Anti-bacterial agents that inhibit bacterial growth or kills bacteria and are a sub-type of antimicrobials. These are drugs used to treat infections, but they sometimes pose a threat of adverse events. Some of these adverse events are neuropsychiatric, which are generally hard to diagnose and is often paid less attention. They account for about 30% of total Adverse drug reactions (ADRs) caused by drugs in patients without mental abnormalities. The spectrum ranges from episodes of seizure to acute psychoses. The article emphasizes the frequency of such adverse events and means to raise awareness among medical practitioners regarding the same. The various neuropsychiatric adverse effects and the agents responsible have been reviewed, along with possible mechanisms and general management.

The information for writing this review was selected by searching for keywords such as Neurotoxicity, GABA, Psychosis, Naranjo scale, and Antibiomania in databases such as Google Scholar, PubMed, Elsevier, etc. After searching the articles in the above-mentioned databases, the articles were screened concerning their importance with our work and according to their title and abstract. Additional articles were discovered by checking the references in the current study’s citations. Using this method, the various neuropsychiatric adverse effects of Antibacterial agents were summarized in this review.

**Keywords:** Neurotoxicity, GABA, Psychosis, Naranjo scale, Antibiomania

**INTRODUCTION**

Antibacterial drugs cover and possess many structural and functional characteristics, and the case of one agent may be different from that of another [1]. While some of these agents are naturally derived, others are synthetic. These agents can be classified based on various features such as the mechanism of action, spectrum of the activity (bacteriostatic/bactericidal) etc. Here, we would use the structural classification of antibacterial agents to explain the neuropsychiatric adverse effects caused by them. The classes of importance mentioned in context are: Beta-lactams, Fluoroquinolones, Nitrofurans, Amino acids, Diaminopyridines, Sulfonamides, Nitrofurandiones, Nitrocatic acid derivatives, Nitroimidazoles, Tetracyclines, Antimycobacterial antibiotics, Macrolides, Sulfones, Nitrobenzen derivatives, Glycylcyclines, Lipopeptides, and Polypeptide antibiotics [1-6].

Antimicrobial-related neurotoxic effects can have a vast array of presentations. Patients with focal sensory system illness, renal inadequacy and old age might be susceptible to these unwanted effects [2]. Conditions such as dizziness, tremors, hallucinations occur in 9-11% of patients on antibiotics [3]. Any antibiotic can cause an increased risk of depression [1]. Other changes in behavioural aspects range from insomnia [4] to acute psychosis [5]. Clarithromycin induced psychosis, for example, have been reported in 4-30% of patients; worst effects are seen on the nervous system in 5% of patients which includes dizziness, anxiety, insomnia, bad dreams, confusion, disorientation and hallucination [6]. Commonly seen neuropsychiatric adverse drug effects upon administration of these antibacterials are seizures, psychosis, encephalopathy, peripheral neuropathy, optic neuropathy, worsening of myasthenia gravis, dizziness/vertigo, headache, and insomnia [1-6], which in detail have been discussed inside. Study publications, case reports and review articles of relevance with respect to the topic, published during 2004-2021 were referred to prepare this review.

**Important neuropsychiatric adverse effects reported upon the use of anti-bacterial drugs**

**Seizures**

Episodes are most commonly associated with antibiotic classes such as penicillin, cephalosporins, carbapenem and fluoroquinolones [2, 4, 7-13]. Other antibiotics associated with seizures include Metronidazole, Nitrofurantoin, Cycloserine, Trimethoprim-sulfamethoxazole (TMP-SMX), Linezolid, Telizid and an overdose of Isoniazid (INH) [11, 14, 15]. The risk of occurrence is higher with Imipenem compared to all other carbapenems [7].

Though mostly generalized tonic-clonic seizures are seen to be associated, cases of simple and complex partial seizures too have been reported [2]. An epileptic condition lasting for more than 30 min is known as Non-convulsive status epilepticus (NCSE), clinically manifested by an altered mental state and associated with continuous epileptiform activity on the encephalogram [10]. Fourth-generation cephalosporin and cefepime have been frequently reported to cause NSCE. Seizures are mostly subclinical, the only clinical feature is a non-localizing encephalopathy, and ultimately Electroencephalogram (EEG) is required to make the diagnosis [2].

Administration of antimicrobials at doses higher than that recommended, age above 50, renal insufficiency, conditions leading to alterations of blood-brain barrier such as the presence of a tumor, make patients susceptible to seizures [7]. Also, a higher incidence was seen when Penicillin or Cephalosporins were in association with Antibiotic-Associated Encephalopathy (AAE) [9]. As with fluoroquinolones, the risk is increased by concomitant use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) [11]. Some antibiotics act by increasing or decreasing plasma levels of Antiepileptic drugs (AEDs) administrated to patients. Whereas certain drugs such as Beta-lactams and Quinolones could possess a proconvulsant activity and Encephalopathy

**Encephalopathy**

Antibiotics such as Metronidazole, Fluoroquinolones, Macrolides, Beta-lactams and Sulfonamides are most likely to cause encephalopathy [2, 7-11, 16]. The various features of AAE have been reviewed by Bhattacharya et al. Based on these features, encephalopathy has been categorized into three classes, Type 1, Type 2 and Type 3 AAE. Encephalopathy beginning within days of antibiotic initiation, with the occurrence of myoclonus or seizures
being common, disturbed EEG, normal Magnetic Resonance Imaging (MRI), which resolves within days are referred to as Type 1 AAE. Examples of antibiotics associated with Type 1 AAE include penicillin and cephalosporins. Characteristics attributed to Type 2 AAE are commencement within days of initiation of therapy, psychotic episodes which occur frequently, the uncommon occurrence of seizures, infrequently abnormal EEG, normal MRI and resolution within days. Antibiotics commonly associated with Type 2 AAE are Procaine penicillin, Sulfonamides, Fluoroquinolones and Macrolides. Type 3 AAE can be attributed to encephalopathy induced by Metronidazole alone. The features include onset post a week of drug commencement within days. Antibiotics commonly associated with Type 2 AAE are Procaine penicillin, Sulfonamides, Fluoroquinolones and Macrolides. Type 3 AAE can be attributed to encephalopathy induced by Metronidazole alone. The features include onset post a week of drug administration with antibiotics of neurotoxic potential. EEG is also helpful in distinguishing an episode of NCSE from encephalopathy. Once diagnosed, the culprit drug shall be replaced with an agent that is not neurotoxic [2].

Psychosis

It is the term used to describe illness in which patients have altered perception of reality as evidenced by delusion and/or hallucinations [17]. Psychosis, that is delusion and hallucinations, were present in 47% of cases and were most commonly associated with Sulfonamides (68%), Quinolones (67%), Macrolide (63%), and Penicillin IM (68%) treatments. In fact, in medical literature, Psychosis is a secondary adverse effect caused by Clarithromycin. Psychosis was least seen in the case of AAE with Cephalosporins (13%) and Metronidazole (24%) [6, 8]. The term used to describe an emergency manic episode in a reaction to antibiotics is 'anti-biomania' or 'Hogd syndome' [8, 18]. It is a rare side effect shown by some antibiotics that resolve after cessation of the treatment. Macrolides and quinolones are comparatively more commonly associated, and at a lower rate are Beta-lactams and Metronidazole [1].

Several case reports and series provides in detail accounts of antibacterial-induced psychosis and their management. The case of Imipenem-cliastratin-induced psychosis by Jacob Ninan et al. describes an episode of acute psychosis upon an increase of the antibiotic dose. The patient experienced intense visual and auditory hallucinations due to Imipenem-cliastratin induced psychosis. According to the literature, the condition resolves in 2 w of discontinuation of the causative agent [13]. A case of Metronidazole-induced psychosis has been discussed by Mil Khandheria et al. The manifestations (paranoia, delusions, auditory hallucinations) shown by the patient met the criteria for substance-induced psychosis as under the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). The patient had been administering Metronidazole (500 mg twice daily). Psychosis resolved 2 d after withdrawal of the drug. The patient was prescribed Glanzapine (5 mg twice daily) if her symptoms were to recur [3]. Withdrawal of the offending agents and administration of Diazepam injection produced an effect in the 28-year old male with INH and ethambutol induced psychosis, reported by Prasad R et al. [17]. We also see Risperidone being used to treat hallucinations caused by Trimethoprim-sulfamethoxazole which was prescribed for Urinary tract infection (UTI). The antibiotic, therefore, was substituted with Nitrofurantoin in this case report by Matej Stubeck [19]. Surprisingly, unlike these cases, Minocycline has been reported to produce improvements in patients with psychotic disorders. The drug has anti-inflammatory properties and is said to be capable of producing an effect on neurotransmitters as well as their receptors [20]. But it was also seen listed among antibiotics causing psychosis, and therefore cannot be ruled out completely off the picture [13].

An example of psychosis associated with type2 AAE is Procaine penicillin (9). The cases show a relationship between psychosis and the administered antibiotic. However, in some cases, the underlying infectious condition itself (and not the antimicrobial) may be associated with exacerbation of psychosis. For example, the prevalence of comorbid infections during episodes of psychosis among schizophrnic patients, especially UTI are high [21]. A similar observation is the association between UTI and acute psychosis seen among geriatric patients [22]. Another relationship between infection and psychosis is marked by the increased risk of psychosis in an offspring whose mother experienced Genito-urinary infections or maternal fever during pregnancy [16].

**Table 1: Drugs causing seizure, psychosis and encephalopathy**

| Condition         | Class of drugs       | Drugs                                                                 | References                                                                 |
|-------------------|----------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------|
| Seizure           | Beta-lactams         | Penicillin, Piperacillin, Cefepime, Cefazolin, Cefuroxime, Ceftazidime, Imipenem, Meropenem | [2, 7-11, 13]                                                              |
|                   | Fluroquinolones      | Ciprofloxacin, Levofloxacin, Ofloxacin, Moxifloxacin, Gatifloxacin, Norfloxacin | [2, 4, 7, 11, 12]                                                          |
|                   | Nitrofurans          | Nitrofurantoin                                                       | [14]                                                                      |
|                   | Amino acid           | Cycloserine                                                         | [15]                                                                      |
|                   | Diaminopyridine-Sulfonamides | Trimethoprim-Sulfamethoxazole                                    | [11]                                                                      |
|                   | Oxazolidinones       | Linezolid, tedizolid                                                |                                                                            |
|                   | Nicotinic acid derivatives | Isoniazid (on overdose)                                         |                                                                            |
|                   | Nitromidazoles       | Metronidazole                                                       |                                                                            |
| Psychosis         | Beta-lactams         | Penicillin, Procaine Penicillin, Procaine benzyl penicillin, Piperacillin, Amoxicillin, Cefalexin, Meropenem | [1, 8, 9, 11, 13, 16, 21, 22]                                               |
|                   | Fluroquinolones      | Ciprofloxacin, Ofloxacin, Norfloxacin, Temafloxacin, Gatifloxacin, Levofloxacin, Moxifloxacin | [1, 2, 4, 8, 9, 11-13, 16-21-25]                                             |
|                   | Macrolides           | Clarithromycin, Clindamycin, Erythromycin                           | [1, 6, 8, 9, 11, 13, 16, 21]                                               |
|                   | Tetracyclines        | Tetracycline, Doxycycline, Minocycline                              | [13, 21]                                                                  |
|                   | Aminoglycosides      | Amikacin, Gentamicin                                                |                                                                            |
|                   | Nitromidazoles       | Metronidazole                                                       |                                                                            |
|                   | Diaminopyridine-Sulfonamides | Trimethoprim-Sulfamethoxazole                                    | [1, 2, 8, 9, 11, 13, 16, 19, 22, 26]                                       |
|                   | Nicotinic acid derivative | Isoniazid                                                         | [11, 13, 17]                                                              |
|                   | Antiinmycobacterial antibiotics | Ethambutol                                                          | [17]                                                                      |
|                   | Amino acid           | Cycloserine                                                         | [3]                                                                       |
| Encephalopathy    | Beta-lactams         | Penicillin, Benzyl penicillin, Piperacillin, Procaine penicillin, Cefepime, Ceftazidime, Cefazolin, Cefuroxime | [2, 7-9, 11-16]                                                          |
|                   | Fluroquinolones      | Gatifloxacin                                                        | [2, 7-9, 11-16]                                                          |
|                   | Macrolides           | Clarithromycin                                                       | [7, 9, 11-16]                                                             |
|                   | Nitromidazoles       | Metronidazole                                                       | [2, 7-9, 11]                                                              |
|                   | Diaminopyridine-Sulfonamides | Trimethoprim-Sulfamethoxazole, Isoniazid (overdose)                  | [11]                                                                      |
|                   | Nicotinic acid derivative | Isoniazid (overdose)                                               | [2, 11]                                                                  |
|                   | Oxazolidinones       | Linezolid                                                           |                                                                            |
|                   | Aminoglycosides      | Gentamicin                                                          |                                                                            |
Peripheral neuropathy

Drug-induced peripheral neuropathy takes place when damage to the nervous system has been caused by a chemical substance. It could be irreversible and may lead to paresthesia. Awareness among healthcare practitioners is important, especially when patients undergoing treatment with these drugs complain of pain, numbness, weakness, paresthesia or autonomic dysfunction. The duration required for the onset of these symptoms ranges from weeks to months [7, 27]. The various types of peripheral neuropathy are classified based on symptoms present—Sensory, motor, sensorimotor, and autonomic. It can also be classified based on pathophysiology or according to the type of nerve fiber affected. Once diagnosed, management requires discontinuation of the offending agent and in the case of INH-induced peripheral neuropathy, Pyridoxine supplementation [11].

It is induced mainly by antibiotic drugs such as Fluoroquinolones, Metronidazole, Linezolid and INH [2, 3, 7, 11, 17, 24]. With INH, the most observed adverse effect concerning the neuropsychological context is peripheral neuropathy itself [11, 17]. The onset of INH-induced peripheral neuropathy varies and may take up to 6 mo. higher doses of INH have been found to increase the risk of developing peripheral neuropathy. Concomitant intake of Pyridoxine is therefore advised [27]. Disease conditions that cause peripheral neuropathy, old age, malnutrition, and pregnancy are risk factors too [11].

As with Fluoroquinolones, in 2013 the Food and Drug Administration (FDA) wanted the label of Fluoroquinolones changed to highlight the risk of peripheral neuropathy [28, 11]. Later in 2014, in a study of 6,226 cases and 24,904 controls, conducted by Mahyar Etmian et al., the risk of peripheral neuropathy with oral Fluoroquinolones were analyzed. The results revealed a risk ratio of 1.83 among current users and 2.07 among current new users [28].

The incidence is as high as 50% with Metronidazole and Linezolid, when these drugs are used for a long duration, or when Metronidazole is used concomitantly with Selective serotonin reuptake inhibitors (SSRIs) [7, 2]. Metronidazole-induced peripheral neuropathy may be present alone or in association with Metronidazole induced encephalopathy (MIE). Linezolid-induced optic neuropathy is often preceded by peripheral neuropathy, which may continue despite the withdrawal of the offending agent and resolution of symptoms of the eye [2, 11].

Polymyxin, Telavancin, Daptomycin, Linezolid and Nitrofurantoin are the agents that account for paresthesia. It is recommended that Linezolid shall be administered only for a maximum duration of 28 d as it may cause paresthesia of extremities of the body. Nitrofurantoin-related peripheral neuropathy is said to begin as paresthesia of distal extremities, which later develops dysesthesia. Other antibiotics capable of causing peripheral neuropathy are Dapsone, Chloramphenicol, Gentamicin, Ethambutol, and Sulfafluazine [2, 7, 11], as shown in table 2.

Optic neuropathy

Antibiotics have also been found to cause optic neuropathy. The causative agents include many antibiotics such as Ethambutol, Linezolid, Ciprofloxacin, Levofloxacin, Chloramphenicol, Metronidazole, INH, Streptomycin and Sulfonamides. Ethambutol and Linezolid were the most commonly reported agents. Manifestations associated with optic neuropathy include painless, progressive loss of vision of both eyes. There could be a reduction in colour vision, i.e., the patient may fail to discriminate between red and green. Optic neuropathy induced by antibiotics is often reversible, which means the patient returns to normal once the drug is withheld [2, 7, 11].

Linezolid-induced optic neuropathy can be identified by some additional features, such as optic disc swelling or pallor, loss of central vision (more than that of peripheral vision). It is reversible in nature. When compared to Linezolid, a better alternative would be Tedizolid since it shows a much lower risk towards the development of optic neuropathy [11].

Risk factors associated with Ethambutol-induced optic neuropathy are prolonged therapy, higher doses, old age (above 60 y), hypertension and renal dysfunction. The onset of the condition may vary from 1-9 mo. The nature of Ethambutol-induced optic neuropathy may be irreversible at times. It can cause permanent loss of vision, though it is unlikely to occur in most patients. In cases where it is reversible, improvement is seen within 3 mo. [11]

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Table 2: Drugs causing peripheral neuropathy, optic neuropathy and exacerbation of myasthenia gravis

| Class of drugs | Drugs |
|---------------|-------|
| Peripheral    | Oxazolidinone, Linezolid, Sulfones, Nitrobenzene derivatives, Sulfonamides, Aminoglycosides, Fluoroquinolones, Lipoproteins, Lipoprotein lipase, Nicotinic acid derivative, Nicotinamide, Nitrofurans, Nitroimidazoles, Antimicrobial agents, macrolides, tetracyclines, Polypeptide antibiotics, Beta-lactam, Telavancin, Daptomycin, Linezolid, Nitrofurantoin, Dapsone, Chloramphenicol, Gentamicin, Ethambutol, Sulfasalazine |
| Neurathy      | Oxazolidinone, Linezolid, Sulfones, Nitrobenzene derivatives, Sulfonamides, Aminoglycosides, Fluoroquinolones, Lipoproteins, Lipoprotein lipase, Nicotinic acid derivative, Nicotinamide, Nitrofurans, Nitroimidazoles, Antimicrobial agents, macrolides, tetracyclines, Polypeptide antibiotics, Beta-lactam, Telavancin, Daptomycin, Linezolid, Nitrofurantoin, Dapsone, Chloramphenicol, Gentamicin, Ethambutol, Sulfasalazine |
| Optic neuropathy | Oxazolidinone, Fluoroquinolones, Nitrobenzene derivatives, Sulfonamides, Aminoglycosides, Nitroimidazoles, Nicotinic acid derivatives, Fluoroquinolones, Macrolides, Aminoglycosides, Tetracyclines, Polypeptide antibiotics, Beta-lactam |
| Exacerbation of Myasthenia gravis | Telavancin, Daptomycin, Linezolid, Nitrofurantoin, Dapsone, Chloramphenicol, Gentamicin, Ethambutol, Sulfasalazine |

*"-indicates that a specific agent was not mentioned among the given references.
Exacerbation of myasthenia gravis

This event has been reported with the use of Polymyxins such as Colistin and Polymyxin B. Among the other antibiotics such as Fluoroquinolones, Macrolides, Tetracyclines, Ampicillin, and Imipenem are the antibiotics implicated [2, 7, 11]. Myasthenia gravis is an autoimmune disorder. Clinical manifestations of Myasthenia gravis are diplopia, ptosis, dysarthria, dysphagia, proximal limb weakness. These symptoms are worsened by activity or towards the end of the day. The exacerbation of this condition could be of seriousness, stretching between mild to severe. When severe, the patient may suffer from respiratory failure and therefore require ventilatory support, as denoted by the term ‘myasthenic crises’. Polymixin injections may lead to a respiratory failure lasting 10-48 h. Close monitoring of symptoms is recommended in patients with myasthenia gravis, taking antibiotic medications [2, 7, 12].

Headache

Fluoroquinolones, Beta-lactams, Oxazolidinones, Sulfonamides, Lipoglycopeptides, Clarithromycin, Polymyxins, Tigecycline, Minocycline, Daptomycin, Nitrofurantoin, INH, Rifampicin, Metronidazole and Dalfopristin-quinupristin, have been reported to cause headache [2, 4, 11, 12, 23, 24, 29].

It is a common side effect seen with Sulfonamides [11]. Among Beta-lactams, headache is said to be common with the use of Doripenem and Ceftaroline [2]. A mild headache could be accompanied by Rifampin administration. Among Oxazolidinones, Linezolid and Tedizolid had headache listed among their most common side effects during the ESTABLISH trial [11]. Clinical trials with Dalbavancin shows that the major neurological side effect associated with the drug is headache, which was experienced by 25% of the subjects [30]. Dalbavancin, as well as Telavancin (another Lipoglycopeptide), are drugs of importance in cases of complicated skin and skin structure infections where Vancomycin fails to produce effect [31]. The safety of Telavancin was assessed in a randomized comparative study conducted by Michael W. Dunne et al. A total of 1778 patients were enrolled. A dose of 500 mg was administered on the first day and 1000 mg on the 8th day for treatment of skin and skin structure infections. The results of the study mention headache as one of the important side effects associated with this drug [32].

Apart from these, Streptogramins are agents whose usage has been limited to the treatment of infections caused by Vancomycin-resistant enterococci (VRE). Headache is the only neuropsychiatric adverse event seen with their use [2].

Dizziness/vertigo

Dizziness and vertigo are conditions that occur as a result of vestibular toxicity [11]. In the case review by Serafina Chimirri et al., Dizziness has been defined as a general term used to express subjective complaints of the patient in connection with the changes in sensation, movement, perception or consciousness. Vertigo, however, is a subtype of dizziness and has been defined as an illusion of movement caused by asymmetric involvement of the vestibular system [33]. As mentioned in table 3, Fluoroquinolones, Polymyxins, Clarithromycin, Metronidazole, Minocycline, Tigecycline, Daptomycin, Gentamicin, Vancomycin, Linezolid, Nitrofurantoin, Rifampin and Ethambutol [2, 4, 6, 11, 12, 17, 23, 24, 29, 33] are the agents found to be associated with Dizziness/Vertigo.

The case report by Boonsong Kiangkitiwat et al. briefly an incident of levofloxacin-induced delirium with psychotic features where the 42-year-old female patient experienced neuropsychiatric adverse effects, including dizziness [4].

### Table 3: Drugs causing headache, dizziness/vertigo and insomnia

| Condition        | Class of drugs                   | Drugs                                      | References                  |
|------------------|----------------------------------|--------------------------------------------|-----------------------------|
| **Headache**     | Macrolides                       | Clarithromycin                             | [11, 29]                    |
|                  | Fluoroquinolones                 | Ofloxacin, GemiFlaxacin, Ciprofloxacin, Moxifloxacin | [2, 4, 11, 12, 23, 24]       |
|                  | Polypeptide antibiotics          | Polymyxin                                  | [11]                        |
|                  | Glycylcyclines                   | Tigecycline                                |                             |
|                  | Oxazolidinones                   | Linezolid, Tedizolid                        |                             |
|                  | Tetracyclines                    | Minocycline                                |                             |
|                  | Sulfonamides                     |                                            |                             |
|                  | Lipopeptides                     | Daptomycin                                 |                             |
|                  | Nitrofurans                      | Nitrofurantoin                             |                             |
|                  | Nicotinic acid derivatives       | Isoniazid                                  |                             |
|                  | Anti-microbial antibiotics       | Rifampin                                   |                             |
|                  | Nitroimidazoles                  | Metronidazole                              | [2]                         |
|                  | Streptogramins                   | Dalbopristin-quinupristin                  |                             |
|                  | Lipoglycopeptides                | Dalbavancin, Telavancin, Oritavancin       | [11, 30-32]                 |
|                  | Beta-lactams                     | Ceftaroline, Cefalozine                    | [11, 34]                    |
| **Dizziness/vertigo** | Fluoroquinolones                | Ciprofloxacin, Ofloxacin, Moxifloxacin, GemiFlaxacin, Levofloxacin | [2, 4, 11, 12, 23, 24, 33]  |
|                  | Nitroimidazoles                  | Metronidazole                              | [2]                         |
|                  | Macrolides                       | Clarithromycin                             | [6, 29]                     |
|                  | Polypeptide antibiotics          | Polymyxin                                  | [2, 11]                     |
|                  | Tetracyclines                    | Minocycline                                | [11]                        |
|                  | Glycylcyclines                   | Tigecycline                                |                             |
|                  | Lipopeptides                     | Daptomycin                                 |                             |
|                  | Aminoglycosides                  | Gentamicin                                 |                             |
|                  | Glycopeptides                    | Vancomycin                                 |                             |
|                  | Oxazolidinones                   | Linezolid                                  |                             |
|                  | Nitrofurans                      | Nitrofurantoin                             |                             |
|                  | Anti-microbial antibiotics       | Rifampin, Ethambutol                       | [11, 17]                    |
|                  | Beta-lactams                     | Amoxicillin-clavulanic acid                | [33]                        |
| **Insomnia**     | Glycylcyclines                   | Tigecycline                                | [11]                        |
|                  | Lipopeptides                     | Daptomycin                                 |                             |
|                  | Oxazolidinones                   | Linezolid                                  |                             |
|                  | Nicotinic acid derivatives       | Isoniazid                                  |                             |
|                  | Polypeptide antibiotics          | Polymyxin B                                |                             |
|                  | Fluoroquinolones                 | Levofloxacin, Moxifloxacin                 | [2, 11, 24]                 |
|                  | Lipoglycopeptides                | Dalbavancin, Telavancin                    | [11, 32]                    |
|                  | Beta-lactams                     | Ceftaroline                                | [11, 34]                    |
|                  | Macrolides                       | Clarithromycin                             |                             |

*indicates that a specific agent was not mentioned among the given references.*
Insomnia

It refers to the difficulty initiating or maintaining sleep, or both. Antibiotics causing insomnia are Fluoroquinolones, Cephalosporins, Macrolides, Tigecycline, Dalbavancin, Telavancin, Daptomycin, Linezolid, INH [2, 4, 6, 11, 12, 23, 29, 32].

In a case series consisting of 3 individual cases published by Arun Kandasamy et al, we see patients with lower respiratory tract infections who underwent Levofloxacin therapy. The patients experienced insomnia which was caused by Levofloxacin itself. The first case is that of a 30-year old male patient who took levofloxacin 500 mg for 5 d on a once-daily basis. Another case is that of a 30-year old female patient who took Levofloxacin 500 mg daily. The last case is that of a patient who self-medicated himself with a 750 mg dose of Levofloxacin. All three patients had their symptoms of anxiety and insomnia resolved once Levofloxacin was stopped. None of the patients took other drugs other than Levofloxacin, nor did any show history of psychiatric illness. Thus, Levofloxacin was the offending agent here [12].

Mechanisms involved in the causation of neuropsychiatric adverse effects by various anti-bacterial agents

For antibiotics associated with psychotic abnormalities such as Fluoroquinolones, Cephalosporins, Penicillins, and Trimethoprim-sulfamethoxazole drugs, several possible mechanisms have been proposed. There is proof as assessed, that anti-infectives can cause intense responses such as seizures. The drugs reaching harmful amounts in the bloodstream, their anti-inflammatory properties and their ability to inhibit prostaglandin E-2, or cause Gamma-aminobutyric acid (GABA) antagonism, and N-methyl-D-aspartate (NMDA) receptor hypo functioning are a few of the possible mechanisms. The last two factors have generally been discussed as mechanisms that serve as the basis for Schizophrenic disorder [8]. Investigations are suggesting that Quinolones such as Levofloxacin cause acute anxiety and insomnia by antagonism of the inhibitory GABA and direct activation of excitatory NMDA receptors. The structural similarity between Fluoroquinolones and GABA could be demonstrated as mechanisms that serve as the basis for Schizophrenic disorder [8].

Another possible explanation for the case report published by Miki Khandheria et al., is that the enzyme, monoamine oxidase (MAO) is reversibly inhibited by Metronidazole. The enzyme involved in the Dopamine pathway is responsible for its breakdown. Thus a decrease in MAO results in excess Dopamine. Since the inhibition is reversible, this explanation backs the fact that the patient recovered after Metronidazole was stopped [3].

Mechanisms involved in the causation of neuropsychiatric adverse effects are elicited. Conditions such as diabetes mellitus, hepatic insufficiency, old age, alcoholism, and family and personal history of mental illness predisposes the patient towards INH-induced neuropsychiatric adverse effects [17, 27].

INH causes increased excretion of Pyridoxine, resulting in this vitamin’s deficiency. As a result, the usual Tryptophan metabolism gets disturbed. Brain pyridoxal-5-phosphate is too inhibited by this antibiotic since this coenzyme is produced from pyridoxine itself. Inhibition of the enzyme results in a decrease in GABA of the brain and other synaptic transmitters. Thus neurological adverse effects are elicited. Conditions such as diabetes mellitus, hepatic insufficiency, old age, alcoholism, and family and personal history of mental illness predisposes the patient towards INH-induced neuropsychiatric adverse effects [17, 27].

Evaluation and management

Diagnostic criteria for psychiatric disorders are mentioned in DSM-IV [17]. The Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) was used to confirm psychosis induced by Imipenem-clindamycin in the case report by Jacob Ninan et al. [13]. Naranjo adverse drug reaction probability scale (table 4) has helped in the assurance of ADRs in many cases referred; A score over 9 demonstrates definite ADR while 5-8 means a probable ADR. Scores 1-4 insights possible ADR, and zero a doubtful ADR [9, 13, 19, 24, 29]. EEG and MRI could be of use in cases of AAE and seizures [2, 9]. A strategy commonly used to confirm substance-induced psychosis is by ensuring the resolution of symptoms with the withdrawal of the drug and their recurrence on rechallenge with the same agent [2, 11, 13, 22, 35,36]. However, performing a rechallenge may not be justifiable at all times [29]. Challenges to the diagnosis of Fluoroquinolone-related neurotoxicity include False-positive urine-opioid immunossay reports caused by their ability to cross-react with the Enzyme immunossay (EIA) screens for opiate drugs [4].

Table 4: Naranjo adverse drug reaction probability scale

| Question                                                                 | Yes | No | Do not know | Score |
|-------------------------------------------------------------------------|-----|----|-------------|-------|
| 1. Are there previous conclusive reports on this reaction?              |     |    |             | +1    |
| 2. Did the adverse event occur after the suspected drug was administered? | +2  | -1 | 0           | 0     |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1  | 0  | 0           | 0     |
| 4. Did the adverse reaction reappear when the drug was re-administered? | +2  | -1 | 0           | 0     |
| 5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1  | +2 | 0           | 0     |
| 6. Did the reaction reappear when a placebo was given?                  | +1  | 0  | 1           | 0     |
| 7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic? | -1  | 0  | 0           | 0     |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1  | 0  | 0           | 0     |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1  | 0  | 0           | 0     |
| 10. Was the adverse event confirmed by any objective evidence?           | +1  | 0  | 0           | 0     |
| Total Score                                                             |     |    |             |       |
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