consequences, including the transfer of antibiotic resistance genes to pathogenic bacteria, highlighting the

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importance of judicious antibiotic use. [3]. The gastrointestinal system harbours a vast population of microorganisms, which are commonly referred to as the gut microbiota. In depth analysis has indicated that the gut microbiota regulates the development and function of the brain, and the disturbances of the microbial community may contribute to neuropsychiatric diseases [4]. The mental health effects linked to antibiotic use are primarily attributed to disruptions in the microbiota-gut-brain axis, which modulates brain functionality and stress-induced behaviours like anxiety and depression. While the exact mechanisms are still unclear, evidence from germ-free animal models supports this association [5]. This review will discuss the ways in which antibiotics impact mental health by acting through the brain-gut-microbiota axis.

Composition of gut microbiota

The gut microbiome becomes increasingly unique to each individual with age, with over thousands of bacteria strains identified. Evidence strongly suggests that dysbiosis of the gut microbiota can contribute to various disorders. This occurs through a complex interplay between colonic microbiota, their metabolic byproducts, and the host immune system, crucial for maintaining intestinal homeostasis [6]. The microbiome is established initially through vertical transmission via the placenta, amniotic fluid, and meconium. Research indicates that newborns born vaginally possessed higher levels of bacteria in their intestines in comparison to those born through caesarean section. However, the main determinant of gut microbiota architecture in adulthood is diet and, to a lesser extent, exercise, but medications, especially antibiotics, play an important role [7].

Mechanism of communication of gut microbiome with the brain:

The gut microbiota can communicate with the brain through various pathways, including endocrine, immune and neural mechanisms. The vagus nerve, a major nerve connecting the gut to the brain, serves as a direct route for microbiota-brain signalling. Certain microbes like Campylobacter jejuni and Lactobacillus rhamnosus JB1 have been shown to alleviate anxiety and depressive symptoms by modulating vagus nerve activity, highlighting the potential role of the gut microbiota in psychiatric disorder development [8]. Short-chain fatty acids (SCFAs), like butyrate and propionate, produced by gut microbes from dietary fibre, cross the blood-brain barrier, interacting with the brain via various mechanisms. They act as endogenous ligands for G protein-coupled receptors (GPCRs), particularly FFAR2 and FFAR3, exerting neuroprotective effects by inhibiting histone deacetylases and modulating gene expression. SCFAs also impact inflammation, hormonal regulation, and vagal afferent interaction, although human research in this area is limited compared to animal studies [9]. The regulation of the gut-brain axis, which encompasses a two-dimensional relationship, is mediated by various neuroactive modulators like brain-derived neurotrophic factor (BDNF) and serotonin, as well as signalling molecules including lipopolysaccharides, tryptophan metabolites, and trimethylamine-N-oxide. These entities play pivotal roles in both the maintenance of overall health and the development of diseases [10]. Tryptophan, serving as a precursor for both serotonin and melatonin, is obtained from dietary intake or the gut microbiome. Serotonin, an essential neurotransmitter in the gut-brain axis, is regulated by the gut microbiota through the degradation of tryptophan along the kynurenine pathway. Additionally, the release of serotonin can be induced by short-chain fatty acids [11]. Peptide YY, glucagon-like peptide-1, gastric inhibitory peptide, cholecystokinin, oxytocin, corticotropin-releasing factor, and ghrelin, primarily found in the gastrointestinal tract, interact with vagus nerve

terminals and immune cells, enabling bidirectional communication between the gut and the brain [12]. Microbes can produce a number of neurotransmitters, including acetylcholine, gammaaminobutyric acid (GABA), norepinephrine, dopamine, and serotonin, while bacterial production or depletion of essential neurotransmitter intermediates such as tryptophan can also affect host production. Depletion of the microbiome is capable of altering specific levels of neurotransmitters, even in the brain [13].

Antibiotics as antidepressants:

The use of antidepressants began with the discovery of isoniazid, a drug for tuberculosis that had unexpected mood-elevating effects. This side effect became the focus of treatment for depression and led to the creation of newer antidepressants [14]. Li et al., conducted a study on the regulation of BDNF expression following antibiotic treatment of experimental bacterial meningitis and concluded that BDNF might play a neuroprotective role in brain damage during bacterial meningitis, and the expression of BDNF messenger RNA and its production might be inhibited after treatment with antibiotics. The findings suggest that both eradicating the bacterial pathogen with antibiotics and adjuvant administration of BDNF might be more beneficial to prevent brain damage [15].

In another meta-analysis of clinical trials of anti-inflammatory drugs, including the antibiotic minocycline, in depressed patients, Kohler-Forsberg et al., revealed that minocycline as an adjunct, had a positiveimpact on depressive symptoms. This conclusion was supported by the findings of Hussain et al., in contrast, a randomized controlled trial carried out by Regen et al., indicated that minocycline did not influence the progression of depression severity [16]. Mello et al., conducted a study using sub-antimicrobial-dose doxycycline (10mg/kg), alone or combined with escitalopram (4mg/kg), in a mouse to investigateits ability to reverse lipopolysaccharide-induced depressive-like changes. They demonstrated thatdoxycycline reduced inflammation and increased protective markers in the brain, suggesting its potential as a strategy for treating depression in the presence of inflammation [17]. Therefore, in brief, certain antibiotics, specifically minocycline and doxycycline, have been documented to exhibit antidepressant properties, while some antidepressants possess antibiotic attributes.

Antibiotics have a generally high tolerance rate, yet they can produce a variety of adverse drug reactions, including neurotoxicity, which can manifest in a range of symptoms such as headaches, delirium, psychosis, and seizures. However, the exact incidence of neurotoxic adverse drug reactions with anti-infectives is uncertain, but it is believed to be less than 1% [18]. Three nested case control studies were carried out by Lurie et al., between 1995-2013, using a vast medical record database from the UK. The research indicated that single antibiotic treatments, such as penicillins and quinolones, were relatedto an increased likelihood of depression. Additionally, a correlation was found between these antibiotics and anxiety, particularly notable with penicillins and sulphonamides exposure [19]. Recently, similar results have been reported in a clinical study based on fluoroquinolones. A survey observed 94 patients who consumed fluoroquinolones reported the following side effects: anxiety disorder (72%), panic attacks (37%), depression (62%), insomnia (48%), and cognitive impairment (33%) [20]. Guida et al., in 2018 discovered that two-week antibiotic cocktail treatment in mice caused depression-like phenotype [21]. Also, another study conducted by Hoban et al. concluded that long-term exposure to antibiotics in adulthood represents a period in which disturbance of the gut bacteria can impact both the brain and behaviour [22]. In a population-

based study, Lavebratt et al., discovered a modest link between early antibiotic exposure and subsequent childhood development of sleep disorders, attention deficit hyperactivity disorder (ADHD), anxiety disorders, and other behavioural and emotional disorders. Further investigation is necessary to confirm the effect sizes across specific diagnostic categories while considering family-related confounders and to ascertain whether the observed associations stem from antibiotic use or the infections being treated [23]. Bhattacharya et al., reviewed 391 cases of antibiotic associated encephalopathy and found that the psychosis present in 47% of the cases, most of them were connected to sulphonamides, fluoroquinolones, macrolides, and intramuscular penicillin treatment [24]. Metronidazole-induced encephalopathy, documented since 1977, manifests with memory loss, disorientation, and various neurological symptoms. The findings of the review carried out by Forth et al., suggest that the use combining probiotic therapy with selective serotonin reuptake inhibitors (SSRIs) is more effective in treating depression and anxiety compared to SSRIs alone [25]. Schizophrenia, a severe and enduring psychiatric condition, is typically treated with antipsychotic medications. In addition to these, antibiotics such as minocycline also been evaluated as add-on treatments for schizophrenia [26]. Alan et al., documented a case of a 16-year-old girl who experienced acute catatonia-like symptoms after taking 1000 mg/day oral clarithromycin for tonsillitis. She was treated with haloperidol and showed gradual improvement after clarithromycin cessation. Upon discharge, she returned to normal functioning within a week [27]. Thus, the use of antibiotics has been linked to an increased risk of depression, anxiety, and other psychiatric illnesses, particularly when multiple or repetitive prescriptions are required, but most patients do not experience psychiatric complications, and the reason for this discrepancy is unknown. Zhang et al., conducted a community based cross-sectional study to examine the association between antibiotic exposure in children and mental health, in which they suggested that ciprofloxacin and fluoroquinolones may be associated with child mental disorders [5]. Here we explore the impact of antibiotics on the brain-gut-microbiota axis and their effect on mental health.

Oxidative Stress:

Oxidative stress, associated with depression, may be exacerbated by antibiotics through gut microbiota disruption, reducing antioxidant production and leading to depression development. Mice treated with antibiotics exhibited depression-like behaviours, elevated oxidative stress, and diminished antioxidant defences, suggesting antibiotic-induced neurotoxicity [18].

Modulation of brain-derived neurotrophic factor:

BDNF plays a noteworthy role in memory and learning. BDNF is necessary for a range of neurologic functions. A reduction in BDNF levels has been linked with atrophy of brain regions that are involved in the processing of emotions, such as the hippocampus. Many studies have shown that BDNF levels are low in depressed patients and are elevated by antidepressants such as SSRIs [28].

The normal gut microbiota influences the expression of BDNF in brain regionssuch as the hippocampus and cortex, which is crucially involved in the development of appropriatebehavioural patterns. Anassociation between the development of behavioural disorders, such as anxiety and cognitive deficits, and altered BDNF levels in different CNS regions was demonstrated both in germ free mice and in adolescent mice after antibiotic treatment-induced dysbiosis [29]. In a rodent study by Zhao et al., it was found that extended exposure to ceftriaxone leads to changes in gut bacteria, decreased BDNF

in the hippocampus, and heightened anxiety, depression and aggression [30].

Direct brain toxicity:

Metronidazole can cause cerebellar toxicity, resulting in varying degrees of limb and gait ataxia and dysarthria. Polymyxins were once discontinued due to concerns about neurotoxicity and nephrotoxicity, but have regained relevance in treating nosocomial infections with the emergence of multi-drug resistant gram-negative bacilli. Neurologic side effects have been reported, with a high incidence of 7% to 27% [31]. Ofloxacin has potential neurotoxicity due to better CNS barrier penetration. A 71-year-old male experienced Tourette-like symptoms such as sweating, insomnia, spitting, echolalia, echopraxia, orofacial and limb automatisms, and hypersalivation. This indicates a possible interaction between the antibiotic and the central dopaminergic system [32]. Vancomycin treatment for ventriculitis has been linked to localised neurotoxic effects. Nava Ocampo et al., documented a neonate's case of ventriculitis, eosinophilia and CSF pleocytosis, developed after intraventricular injection of vancomycin for Enterococcus fecalis. This effect was thought to be mediated by vancomycin-induced inflammationin the cerebrospinal fluid (CSF) [33]. Hence, neurotoxicity is common among many groups of antibiotics, especially in at-risk patients, and can range from ototoxicity, neuropathy, and neuromuscular blockade to confusion, nonspecific encephalopathy and seizures.

Effect on gut diversity and gut hormone:

The impact of antibiotics on the gut microbiome is well-documented, with factors like age and route of administration influencing their effects. Studies have shown that while antibiotics can cause rapid shifts in bacterial populations, the microbiome often recovers to its original state within a few months. Additionally, research suggests that short-term antibiotic courses may not significantly affect gut hormone regulation in healthy individuals [34]. Fröhlich et al., conducted an experiment involving adult mice exposed to multiple antibiotics. The study findings emphasized the crucialinvolvement of cerebral neuropeptide Y system and circulating metabolites in the cognitive decline and disruption of cerebral signalling molecules causedby antibiotic-induced gut dysbiosis [35]. Li et al, demonstrated that rifaximin alleviated depressive-like behaviour induced by chronic unpredictable mild stress. Rifaximin increased the abundance of Lachnospiraceae and Ruminococcaceae in the gut, positively correlating with elevated butyrate levels in the brain [36]. One week of rifaximin intervention affected the prefrontal and cingulate low beta oscillation in response to social stress and the prefrontal and cingulate alpha oscillation in the resting state, according to a study by Wang et al [37]. Thus, proving that rifaximin possess stress reducing properties.The results enhance comprehension of the effects of antibiotics on gut microbiota and gut hormones and endorse the idea that alterations in gut microbial diversity play a crucial role in the pathophysiology of antibiotic-related depression.

Blood-Brain-Barrier and Neurotransmitters:

Changes in the gut microbiome caused by antibiotics can affect the integrity of the blood-brain barrier (BBB), linking antibiotic-induced microbiome alterations to mental health. Studies suggest that antibiotics may increase depression risk by influencing BBB permeability. Animal studies show that antibiotics like penicillin can alter the BBB and induce behavioural abnormalities, while introducing ampicillin in mice leads to depression-like behaviour and reduced expression of proteins associated with BBB integrity in the hippocampus, indicating BBB disruption as a factor in antibiotic-induced depression [18]. Antibiotics targeting Lactobacillus and Bifidobacteria strains, known

for their GABA production, could diminish in vivo GABA levels in the gut, affecting gut-brain axis interactions. This includes penicillins, macrolides, and other antibiotics that may disrupt these beneficial bacterial populations [38].Zareifopoulos et al., concluded that antimicrobial drugs can impact the CNS in a manner dependent on dosage, with certain drugs possessing psychotropic properties. Certain drugs, such as clarithromycin, beta-lactams, and fluoroquinolones, may act as CNS stimulants via GABA-A agonism, leading to mania and seizures. Additionally, linezolid is a monoamine oxidase inhibitor. These antibiotics should be used with caution in patients using anti-depressants [39]. Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are generally characterised by abnormal aggregation and deposition of specific proteins. In AD, the main protein that deposits is amyloid beta (Aβ), while in PD, the main protein that deposits is alpha-synuclein (α-syn), which can disrupt neurotransmission. Zare et al., showed geldanamycin pre-treatment can notably reduce depression- and anxiety- like behaviours in Aβ - injected rats [40]. Yurtsever et al., conducted a study on adult zebra fish that were exposed to rifampicin for 3 weeks and found that rifampicin was effective in reducing neuroinflammation, hinting at its potential as a viable approach to mitigating mitochondrial dysfunction associated with disrupted calcium balance in PD. Rifampicin has a notable brain protective impact in various experimental models, including pre-clinical models of AD, and substantial clinical evidence for the neuroprotective properties that enhance cognitive function [41].

LIMITATIONS:

Understanding the impact of antibiotics on mental health is challenging due to their diverse structures and the complexity of factors involved, such as infections acting as confounders. Mechanistic studies in humans are lacking, making it hard to discern how antibiotics contribute to psychiatric risks. Most studies focus on short-term outcomes, leaving long-term effects, especially across antibiotic classes, poorly understood. Moreover, distinguishing antibiotic effects from those of the infection itself remains challenging, complicating the assessment of mental health changes.

CONCLUSION:

Antibiotics exhibit dual effects on mental health, with some, like minocycline and doxycycline, potentially alleviating depression, while others can induce depression, anxiety, and psychotic disorders. This phenomenon is linked to disruptions in the gut microbiota and the gut-brain axis. Understanding which antibiotics pose risks to mental health and investigating their mechanisms are essential for mitigating unintended impacts and addressing antibiotic resistance. Clinicians must remain vigilant about these complexities in antibiotic therapy.

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