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REVIEW

Antibiotic-induced neuropsychiatric toxicity: epidemiology, mechanisms and management strategies – a narrative literature review

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Abstract

Antibiotics are amongst the most prescribed medications globally in both inpatient and outpatient settings. Antibiotic-induced neuropsychiatric toxicity is relatively uncommon; yet, when it occurs, it can lead to severe morbidity ranging from dizziness and confusion to seizure and psychosis. However, the actual incidence rate of these adverse events may be higher due to underdiagnosis or misdiagnosis as they are commonly confused with clinical manifestations of different neuropsychiatric conditions. The incidence and mechanism of antibiotic-induced neuropsychiatric toxicity vary between different antibiotic classes and clinical presentation (i.e. neurotoxicity *versus* psychiatric toxicity). However, the exact mechanism by which antibiotics can cause neuropsychiatric toxicity remains unclear. This article reviews the epidemiology of antibiotic-induced neuropsychiatric toxicity, explores potential mechanisms of this adverse event, investigates variations in frequency and clinical presentations between different antibiotic classes causing neuropsychiatric toxicity, and discusses management strategies.

Keywords: antibiotic, neuropsychiatric toxicity, neurotoxicity, psychiatric toxicity.

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Introduction

Epidemiology

In the annals of medical history, antibiotics stand as one of the most significant advancements in healthcare, offering treatment for diseases that were once life-threatening. However, a growing body of evidence has attracted the attention of clinicians and researchers to the direct association between antibiotic use and neuropsychiatric effects, ranging from mood disturbances to seizures.[1–6] In 2016, fluoroquinolones (FQs), formerly the third most prescribed antibiotic class in the USA, underwent a significant revision to their FDA boxed warning to now encompass central nervous system (CNS) effects, including psychosis. This distinctive update positions them as the only antibiotic class currently to bear such a boxed warning.[7] The true prevalence of neuropsychiatric toxicity induced by antibiotics remains elusive, primarily because of the challenge of distinguishing between the effects attributable to the antibiotic and those stemming from the infection itself. However, what is understood is that the incidence of CNS effects varies depending on the specific agent employed.

The overall prevalence of psychosis as an adverse drug reaction (ADR) for individual antibiotics has been estimated to range from 0.3% to 3.8% according to the FDA Adverse Event Reporting System (FAERS).[3] Specific antibiotics, including penicillins, FQs, macrolides, cephalosporins and doxycycline, have been associated with significantly increased odds of psychosis, with odds ratios (ORs) ranging from 1.67 to 9.48.[3] Additionally, the presence of risk factors, such as renal impairment and CNS diseases, can significantly elevate the risk of neuropsychiatric toxicity. For instance, cephalosporins, which are primarily eliminated through the kidneys, have been

shown to increase the risk of neurotoxicity to over 20% in patients with renal impairment and CNS abnormalities.[8,9] This data emphasizes the importance of considering patient-specific factors, such as the presence of renal impairment, especially because most antibiotics are renally cleared, when assessing the risk of antibiotic-induced neuropsychiatric toxicity, providing a clearer understanding of its epidemiology.

Furthermore, numerous case reports and retrospective studies also suggest that the prevalence of not just anxiety and depression but psychosis, hallucinations, and even suicidal behaviour may be more frequent with the use of FQs.[6,10] An analysis of the World Health Organization's ADRs database found that, of 1,627 cases of suicidal behaviour, 608 (37.4%) occurred following exposure to quinolones.[6] In a systematic review of 47 cases, macrolides were found to be the incriminating agents in 18 cases of antibiotic-induced mania.[11]

Clinical presentation

Herein, antibiotic-induced neurotoxicity refers to damage to the nervous system caused by antibiotic exposure, manifesting as structural or functional changes due to the direct toxic effects of the antibiotics. Symptoms may include headaches, dizziness, confusion, seizures and other cognitive impairments. Antibiotic-induced psychiatric toxicity, on the other hand, refers to adverse effects on mental health caused by antibiotic exposure, with symptoms such as mood changes, anxiety, depression, hallucinations and other behavioural changes. Antibiotic-induced neuropsychiatric toxicity encompasses both neurotoxicity and psychiatric toxicity, referring to toxic effects that impact both the nervous system and mental health due to antibiotic exposure. It includes a wide range of symptoms that affect cognition, behaviour and emotions.

The onset and severity of neuropsychiatric symptoms from antibiotics can vary widely and may encompass a range of symptoms affecting the CNS. Symptoms typically present acutely following a single dose or within a few days of antibiotic treatment.[1,12] Patients may present with milder symptoms, such as mild to moderate anxiety and agitation, or with more severe manifestations such as psychosis and mania. In some cases, profound depression that escalates to suicidal behaviours has also been observed.[1,3,6,10,12,13] Cases were found to be reported following various routes of administration, including intravenous, oral and topical (ophthalmic) routes. Tripathi et al. described a woman with no previous medical or psychiatric history who began using a quinolone ophthalmic solution prescribed for bacterial conjunctivitis.[14] Two hours following the first dose, the woman began to experience visual and auditory hallucinations, disorganized speech and behavioural disturbances. Her symptoms subsided after 12 hours following medication withdrawal. Seetharam et al. report a case of antibiotic-induced non-convulsive status epilepticus in which a 71-year-old man diagnosed with a duodenal ulcer was started on amoxicillin and clarithromycin.[15] Two days later, he began experiencing episodes of unprovoked generalized tonic-clonic seizures followed by non-convulsive status epilepticus. On day 3, clarithromycin was stopped. He improved over the next 36 hours, seizure-free.[15] Thus, whilst the onset of symptoms varies, most occur within 72 hours of treatment initiation, resolving upon discontinuing the offending antibiotic. Although it remains unclear why certain individuals are affected, several case reports indicate that advanced age and renal impairment play a significant role, especially amongst certain classes of antibiotics.[3,4,16] Of 183,265 ADRs reported in the FAERS, 19,628 (10.7%) were psychiatric, including 2,955 psychosis ADRs. Compared to minocycline, there was a significant increased odds of psychosis for other tetracyclines, penicillins, FQs, macrolides and cephalosporins.[3] Furthermore, in 2023, a total of 14,407,157 FAERS reports were analysed to assess the risk of antibiotic-induced seizures, revealing that 10 antibiotics are significantly associated with the risk of seizures.[17] The study utilized disproportionality analysis to identify these associations, including the reporting OR. Amongst the antibiotics identified, imipenem-cilastatin exhibited the highest reporting OR for seizures. The onset times of seizures were consistent with a pattern of increasing risk over time, highlighting the critical need for careful monitoring of seizure risks in patients receiving these antibiotics.[17]

Antibiomania, an increasingly popular term that first appeared in 2002, is used to describe manic symptomatology induced by antibiotics.[18] Meszaros et al. provide a case of amoxicillin-clavulanic acid-induced mania in a patient with no previous psychiatric history. Following a single day of treatment, the patient began to experience feelings of dying and developed auditory hallucinations. A few days into treatment, the patient's family noted a progressive change in his behaviour, with increased physical activity, elevated mood, and ideas of wanting to be in contact with God.[1]

Risk factors

The more permeable the antibiotic is across the blood–brain barrier (BBB), the higher its concentration in the CNS, and hence the higher its CNS toxicity-related risk.[19] This permeability is influenced by factors such as the specific type of antibiotic agent and the presence of inflammation.[19] BBB permeability varies based on the drug's lipophilicity (the more lipophilic, the greater BBB penetrability), molecular weight and size (smaller size improves BBB permeability), drug-protein binding (low protein binding improves CNS penetration), and molecular charge (neutral molecules

tend to penetrate the BBB well).[20] Trends in available case reports and series suggest several potential risk factors for antibiotic-induced neuropsychiatric toxicity. These factors may include but are not limited to the use of concomitant antibiotics, repeated antibiotic exposure, advanced age and renal impairment.[3,11,15,16] Concomitant administration of other antibiotics was documented in 11 of 27 case reports of quinolone-induced psychosis.[21] Antibiotic-induced neuropsychiatric effects as a result of renal impairment can be most plainly seen following the administration of cephalosporins, a class of antibiotics that primarily rely on renal excretion. A retrospective review and case series totalling 13 patients with acute renal failure revealed that each patient developed cognitive side-effects after non-renally adjusted cefepime initiation.[22] Shahar et al. detail the case of a 56-year-old man with stage 5 chronic kidney disease on dialysis, treated with ertapenem for *Enterobacter cloacae*, a catheter-related bloodstream infection.[16] After 13 days of treatment, he was found in an acute confusional state that later advanced to auditory and visual hallucinations. Complete resolution of his symptoms occurred within 10 days following the withdrawal of ertapenem. Whilst the risk of antibiotic-induced neuropsychiatric effects associated with personal or family history of mental illness remains inconclusive due to various confounders and a lack of strong evidence, it should still be considered a potential risk factor. In a review by Palma-Alvarez et al. of 27 patients who experienced psychiatric symptoms following antibiotic administration, three individuals had previously experienced psychiatric symptoms that had nevertheless resolved prior to antibiotic administration.[21] Additionally, three cases reported a family history, with one linked to schizophrenia and two to bipolar disorder. The risk factors that can precipitate antibiotic-induced neuropsychiatric toxicity are summarized in Table 1.

Surprisingly, a retrospective study suggested a potential protective effect of antibiotics against psychiatric disorders in hospitalized patients, though these findings require cautious interpretation due to several limitations.[23] This retrospective cohort study analysed data from 61,769 patients to investigate the relationship between antibiotic exposure and the risk of psychiatric disorders. The study included 20,214 adults who received antibiotics during hospitalization and 41,555 hospitalized adults without antibiotic exposure. The study was limited in generalizability as it focused only on hospitalized patients and did not differentiate between antibiotic classes or between the conditions for which they were prescribed. The findings also show variation in protective effects based on age and sex, indicating that results may not be uniformly applicable across different demographic groups. Importantly, the idea of using antibiotics for conditions like depression is controversial and raises worries about antibiotic resistance and other unintended problems. Whilst two small pilot randomized controlled studies suggest promising results regarding minocycline as an adjunctive treatment for major depressive disorder, it is important to approach these findings with caution, especially considering the broader context of antibiotic use.[24,25] These studies focus specifically on minocycline and do not imply efficacy for other antibiotics. It is important to avoid overgeneralization and to weigh the potential benefits against the risks, including the development of antibiotic resistance. Further research is necessary to fully understand the therapeutic effects of minocycline in major depressive disorder and to explore alternative treatment options that do not carry the same risks associated with antibiotic use.

Methods

In this narrative literature review, a PubMed search was conducted in November 2023 including all articles published before this date using the following keywords: "antibiotic AND neuropsychiatric toxicity," "antibiotic AND neurotoxicity," "antibiotic AND psychiatric toxicity" and "antibiotic AND psychosis". This search yielded various types of studies and reviews, including clinical trials, observational studies, narrative reviews, clinical guidelines and meta-analyses. The scope of the search was limited to papers published in English. The data gathered from this search contributed to the formation of this article.

Review

Potential mechanisms and pathways

Brain–gut microbiota axis

The human microbiota is a diverse and complex collection of microorganisms that lives both within and on the human body. In recent years, much research has focused on the role of the gut microbiome in the pathophysiology of multiple disease states. Here, we focus on the multifactorial relationship between human microbiomes, antibiotics and mental health. Interestingly, the adult intestine contains an estimated 2.2 pounds of gut bacteria, approximately the same weight as the developed human brain.[26] Certain antibiotics are broad-spectrum, meaning that, apart from targeting disease-causing bacteria, they also have a direct effect on other microbiomes and host physiology. Because the gastrointestinal tract contains the greatest number of bacteria in the body, it is frequently the target site for antibiotic activity. Yadav et al. showed that a 7-day course of broad-spectrum antibiotics can alter the gut microbiome for several weeks afterward.[27] Given the bidirectional relationship between the CNS and the enteric nervous system (ENS), antibiotics impact the gut microbiome and can negatively affect the CNS and mental health of the host. Recent literature

Table 1. Comparison of neuropsychiatric toxicity characteristics between antibiotics classes.

Antibiotic	Blood–brain barrier permeability	Dose dependent	Proposed mechanism of action for neuropsychiatric toxicity	Risk factors	Clinical presentations
Penicillins	Varies	Yes	Antagonism of GABA-A receptors, direct neurotoxic effect of beta-lactam ring	History of CNS diseases, renal impairment, elderly age	Encephalopathy, behavioural changes, myoclonus, seizures, and, in rare cases, psychosis
Cephalosporins	Varies	Yes	Antagonism of GABA-A receptors, direct neurotoxic effect of beta-lactam ring	Renal impairment, pre-existing CNS conditions	Seizures, encephalopathy, occasionally psychosis
Carbapenems	Moderate to high	Yes	Antagonism of GABA-A receptors, direct neurotoxic effect of beta-lactam ring	Renal impairment, high doses, CNS disorders	Seizures, confusion, encephalopathy
Fluoroquinolones	High	Unknown (occurs at various doses)	Antagonizing GABA-A receptors, NMDA receptor activation	Elderly, concomitant use of NSAIDs or antipsychotics	Insomnia, dizziness, headache, seizures, psychosis
Aminoglycoside	Low	Yes (particularly in renal impairment)	NMDA receptor activation	Renal impairment, prolonged therapy, high doses	Ototoxicity and nephrotoxicity more common
Macrolides	Varies	Yes	Potential GABA-A antagonism, drug interactions	Pre-existing psychiatric disorders	Hallucinations, mania, delirium, psychosis
Trimethoprim/ sulfamethoxazole	High	Yes	Potential neuroinflammation, folate pathway interference	Renal impairment, prolonged use, high doses	Delirium, aseptic meningitis, psychosis
Oxazolidinones	Moderate to high	Yes (common with prolonged use)	Interaction with monoamine neurotransmitters (monoamine oxidase inhibition)	Coadministration with serotonergic drugs, prolonged use	Serotonin syndrome, peripheral and optic neuropathy
Metronidazole	High	Unknown	GABA receptor inhibition, oxidative stress and free radical damage in neurons	High doses, prolonged therapy	Peripheral neuropathy, encephalopathy, seizures

CNS, central nervous system; GABA, gamma-aminobutyric acid; NSAIDs, non-steroidal anti-inflammatory drugs.

has confirmed that the gut microbiota interacts with the host CNS via the gut–brain axis (GBA).[28–30] Although the mechanisms underlying the GBA are poorly understood, it is thought to monitor gut functions and serve as a communication channel between the brain and peripheral intestinal functions to ensure homeostasis. One of the most compelling pieces of evidence of gastrointestinal microbe–brain interaction was reported by Morgan in 1991, showing the dramatic improvement in patients with hepatic encephalopathy after oral antibiotics administration and subsequent reduction in the production of gut-derived neurotoxins.[31] Additionally, a large population cohort study conducted by Valles-Colomer et al. showed that patients with major depressive disorder present with alterations in their gut microbiota composition.[32] This observation was confirmed by two studies

conducted by Kelly et al.[33] and Zheng et al.[34] Further, faecal microbiota transplantation of stool obtained from patients with major depressive disorder induced depression-like conditions in mice.[33,34] Additionally, isoniazid, an antibiotic developed in the 1950s for tuberculosis, incidentally led to the discovery of the first antidepressants (Iproniazid). Patients treated with isoniazid reported unexpected mood improvements. This finding encouraged deeper exploration into the mechanisms of depression, ultimately contributing to the development of key antidepressant categories: monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors.[35]

One systematic review included three in vivo studies that examined the impact of clarithromycin administration on the intestinal microflora of healthy volunteers.[36] In brief, all three studies reported transient reductions in *Enterobacteriaceae*, sustained reductions in *Lactobacilli* and *Bifidobacteria*, and suppression of anaerobic bacteria after administration of clarithromycin.[37–39] Specifically, the in vivo study conducted by Brismar et al.[38] compared the effects of clarithromycin and erythromycin, and found more pronounced alterations in the microflora of those who received erythromycin than in those receiving clarithromycin. Another in vivo study evaluating erythromycin reported a decreased abundance of aerobic and anaerobic faecal flora in healthy volunteers following administration of erythromycin 500 mg twice daily for 7 days.[40] Additionally, all strains of bifidobacteria, regardless of the species, are relatively sensitive to macrolides.[41] Given the fact that bifidobacteria are considered to have mental health benefits and strains of bifidobacteria have been demonstrated to impact stress responses, it is tempting to speculate that this action of antibiotics may have negative mental health consequences. In support of this view is the fact that, in a rodent study, both clindamycin and amoxicillin were found to increase depressive-like behaviours.[42] Given the accumulation of supporting evidence to suggest brain development and function are dependent on the diversity and structure of the gut microbiota, it may be safe to assume that the administration of macrolides may influence mental health via alterations in gut microbiota diversity.[43]

Inhibitory and excitatory neurotransmitter receptors

The vagus nerve is the longest cranial nerve in the body, with extensive connections and networks with the peripheral organs. Recent evidence indicates that the vagus nerve serves as the bidirectional highway between the gut and brain. Bravo et al. showed that, compared to normal mice, vagotomized mice do not experience neurochemical and behavioural changes after ingestion of lactic acid bacteria, thus demonstrating the importance of the vagus nerve in the GBA.[44] Additionally, receptors on vagal nerve fibres, such as those for serotonin (5-HT) and peptide receptors, may also facilitate these neurotransmitter pathways. Although the vagus nerve is in contact with all layers of the gut wall, its fibres do not cross the gut barrier and thus have to rely on the 200-million-plus neurons in the ENS to communicate with them. The ENS system is a complex network that cooperates with intestinal microbes, the immune system and the endocrine system to maintain homeostasis in the intestinal microenvironment.[45] The ENS contains more than 90% of 5-HT found in the body and the synthesis and release of 5-HT are modulated by short-chain fatty acids produced by spore-forming *Clostridiales*.[46] Short-chain fatty acids, such as butyrate and propionate, are metabolic byproducts of gut bacteria and act through G-protein coupled receptors to influence brain activity.[47] Finally, the gut microbiome can influence serotonergic transmission by regulating the availability of tryptophan, a 5-HT precursor.

Besides 5-HT, recent studies show that gut bacteria are capable of synthesizing other neurotransmitters, such as gamma-aminobutyric acid (GABA) and dopamine, found in the human brain. Although these neurotransmitters (including 5-HT) cannot cross the BBB, their amino acid precursors (glutamate, tyrosine, tryptophan) are derived from a specific diet and the gut microbiome and thus transported across the BBB to be converted into the corresponding neurotransmitters.[48] For example, Desbonnet et al. showed that the probiotic *Bifidobacteria* can increase the amount of tryptophan in the gut and, thus, subsequently decrease the rate of depression in rodents.[49] Furthermore, some *Lactobacilli* species can alter GABA metabolism and can thus improve metabolic and depressive-like behavioural abnormalities in mice.[50]

Other mechanisms

Several other potential mechanisms of antibiotic-induced neuropsychiatric toxicity have been proposed, including drug interactions with CYP450 enzymes and adverse effects of lipid-soluble active metabolites on the CNS (e.g. clarithromycin active metabolite 14-hydroxyclarithromycin).[3,51] Another possible mechanism could be through the alteration of cortisol and prostaglandin levels via CYP3A4 inhibition leading to increased neuropsychiatric effects.[52] Further in vivo studies are needed to identify the likely multifactorial mechanisms responsible for antibiotic-induced neuropsychiatric effects.

Specific antimicrobial agents

Beta-lactam antibiotics

Neuropsychiatric toxicity caused by beta-lactams, although uncommon, is a well-recognized adverse effect for this class of antibiotics. The toxicity can range from mild symptoms, such as confusion or agitation, to severe

manifestations like seizures or psychosis.[53,54] The exact mechanisms by which beta-lactam antibiotics can cause neuropsychiatric toxicities are not entirely understood. However, some proposed mechanisms include the direct neurotoxic effect of beta-lactams, especially in patients with renal impairment as most beta-lactams are primarily excreted renally, or an antagonizing effect of GABA neurotransmission in the CNS (an inhibitory neurotransmitter).[55] The ability of beta-lactam antibiotics to achieve high cerebrospinal fluid (CSF) concentrations is associated with a higher risk of neuropsychiatric toxicity.[20] Factors such as antibiotic dose, route of administration and BBB permeability can all play an essential role in determining beta-lactam concentrations in the CNS.[55]

Beta-lactams: penicillins

Several factors can increase the risk of penicillin-induced CNS toxicity. First, penicillin-induced neuropsychiatric toxicity seems to be dose dependent, and higher antibiotic doses are usually associated with a higher risk of neuropsychiatric toxicity, particularly in patients with renal insufficiency.[55] Second, the intrathecal administration of penicillin appears to have the most significant risk of CNS toxicity amongst all other routes of administration.[56] In regards to BBB permeability, some penicillins can achieve better CSF concentration than others. For example, penicillin G, nafcillin, oxacillin, ampicillin and piperacillin have excellent BBB permeability compared to other penicillins.[20] Penicillin G has moderate lipophilicity and is a relatively small molecule, which may explain its good CNS penetration ability. Although ampicillin is slightly more polar due to the additional amino group, it can still achieve a good CSF concentration due to its moderate lipophilicity (mainly when used in higher doses).[57] Nafcillin and oxacillin have different side chains than other penicillins, enhancing their lipophilicity and allowing good CNS penetration. Although piperacillin, an extended-spectrum penicillin, has a larger size and is more polar than other penicillins mentioned above, it can still penetrate the CNS; however, it is not as robust as penicillins with a smaller molecular size and less polarity.[19]

Historically, the epileptogenic effect of the penicillin family was first discovered by Walker et al. in 1945.[58] Animals used in the experiment experienced myoclonic jerks and tonic-colonic seizures shortly after the administration of penicillin to their cerebral cortex.[58–60] However, a case report linked penicillin G to the development of seizures in human when 500,000 units were inadvertently given intrathecally to a 27-year-old woman.[56] Five hours after receiving a large single dose of intrathecal penicillin, the patient experienced an initial clonic seizure lasting 30 seconds, followed by ten more convulsion episodes. Treatment included several doses of an anticonvulsant and the withdrawal of 25 cm^3 of spinal fluid. After these interventions, the patient improved, with an uneventful course and quick recovery starting 36 hours post-convulsions.[56] Later, it was found that the risk of penicillin-induced CNS toxicity was not only limited to the intrathecal route but could also could with the intravenous route of administration.[61] Since then, the CNS toxicity caused by penicillins has gained broader recognition.[62–66] Interestingly, one particular penicillin, amoxicillin, has been linked to aseptic meningitis.[64,67] A literature review including 21 patients with amoxicillin-induced aseptic meningitis showed that this toxicity typically occurs 3 hours to 7 days after antibiotic initiation and lasts 1–4 days after amoxicillin discontinuation; headache and fever were the most common symptoms.[67] Whilst CSF findings were significant for leukocytosis with lymphocytic predominance and elevated protein, the CSF culture was negative.[67] The proposed mechanism by which amoxicillin can cause aseptic meningitis is thought to be through T cell stimulation.[68] Moreover, the administration of procaine penicillin intramuscularly was associated with Hoigne's syndrome, a specific neuropsychiatric syndrome characterized mainly by psychotic symptoms such as anxiety, panic attacks, depersonalization, and auditory, visual, and somatosensory hallucinations or delusions.[69] The psychological symptoms are usually accompanied by adrenergic hyperstimulation (e.g. high blood pressure, tachycardia and shortness of breath) and generalized seizures.[69] The incidence of the syndrome is estimated to be between 0.8 and 16.8 per 1000 intramuscular injections, with the symptoms typically beginning within seconds to minutes after the injection.[69] Some proposed mechanisms of procaine penicillin-induced Hoigne's syndrome include a direct toxic effect from procaine with presumed limbic kindling and embolic phenomena in brain vessels due to accidental penetration of procaine penicillin in the vascular system during intramuscular administration.[70] Piperacillin has also been reported to cause CNS toxicity, particularly encephalopathy.[71,72] Rarely, coma and seizure can occur, especially in patients with renal impairment and underlying brain abnormalities.[65,66] Symptom onset usually occurs within 24 hours to 8 days of piperacillin initiation. High flux haemodialysis was associated with a rapid reduction in serum piperacillin concentration and subsequent clinical improvement of piperacillin-induced CNS toxicity.[73] Finally, ampicillin has been associated with neurotoxicity, particularly in low-birth-weight neonates. It is believed that ampicillin-induced CNS toxicity in neonates is primarily driven by the high CSF concentration in this population due to underdeveloped kidneys and increased BBB permeability because of cerebrovascular system immaturity.[63]

Beta-lactams: cephalosporins

Cephalosporin-induced neuropsychiatric toxicities are similar to those caused by penicillins. Amongst the cephalosporins, cefepime is notably associated with higher rates of neurotoxicity.[8] Patients with cefepime-induced

CNS toxicity may present with encephalopathy, myoclonus and non-convulsive status epilepticus.[74–77] The symptoms typically start within 4 days of cefepime initiation and resolve within 1–3 days after discontinuation.[78,79] Although cefepime is not highly lipid soluble, it has moderate to good CNS penetration due to its low molecular weight and relatively low protein binding.[80,81] Renal failure and pre-existing brain damage were found to be risk factors for cefepime-induced CNS adverse events.[8] The incidence of cefepime-induced neurotoxicity was found to be 1% in patients with medical illness without renal impairment, 15% in critically ill patients, and 4.1% in patients with haematological malignancies.[82,83] Moreover, the incidence was found to be 7.5% in patients with end-stage renal disease (ESRD) and 22.2% in patients with both ESRD and underlying CNS abnormalities.[8,9] Due to the risk of cefepime-induced neurotoxicity, particularly in critically ill patients and in patients with ESRD, a therapeutic drug monitoring approach may be warranted in the future to reduce the risk.[84,85] Whilst cefepime is the most notorious cephalosporin with regards to CNS toxicity, several other cephalosporins have been reported to be associated with neuropsychiatric toxicity such as ceftazidime, cefazolin and, to a lesser extent, ceftriaxone and cefotaxime.[86–88] Interestingly, some case reports have linked certain cephalosporins with aseptic meningitis. One case report showed an association between cefotaxime and aseptic meningitis with possible cross-reaction to ceftriaxone. In contrast, another case report has linked ceftazidime to aseptic meningitis with possible cross-reaction to cefazolin and cephalexin.[89,90] Furthermore, Hoigne's syndrome occurred immediately after intravenous administration of ceftriaxone and resolved upon discontinuation of the antibiotic.[91]

Beta-lactams: carbapenems

Seizures induced by carbapenems are the most well-documented compared to other beta-lactam antibiotics.[92] A meta-analysis that included 169 studies demonstrated that the risk of carbapenem-induced seizure was 1.87 times higher than the risk caused by other antibiotics.[92] Amongst carbapenems, imipenem appears to be the driver behind this high seizure risk.[92] The ORs comparing the seizure risk associated with imipenem, meropenem, ertapenem and doripenem to that of other antibiotics were found to be 3.50 (95% CI 2.23–5.49), 1.04 (95% CI 0.61–1.77), 1.32 (95% CI 0.22–7.74) and 0.44 (95% CI 0.13–1.53), respectively.[92] The 2004 Infectious Disease Society of America (IDSA) bacterial meningitis guideline recommended the use of meropenem over imipenem due to the increased risk of seizures with imipenem.[93] Moreover, in the 2017 IDSA guidelines for healthcare-associated ventriculitis and meningitis, meropenem is the only carbapenem specifically recommended for use either as part of empirical therapy or in treating meningitis caused by multidrug-resistant gram-negative bacteria.[94] Imipenem possesses a more basic C-2 side chain structure than other carbapenems, which can contribute to higher neurotoxicity risk.[95] Furthermore, imipenem is always used together with cilastatin to inhibit dehydropeptidase, a renal enzyme responsible for imipenem degradation, which may also play a role in reducing imipenem active efflux from the CSF, enhancing imipenem concentration in the CNS.[96] However, newer studies have shown inconsistent findings regarding the differences in seizure risk amongst carbapenem members.[97,98] A comprehensive retrospective cohort study involving 5,566 infants found that the incidence of seizures did not significantly differ between those treated with meropenem and those receiving imipenem/cilastatin as indicated by an adjusted OR of 0.96 (95% CI 0.68–1.32).[97] Interestingly, the drug labelling approved by the FDA indicated that the frequency of seizures is 0.4% for imipenem and 0.7% for meropenem.[99,100] More research is required to elucidate the risk of seizures linked to each carbapenem within particular populations.

Although carbapenem-induced psychiatric toxicity is rare, a case report describes a 56-year-old man with ESRD on dialysis who experienced psychiatric toxicity whilst on ertapenem.[16] After 13 days of treatment, the patient developed acute confusion and auditory and visual hallucinations. Extensive investigations found no other cause, and symptoms resolved within 10 days of discontinuing ertapenem. This suggests a possible link between ertapenem and psychiatric toxicity, emphasizing the need for careful monitoring in patients with renal impairment.

Fluoroquinolones

Historically, nalidixic acid is considered the first quinolone discovered in 1962. Nalidixic acid is a first-generation quinolone with a narrow activity spectrum and a poor pharmacokinetic profile.[101] FQs, which have a fluorine atom added to their quinoline ring making them more lipophilic, such as ciprofloxacin, have an expanded spectrum of activity and improved pharmacokinetic properties. FQs have excellent tissue penetration, including penetration into the CNS, compared to quinolones.[101] The lipophilicity, in addition to other factors such as low protein binding and relatively small molecular size, may explain the excellent BBB permeability of FQs.[101] Intriguingly, the ability of FQs to penetrate the CNS does not consistently align with their likelihood of causing seizures, meaning that FQ-induced seizures are not dependent on their concentration in the CNS.[19] Interestingly, the chemical structure of FQs can play an essential role in their neurotoxicity risk. For instance, FQs that have a quinolone ring with 7-pyrrolidine (e.g. tosufloxacin and clinafloxacin) or 7-piperazine (e.g. ciprofloxacin and norfloxacin) have a strong association with epilepsy.[102]

Unfortunately, despite the advantages of FQs, such as a broad spectrum of activity, improved pharmacokinetic profile, and availability of different routes of administration, this antibiotic class has been associated with musculoskeletal, neurological and psychiatric toxicity.[103] The neuropsychiatric toxicity of FQs may include confusion, encephalopathy, tremors, psychosis, myoclonic jerks or seizures.[55] Furthermore, certain FQs, such as ofloxacin, have been linked to causing Tourette-like syndrome, characterized by repetitive, involuntary movements and vocal sounds called tics.[104] Ciprofloxacin was found to be associated with extrapyramidal manifestations such as dysarthria and gait disturbances.[105] The neuropsychiatric toxicity of FQs is dose dependent and can occur within 1–2 days after starting the antibiotic.[55] FQs are thought to cause neuropsychiatric toxicity through various mechanisms, including antagonizing GABA-A receptors and NMDA receptor activation.[19]

Moreover, other studies of FQs underscore their association with severe neuropsychiatric toxicities and other serious side-effects. One study detailed regulatory advisories due to FQ-related risks of neuropsychiatric issues, aortic aneurysms and long-term disabilities, advocating restricted use for uncomplicated infections.[106] Another study used animal models and patient surveys to confirm these findings, with mice showing behavioural changes post-ciprofloxacin exposure and patients reporting significant neuropsychiatric symptoms after FQ use.[107] Neuropsychiatric symptoms include anxiety, depression, insomnia, panic attacks, clouded thinking, depersonalization, suicidal thoughts, psychosis, nightmares and impaired memory.[107]

Furthermore, FQs are associated with serious, persistent multi-symptom adverse effects, as demonstrated in a case series study by Golomb et al.[108] The study highlights four cases of previously healthy adults who developed severe symptoms whilst on FQs, which continued and progressed after discontinuation. These symptoms encompass a range of neurological and psychiatric disturbances, including peripheral neuropathy, cognitive dysfunction and psychiatric disorders, suggesting a link to neuropsychiatric toxicity. The potential mechanism underlying these severe reactions is likely FQ-induced mitochondrial damage, as FQs are known to cause delayed mitochondrial toxicity.

Aminoglycosides

Aminoglycosides represent another class of antibiotics that have been linked to CNS toxicity, particularly ototoxicity.[19] Although aminoglycosides have minimal plasma protein binding compared to other antibiotics, they have poor BBB permeability when administered intravenously due to their high polarity and hydrophilic nature.[109] Both gentamicin and tobramycin failed to achieve detectable intraventricular drug concentrations after intravenous administration in infant patients with confirmed bacterial ventriculitis (gentamicin) or suspected meningitis (tobramycin).[110] However, when intraventricular administration was added to the intravenous route, ventricular CSF concentrations reached or exceeded the minimum inhibitory concentration for most sensitive pathogens.[110]

Aminoglycoside-induced CNS toxicity is thought to be dose dependent. One in vivo study administered intra-striatal injections of neomycin in rats and showed dose-dependent striatal damage manifested as increased gliosis.[111] Striatal damage can cause major motor and cognitive issues; therefore, it is better to avoid intra-striatal neomycin unless it is the only option and no safer alternatives exist. The ototoxicity induced by aminoglycosides can present as vestibular symptoms, such as vertigo, dizziness and ataxia, in addition to cochlear symptoms such as tinnitus and hearing loss. Acute ototoxicity is thought to be caused by calcium antagonism and ion channel blockage, whilst chronic ototoxicity results from aminoglycoside reaching perilymph and endolymph and infiltrating hair cells.[112] The mechanism by which aminoglycoside causes hearing loss is thought to be through the excitotoxic activation of cochlear NMDA.[111] Although ototoxicity is the most common CNS toxicity related to aminoglycosides, other toxicities such as peripheral neuropathy, encephalopathy and neuromuscular blockage have been reported.[55] A case series study included four patients with gentamicin-induced peripheral neuropathy and encephalopathy.[113]

In a population-based retrospective cohort study from Manitoba, Canada, examining over 221,000 children, early-life exposure to aminoglycosides was linked to a significant increase in the risk of mood and anxiety disorders in children. Specifically, postnatal exposure to aminoglycosides, along with other antibiotics like tetracyclines, quinolones, sulfonamides and trimethoprim, showed a 33% increased risk of developing mood and anxiety disorders, suggesting that aminoglycosides may be a potential risk factor for these conditions.[114]

Macrolides

Macrolides are basic, lipophilic compounds that penetrate well into tissues. However, macrolides have high affinity for P-glycoprotein, an abundant transporter protein at the BBB, which may contribute to efficient removal of macrolides from the CNS.[115] One study evaluated 30 patients to determine the distribution of azithromycin into brain tissue, CSF and aqueous humour of the eye.[116] All patients received a single 500 mg oral dose of azithromycin. The mean concentrations of azithromycin in brain tissue 24, 48, 72 and 96 hours after administration were 2.63±2.58, 3.64±3.81, 0.74±0.37 and 0.41 µg/g,

respectively.[116] In contrast, the concentrations of azithromycin in CSF and aqueous humour of the eye were very low or undetectable. These data show that azithromycin appears to be widely distributed into brain tissue but not into CSF or aqueous humour of the eye. Conversely, one study reported the penetration of clarithromycin into the CSF of four healthy volunteers after 1 or 2 oral doses of 500 mg.[117] CSF levels of clarithromycin were 2.3% of simultaneous plasma levels after one dosing. With multiple doses, steady-state therapeutic concentrations of clarithromycin and its metabolite were achieved. Similarly, a case report of chronic *Mycobacterium abscessus* meningitis was treated with clarithromycin 1000 mg twice daily for 24 days, then samples of serum and CSF were simultaneously obtained to determine clarithromycin concentrations.[118] CSF levels of clarithromycin and its metabolite in the presence of meningeal inflammation were 15–18% of simultaneous serum levels of clarithromycin and 25–27% of its metabolite. The levels were 15–17-fold higher than the minimum inhibitory concentration for clarithromycin (0.125 µg/ml).[118] Similarly, for erythromycin, in the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid but the passage of the drug across the BBB increases in meningitis.[119,120] All together, these data suggest that CNS penetration is adequate and despite ineffective treatment of bacterial CNS infections, may effectively contribute towards neurotoxicity or drug-induced psychosis.[117–120]

In vivo studies also demonstrate adequate concentrations of macrolides achieved in the CNS. One in vivo study examined the effectiveness of clarithromycin in a rabbit model of pneumococcal meningitis and demonstrated excellent clarithromycin CSF penetration that was dose dependent.[121] Another study reported dose-dependent anxiety-like behaviours in mice after intraperitoneal clarithromycin administration for 7, 14 and 21 continuous days.[122] The clarithromycin dosage administered (100 mg/kg) to the mice was biologically equivalent to the clinical dosage used in patients (500–1000 mg per person). Then, using mass spectrometry-based lipidomics and RNA-sequencing analysis, the study investigators found that clarithromycin exposure led to altered gene expression and dysregulation of glycerophospholipids of the cerebral cortex in mice. As these changes may cause structural defects of the neuronal membrane, signal transduction and cholinergic function deficits, the authors speculate that this mechanism may mediate clarithromycin-related neurobehavioural abnormalities through dysregulation of glycerophospholipid metabolism.[122] Several other potential mechanisms of macrolide-induced neuropsychiatric toxicity have been proposed, including drug interactions (metabolism through isoenzyme CYP3A4), adverse effects of the lipid-soluble active metabolite of clarithromycin (14-hydroxyclarithromycin) on the CNS, and interactions with glutaminergic and GABA pathways.[51]

Literature describing the central effects of erythromycin and azithromycin is relatively limited to cases of psychosis and hallucinations in elderly patients, which suggest a dose-dependent effect like clarithromycin and beta-lactams.[51] Compared to the other macrolides, clarithromycin has the most evidence linked to neuropsychiatric effects. One study utilized data from the FAERS to examine the prevalence of spontaneously reported ADRs of psychotic symptoms in adults with antibiotics.[3] The data were collected from inception through March 2020 and included 23 different antibiotics, comprising 183,265 adverse event reports and 2955 psychosis ADRs. In total, 27,882 ADRs were reported with the macrolide class. Of those, 801 (2.9%) had psychotic symptoms and 507 (1.8%) were hallucinations. Within the macrolide class, more psychosis ADRs were reported for clarithromycin (n=710) compared to azithromycin (n=46) or erythromycin (n=45). When compared to minocycline, all macrolides demonstrated a significantly increased risk for psychotic symptoms (OR 7.04, 95% CI 4.56–10.87) and hallucinations (OR 7.20, 95% CI 4.14–12.49). Clarithromycin demonstrated the highest risk for psychotic symptoms (OR 9.48, 95% CI 6.14–14.65) and hallucinations (OR 9.47, 95% CI 5.45–16.46) compared to any other antibiotic in the study.[3] Clinicians should consider the risk for psychosis ADRs associated with clarithromycin before prescribing to vulnerable patient populations with psychotic disorders.

Trimethoprim/sulfamethoxazole

Both trimethoprim (TMP) and sulfamethoxazole (SMX) are small lipophilic molecules that readily cross the BBB.[123] The mean serum half-lives of SMX and TMP are 10 and 8–10 hours, respectively.[124] Pharmacokinetic studies suggest little correlation between meningeal inflammation and concentrations of TMP and SMX in CSF.[125] The excellent penetration of TMP-SMX into the CSF provides a rationale for its use in CNS infections, including meningitis. Trimethoprim binds to dihydrofolate reductase and inhibits folic acid synthesis. Folic acid deficiencies have been associated with neurocognitive disorders such as dementia and depression.[126] Whilst the mechanism for TMP-SMX-induced psychosis and CNS toxicity is not definitively known, it is possible that folic acid deficiencies caused by TMP could contribute towards neurological toxicity.[127]

Several neuropsychiatric adverse effects are listed within the package insert for TMP-SMX, including hallucinations, depression, apathy and nervousness.[124] Other rare adverse neurological effects have been reported, including tremor and gait disturbances, each resolving with dose reduction or discontinuation of therapy,

respectively.[128,129] Upon further examination of the FAERS data, TMP-SMX was found to have 22,697 reported ADRs, where 168 (0.7%) reactions were psychotic symptoms and 134 (0.6%) reactions were hallucinations.[3] Further, there are several case reports in the literature that have implicated an association between TMP-SMX and psychosis. Most cases have arisen from pneumocystis pneumonia treatment in immunocompromised patients or treatment of urinary tract infections in immunocompetent patients, and psychotic symptoms typically begin within 3 days of drug initiation.[127,130–132] Whilst symptoms are reversible and usually resolve within 24 hours after prompt drug discontinuation, one case described a slow return to baseline mental status after 10 days.[133] Clinicians should be aware of the presentation of TMP-SMX-induced psychosis, which consists not only of hallucinations but also delusions, confusion, agitation, depression and suicide attempts because prompt discontinuation often leads to symptom resolution.[3,124]

Oxazolidinones

Oxazolidinones exhibit a favourable pharmacokinetic profile with excellent bioavailability (>90%) and good brain tissue penetration.[134] Currently, two oxazolidinones have been FDA approved: linezolid and tedizolid. Both linezolid and tedizolid are reversible inhibitors of monoamine oxidase in vitro.[134] In a murine head twitch model, linezolid significantly increased the number of mouse head twitches, suggesting increased serotonergic activity. In contrast, tedizolid was negative in the model, which signified no increase in serotonergic activity.[135] These results suggest that, compared to linezolid, there will be less monoamine oxidase inhibition and therefore fewer drug interactions with serotonergic and adrenergic agents for tedizolid, thus reducing the risk for serotonin syndrome.[136]

One pharmacovigilance study evaluated FAERS data for linezolid and tedizolid.[137] Between 2014 and 2020, 271 and 11,259 adverse events were reported for tedizolid and linezolid, respectively. Of those, 1.5% of tedizolid and 2.5% of linezolid cases were serotonin syndrome.[137] There was no significant difference in the odds of serotonin syndrome observed between oxazolidinones (OR 0.58, 95% CI 0.21–1.58).[137] A population-based, retrospective cohort study evaluated the risk of serotonin syndrome in elderly patients receiving linezolid.[138] The results demonstrated that less than 0.5% of patients developed serotonin syndrome and concurrent antidepressants did not significantly increase the risk of serotonin syndrome. Therefore, it is generally not necessary to withhold linezolid or tedizolid from patients receiving antidepressant pharmacotherapy but rather careful use and close observation for signs and symptoms of serotonin syndrome is suggested.[51] Common presentations of serotonin syndrome include muscle rigidity, hyperreflexia, hyperthermia, hypertension and altered mental status. Severe cases may lead to shock and become life-threatening.[138]

Metronidazole

Metronidazole crosses the BBB and can result in CNS effects.[139] Whilst the mechanism for metronidazole-induced neurotoxicity is unknown, one proposed mechanism involves its inhibitory effect on the GABA receptor. Magnetic resonance imaging studies indicate histological findings similar to Wernicke's encephalopathy, which suggests that cytotoxic and vasogenic oedema may represent another possible mechanism of its neurotoxicity.[139]

Upon further examination of the FAERS database, metronidazole was amongst the top three antibiotic classes with the greatest odds of psychosis.[3] Specifically, metronidazole was found to have 11,168 reported ADRs, where 283 (2.5%) reactions were psychotic symptoms and 182 (1.6%) reactions were hallucinations. In a case report, metronidazole-induced encephalopathy was reported for a patient being treated for cerebral abscess.[140] Two additional cases of metronidazole-induced cerebellar dysfunction were reported.[139] The onset of symptoms can vary from 2 hours to more than 7 weeks after metronidazole administration though prior metronidazole administration may contribute towards an earlier development of symptoms.[141,142] Whilst the pathophysiology of metronidazole neurotoxicity remains unclear, the effects are usually reversible and do not seem to be related to dose or duration. Recovery times can vary, with one patient reporting gradual improvement in his symptoms over a period of 10 months.[141]

Antibiotic-induced neuropsychiatric toxicity: management strategies

The management strategy for antibiotic-induced neuropsychiatric toxicity should be considered even before selecting the antimicrobial regimen. As previously described, there are variations amongst antibiotic classes and often amongst the individual members of each class in terms of neuropsychiatric toxicity risk due to differences in physicochemical properties and BBB permeability.[55] Additionally, many risk factors can increase the risk of antibiotic-induced neuropsychiatric toxicity significantly such as the presence of renal disease, CNS disease and others.[19] Taking all these factors into consideration before selecting the antimicrobial regimen can play a crucial role in minimizing the occurrence of neuropsychiatric toxicity. As mentioned previously, antibiotic-induced neuropsychiatric toxicity is commonly confused with clinical manifestations of different neuropsychiatric conditions and sometimes confused with CNS toxicity caused by drugs other than antibiotics. Therefore, a thorough investigation should

be made by clinicians to distinguish whether the CNS toxicity is related to antibiotic administration or not. If neuropsychiatric toxicity arises following the start of antimicrobial treatment, it is essential to link this toxicity to the specific symptoms and the timing of their occurrence with the given antibiotic. Once this association is confirmed, the antibiotic should be discontinued or replaced with an alternative, as deemed appropriate. However, in severe cases, the temporary initiation of anticonvulsants, antipsychotics or sedative agents may be necessary to effectively manage the neuropsychiatric toxicity.[56,95,143]

Discussion: significance for healthcare providers

It is crucial to acknowledge that the evidence supporting the risk of neuropsychiatric side-effects of antibiotics primarily stems from case reports and case series. Whilst data from large randomized controlled trials are lacking, trends in the available literature are discernible. When selecting an antibiotic agent, gathering all pertinent medical information from the patient and assessing for potential risk factors is essential. Nevertheless, depending on the pathogen, the use of certain antibiotics may be unavoidable. In instances where antibiotic-induced neuropsychiatric symptoms are suspected, the first consideration should be the discontinuation of the offending antibiotic. Clinicians should consider transitioning to an alternative antibiotic with a lower likelihood of causing neuropsychiatric effects. Supportive care, including psychological support and counselling, may prove beneficial for individuals grappling with anxiety, depression or other neuropsychiatric symptoms. In most cases, neuropsychiatric effects begin to subside after the medication has been withdrawn. For those individuals in whom symptom resolution does not occur within a few days, clinicians must consider other causes. It is important to note that prolonged antibiotic use also has the potential to induce alterations in the microbiome, offering one possible explanation for persistent psychiatric symptoms.[2,13] Recognizing the potential for these effects in individuals at high risk can aid in averting misdiagnosis, unwarranted treatments and overall costs to the patient.

Conclusion

In conclusion, this comprehensive review highlights the complex and relatively underrecognized phenomenon of antibiotic-induced neuropsychiatric toxicity. Whilst antibiotics are critical in treating infections, they can, in rare cases, lead to a range of neuropsychiatric symptoms, from mild anxiety to severe psychosis, with factors like age and renal impairment heightening susceptibility. These effects are often misdiagnosed due to symptom overlaps with other neuropsychiatric disorders, suggesting that actual incidence rates may be higher. The varied clinical presentations and mechanisms, particularly the influence on the GBA, emphasize the need for careful antibiotic selection and management strategies. For clinicians, this means prioritizing patient history and risk factors in antibiotic choice, and remaining vigilant for neuropsychiatric symptoms during treatment to ensure prompt action and prevent misdiagnosis, thus alleviating patient suffering and decreasing healthcare expenses.

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