

CHAPTER TWENTY-ONE

Globalising Education on Neuropsychiatric Effects of Antibiotics

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Abstract

Antibiotics are well known for fighting infections, but what is often left out of the discussion is their impact on mental health. Their misuse - and even prescribed use - can disrupt the balance of gut bacteria, which plays an important role in how the brain functions. This disruption may cause neurotransmitter imbalances, subsequently leading to several neuropsychiatric disorders. As the world becomes more connected, it is important for healthcare workers to understand these effects. Improving education and encouraging global collaboration will help ensure antibiotics are used more wisely, support mental well-being, and allow exploration of safer alternative ways to treat infections.

Keywords: Globalising Education, Neuropsychiatric, Effects, Antibiotics.

Introduction

Antibiotics are widely recognised for their critical role in combating bacterial infections, revolutionising modern medicine by significantly reducing morbidity and mortality. However, the effects of antibiotics extend beyond their primary role in eradicating pathogens. Although antibiotics are developed to target bacteria, they can have unintended effects on the Central Nervous System (CNS), leading to a variety of neuropsychiatric manifestations. The neuropsychiatric effects of antibiotics encompass a wide spectrum of symptoms, ranging from mild cognitive disturbances and mood changes to more severe outcomes such as anxiety, depression and psychosis.

It is currently believed that antibiotic misuse can induce drug resistance and increase the risk of depression because of the disturbance of intestinal flora (Fan *et al.*, 2022). These effects are often transient and reversible, but they can be distressing for patients and challenging for clinicians to manage. Importantly, these adverse effects are not limited to instances of antibiotic

misuse or overuse. They can occur even when antibiotics are administered at standard therapeutic doses. The case report by Iqbal *et al.* (2022) demonstrated that antibiotics such as Trimethoprim-sulfamethoxazole (TMP-SMX) can induce neuropsychiatric effects, including psychosis, even when prescribed appropriately and not misused. This, again, highlights the need for clinicians to be vigilant about the potential CNS effects during treatment.

These effects should be understood for optimising patient care, particularly in vulnerable populations such as the elderly and those with crucial pre-existing neurological or psychiatric conditions.

Emerging Research on Antibiotics' Unintended Mental Health Effects

Nearly all antibiotic agents have been associated with Central Nervous System effects. These effects can be uncommon, but they can be severe (Skelly *et al.*, 2019). A study highlights how antibiotics can influence brain chemistry and behaviour by disrupting the gut microbiome. This disruption has been linked to an increased risk of depression and anxiety (Dinan & Dinan, 2022), suggesting a complex interplay between gut health and mental health. The gut microbiome, which has long been recognised for its role in digestion and immune function, has been found to also play a significant role in brain health through the gut-brain axis.

Gut Microbiome and Its Role in Health

The gut microbiome is a highly complex and dynamic microbial community, encompassing almost 39 trillion microbial cells, which includes bacteria, viruses, fungi that live in and on us (Kumari *et al.*, 2022). A healthy gut with diverse microbes is vital for normal brain functions and emotional behaviours (Suganya & Koo, 2020). Gut bacteria break down fibers from food to produce Short Chain Fatty Acids (SCFAs), which help the gut by reducing inflammation, and supporting brain function. Beneficial bacteria, such as Bifidobacteria, produce tryptophan needed to make serotonin, a neurotransmitter that affects mood and sleep. *Lactobacillus* makes Gamma-Aminobutyric Acid (GABA), promoting calmness (Dinan & Dinan, 2022).

Antibiotics' Impact on the Gut Microbiome

Though antibiotics are highly effective against infections, their broad-spectrum action can unintentionally disrupt the delicate balance of the gut

microbiome. Antibiotics disrupt the delicate balance of the gut microbiome through the following ways:

- **Non-Discriminatory Action:** Antibiotics disrupt the gut microbiome by indiscriminately killing beneficial and harmful bacteria (Zimmermann and Curtis, 2019). Unlike targeted therapies, antibiotics often do not differentiate between "good" and "bad" bacteria. This means they can wipe out beneficial bacteria alongside the harmful ones causing the infection.
- **Shifting the Landscape:** The loss of beneficial bacteria disrupts the overall composition of the gut microbiome. In this disrupted state, this gives room for pathogens like *Clostridioides difficile* to overgrow (Ramírez *et al.*, 2020).
- **Reduced Diversity:** Antibiotic use can reduce gut microbiota species diversity and alter metabolic activity leading to recurrent *Clostridioides difficile* infections (Ramírez *et al.*, 2020). Reduced diversity can promote dysbiosis (an imbalance within a community of microorganisms living together — a microbiome), as some bacteria may become overly dominant, leading to an imbalance in the production of metabolites.

How Does the Gut Microbiome Communicate with the Brain?

The Gut-Brain Axis

The gut microbiome is comprised of all the microorganisms in the gut including bacteria, viruses, and fungi and the bi-directional communication between the gut and brain mediated via actions of bacteria is referred to as the “microbiota-gut-brain axis” (Olavarria-Ramírez *et al.*, 2023). The gut microbiome communicates with the brain through a complex network of nerves, hormones, and immune messengers. One of the primary neural routes is the vagus nerve, which transmits signals (neurotransmitters) between the gut and the brain (Ashique *et al.*, 2024).

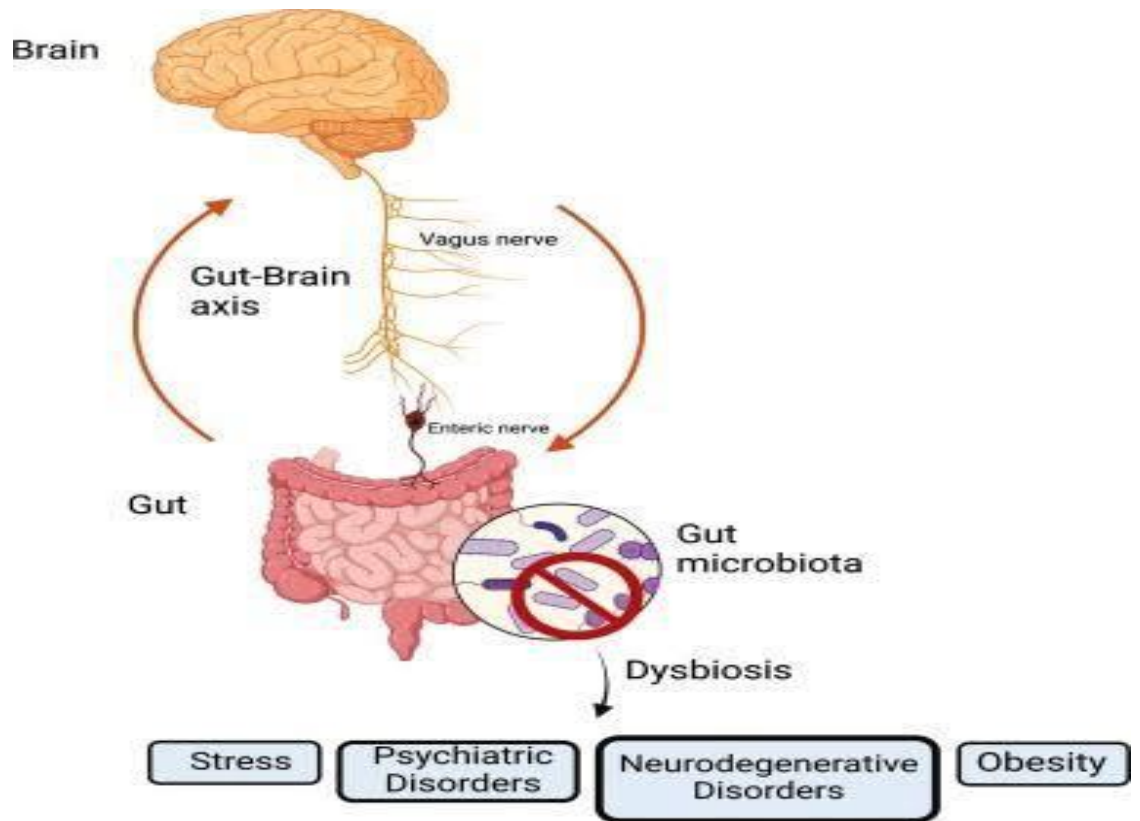


Figure 1: Gut-Brain Axis

Source: (Singh *et al.*, 2024).

Neuropsychiatric Effects Associated With Antibiotics

Anxiety

Anxiety disorders are a group of mental health diagnoses characterised by excessive, persistent, and irrational fear or worry about everyday situations or events. Fluoroquinolones, a class of antibiotics used to treat serious bacterial infections, including respiratory, urinary tract, and skin infections, are associated with psychiatric adverse events such as anxiety (Xie *et al.*, 2024).

Depression

Depression is a common mental disorder with persistent depressed mood and common symptoms like inferiority, pessimism and suicide behaviour (Meng *et al.*, 2022). As a serious mental illness, depression is recognised as a disease associated with the gut microbiota and the brain–gut axis (Wen-Zhi *et al.*,

2020). Dinan and Dinan study in 2022 found that antibiotic exposure is associated with an increased risk of depression. A single course of antibiotics was linked to a higher risk of depression, with penicillins and quinolones. The risk of depression increased with repeated antibiotic use.

Mania

Mania is a mental illness characterised by increased talkativeness, rapid speech, decreased need for sleep, racing thoughts and distractibility (Dailey & Saadabadi, 2023). Meszaros *et al.* (2021) reported a case of antibiotic-induced mania in a 50-year-old man with no prior psychiatric history. The patient initially started treatment with amoxicillin-clavulanic acid for left basal pneumonia and later switched to clarithromycin. Shortly after beginning the antibiotic therapy, the patient developed psychiatric symptoms, including logorrhea (excessive talking), elevated mood, irritability, increased physical activity, and delusions, which were consistent with a manic episode. Upon stopping clarithromycin, the patient's symptoms improved within 12 hours, supporting the diagnosis of a clarithromycin-induced manic episode. However, when amoxicillin-clavulanic acid was reintroduced for the pneumonia, the psychiatric symptoms reappeared. After discontinuing the second antibiotic, the patient was symptom-free approximately one week after. The case highlights the potential for antibiotics such as clarithromycin and amoxicillin-clavulanic acid to induce manic episodes as a rare but serious side effect.

Psychosis

Psychosis is a clinical syndrome associated with impairments in multiple domains including functioning, thought, behaviour, and cognition (Kilciksiz *et al.*, 2020). It is a severe mental disorder characterised by a loss of touch with reality. The most common antibiotics leading to the development of psychosis are penicillin, fluoroquinolones, cephalosporins, Linezolid and anti-tuberculous drugs (Maqsood *et al.*, 2022).

Table 1: Neuropsychiatric Effects Linked to Antibiotic Use

Antibiotic Class	Neuropsychiatric Effect	Reference
Beta Lactams e.g Penicillin and Cephalosporins	Psychosis, Mania, Depression	(Guglielmo, 2021; Meszaros <i>et al.</i> , 2021; Lam, 2021; Liu <i>et al.</i> , 2022; Maqsood <i>et al.</i> , 2022)
Macrolides e.g	Mania, Depression	(Lam, 2021; Liu <i>et al.</i> , 2022)
Fluoroquinolones e.g	Psychosis, Anxiety, Mania	(Guglielmo, 2021; Maqsood <i>et al.</i> , 2022; Xie <i>et al.</i> , 2024)
Tetracyclines	Depression	
Sulfonamides	Psychosis	(Liu <i>et al.</i> , 2022)
		(Iqbal <i>et al.</i> , 2022)

Susceptibility Factors

A. Age as a Determinant

Age is a critical factor influencing susceptibility to antibiotic-induced neuropsychiatric effects.

- **Pediatric population:** The developing brain in children is particularly sensitive to external influences. Antibiotic exposure during critical developmental periods may have long-term consequences for brain function and mental health. A study by Slykerman *et al.* (2019) found that children exposed to antibiotics during the first six months of life had significantly lower cognitive and verbal comprehension abilities at

age 11, as well as increased risks of attention-deficit hyperactivity disorder (ADHD), anxiety, and emotional problems after adjusting for confounding factors like breastfeeding.

- **Geriatric population:** Elderly individuals are more likely to experience adverse drug reactions due to age-related physiological changes, including decreased renal and hepatic function, and polypharmacy. The study by Liu *et al.*, 2021 suggested that exposure to certain antibiotics, particularly azithromycin, sulfaclozine, tetracyclines, and veterinary antibiotics, may be associated with an increased risk of depression in elderly individuals.

- **Pre-existing Mental Health Conditions**

Individuals with pre-existing mental health conditions are at heightened risk of experiencing exacerbated symptoms or developing new psychiatric problems after antibiotic use.

Strategies for Mitigating Risks

To mitigate the risks posed by antibiotics on the gut microbiome and the potential neuropsychiatric symptoms that may arise from this disruption, several strategies can be implemented:

Healthcare providers should:

- Administer antibiotics only when necessary.
- Discontinue the offending antibiotic and switch to a safer alternative if neuropsychiatric symptoms arise (Althubyani *et al.*, 2024)
- Choose narrow-spectrum antibiotics over broad-spectrum (Avis *et al.*, 2021).

Patients should:

- Take probiotics/prebiotics to restore gut microbiome (Ashique *et al.*, 2024; Yoo *et al.*, 2024).

Prebiotics and probiotics play crucial roles in gut health. Prebiotics are non-digestible fibers that serve as food for beneficial gut bacteria, promoting their growth and activity. Common sources include bananas, onions, garlic, and whole grains. Probiotics, on the other hand, are live microorganisms that provide health benefits when consumed, found in fermented foods like yogurt,

kefir, and sauerkraut. Together, they help maintain a balanced gut microbiota, supporting digestion and overall health. Probiotic supplementation during the perinatal and infant period can restore gut microbiota imbalance, especially with mixtures of *Lactobacillus* and *Bifidobacterium* strains (Navarro-Tapia *et al.*, 2020).

Future Prospects

Antibiotic-specific effects: One crucial aspect of future research is to delve deeper into the differential effects of various antibiotic classes on the gut microbiome and neurotransmitter systems i.e development of selective antimicrobials that target harmful bacteria without disrupting the gut microbiome (Avis *et al.*, 2021).

Alternative Antimicrobial Strategies

- a. **Phage therapy:** This involves the use of bacteriophages to fight bacteria (Tamma and Suh, 2021). Phage therapy, the therapeutic use of bacteriophages to combat bacterial infections, is gaining increasing attention as a promising alternative to traditional antibiotics. Bacteriophages are viruses that specifically infect bacteria, offering the potential for high specificity and minimal impact on the microbiome.
- b. **Host-Directed therapy:** Host-directed therapies represent another promising approach to combating bacterial infections while minimising the impact on the microbiome. The goal of host-directed treatments is to strengthen the immune system of the host, and improve the host's capacity to recognise and react to infections (Gholap *et al.*, 2024). Instead of directly killing bacteria, these strategies focus on bolstering the host's immune response, enabling the body to fight off the infection more effectively.
- c. **Natural products:** Natural antimicrobial compounds are the best alternative for controlling bacterial infections and reducing drug resistance due to their lack of severe side effects, low cost of production, and biocompatibility (Nourbakhsh *et al.*, 2021). Exploring plant-derived compounds and other natural products with antimicrobial properties could lead to the discovery of novel agents with minimal side effects. (Nourbakhsh *et al.*, 2021).

Conclusion

Antibiotics are essential for treating bacterial infections, but their unintended effects on the gut microbiome and brain health cannot be ignored. Disrupting beneficial gut bacteria can reduce neurotransmitter production and short-chain fatty acids, potentially leading to mental health issues. Understanding the gut-brain connection allows for better patient care, especially for vulnerable populations like children, the elderly, and individuals with pre-existing conditions. To minimise risks, monitored antibiotic use, probiotic support, and further research are crucial.

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