ABSTRACT

Purpose: Mild adverse drug reactions typically associated with antimicrobials are familiar to most clinicians. However, rare phenomena, such as neurotoxicity, are often unpredictable and potentially unexpected. The toxic effects of antimicrobials on the central nervous system are often underreported and the mechanism(s) may be mixed or obscure. Geriatric patients are at increased risk for adverse drug reactions given physiologic alterations affecting pharmacokinetic processes. A dearth of information exists regarding neurotoxic presentations precipitated by antimicrobial use in the geriatric population. The purpose of this review is to present the available literature on neurotoxic effects of antimicrobials in geriatric patients, with an emphasis on manifestations of psychosis or delirium, or both.

Methods: A comprehensive literature search of the PubMed, Medline via Ovid, and Embase databases was conducted from 1966 to 2014. It included systematic reviews, randomized controlled trials, observational studies, case series, and case reports that involved neurologic effects, specifically delirium and psychosis associated with antimicrobial use.

Findings: Various antimicrobial classes are implicated with neurotoxicity. The classes with the most reported cases include fluoroquinolones, macrolides, sulfonamides, nitrofurans, and β-lactams. A higher risk of developing various symptoms of neurotoxicity was found in the elderly with use of piperacillin and tazobactam, cephalosporins, carbapenems, aminoglycosides, trimethoprim and sulfamethoxazole, nitrofurantoin, linezolid, and possibly the fluoroquinolones. Potential mechanisms of neurotoxicity differ between the agents. The etiology of neurotoxicity with some agents is not fully elucidated. Incidence may increase with reported risk factors, renal dysfunction, or drug interactions.

Implications: Awareness of antimicrobials causing or contributing to neurotoxic events may enhance clinical decisions in diagnosis and management when such incidents occur. (Clin Ther. 2014;36:1489–1511) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key word: elderly, neurotoxicity, antimicrobials, central nervous system.

INTRODUCTION

As of 2012, about 1 in every 7 Americans is aged 65 years or older (approximately 14% of the US population).1 The Healthcare Cost and Utilization Project reported that geriatric individuals represented 40% of hospitalized adults and nearly half of all health care dollars spent on hospitalization.2 Infectious diseases, including pneumonia, influenza, and septicemia, are among the 10 leading causes of death in this population.3 Antimicrobial agents are considered part of the foundation to combating life-threatening forms of these illnesses.4,5 Despite the reported survival benefits with use, these agents are associated with adverse effects that could harm recipients.6 Most antimicrobials are associated with mild adverse effects (eg, gastrointestinal discomfort with oral administration of amoxicillin and clavulanate) that are well known to prescribers. Neurotoxic adverse effects, such as delirium and psychosis, are unexpected and unpredictable. Symptoms can easily be
The geriatric population is at an increased risk of experiencing adverse drug reactions (ADRs) due to alterations in pharmacokinetic (PK) properties. PK changes associated with advanced age include distortions in drug absorption, distribution, metabolism, elimination, and protein binding, all of which enhance the risk of ADRs.\textsuperscript{5,6} The body’s fat can double by age 75 years, with decreased muscle mass, altering PK changes of lipophilic drugs.\textsuperscript{7} Neurotoxicity refers to the capability of inducing adverse effects in the central nervous system (CNS), peripheral nerves, or sensory organs. The International Labour Organization (an agency of the United Nations) reports a chemical to be neurotoxic if “it is capable of inducing a consistent pattern of neural dysfunction or change in the chemistry or structure of the nervous system.”\textsuperscript{8} Findings of chemical neurotoxicity include abnormalities in relevant biochemical parameters, EEG findings, psychological and behavioral testing, neurologic examinations, and axonopathy and cell death.\textsuperscript{8} Toxic effects of antimicrobials on the CNS are often under recognized and the mechanism may be as mixed or obscure as the risk factors that contribute to these ADRs. A paucity of information currently exists regarding neurotoxic presentations precipitated by antimicrobial use in the geriatric population. The purpose of this review is to present the available literature on neurotoxic effects of antimicrobials in geriatric patients, with an emphasis on manifestations of psychosis or delirium, or both.

**Literature Search Strategy**

The articles included in this review were chosen after a search of the published English language medical literature. A secondary search was performed via review of the references found from the initial search. Non-English abstracts were included from the secondary search if an abstract was available in English language. The search was conducted from 1966 to 2014 using PubMed, Medline via Ovid, and Embase, and included systematic reviews, randomized controlled trials, observational studies, case series, and case reports that involved neurologic effects, specifically delirium and psychosis associated with antimicrobial use. Search terms included *psychosis, delirium, mania, encephalopathy, neurologic, neurotoxicity, CNS event, elderly, and geriatric*. Drugs searched included ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, gemifloxacin, quinolone, fluoroquinolone, macrolide, azithromycin, clarithromycin, erythromycin, sulfonamide, trimethoprim-sulfamethoxazole, \(\beta\)-lactam, penicillin, piperacillin and tazobactam, amoxicillin and clavulanate, ampicillin, amoxicillin, ticarcillin, ticarcillin-clavulanate, cephalosporin, cefepime, ceftazidime, cefdinir, cepodoxime, cefazolin, cephalaxin, carbapenem, imipenem, imipenem-cilastatin, meropenem, ertapenem, doripenem, oxazolidinone, linezolid, aminoglycoside, streptomycin, tobramycin, gentamicin, amikacin, tobramycin, neomycin, kanamycin, nitromidazole, metronidazole, tinidazole, polymyxin, colistin, polymyxin B, lincosamide, clindamycin, lincomycin, nitrofurantoin, tetracycline, minocycline, doxycycline, daptomycin, azole antifungal, itraconazole, fluconazole, voriconazole, posaconazole, amphotericin B, and antifungals. All randomized controlled trials were included and results from smaller, nonrandomized, open-label studies were included provided that the studies had adequate methodology as judged by the authors. For drugs with limited information, case reports and case series were included to provide a comprehensive review.

**Fluoroquinolones**

The fluoroquinolone class is frequently utilized in the management of infectious diseases due to its broad spectrum of activity. Ciprofloxacin, moxifloxacin, and levofloxacin are the most commonly used utilized quinolones in the United States. Neurotoxicity, although not a usual side effect, occurs in 1%–2% of patients taking this class of drugs.\textsuperscript{9} These are often reported of excitatory CNS effects, including insomnia, headache, and dizziness.\textsuperscript{9} The incidence in the elderly is not clearly delineated, however, the available evidence is summarized.

The interaction between quinolones and neurotransmitters is responsible for the majority of neurologic adverse effects seen with these agents. Quinolones are structurally related to \(\gamma\)-aminobutyric acid (GABA) and the ability of quinolones to displace GABA at the receptor-binding site is influenced greatly by the side chain located at the 7-position of quinolones. The displacement of GABA from its binding site...
by quinolones has been shown to produce epileptogenic neurotoxicity. This has been shown in vitro to vary based on agent; trovafloxacin has the strongest effects, while more widely available agents, such as moxifloxacin and ciprofloxacin, have less effects, respectively; the data are lacking on levofloxacin.\(^9\) Hori et al\(^10\) noted fluoroquinolone interactions with GABA-receptor binding are weak and cannot fully explain CNS effects. In addition to interference with GABA transmission, fluoroquinolones have been reported to affect in vitro activation of the N-methyl-\(\beta\)-aspartate receptor; in vivo data are lacking.\(^11\) Some fluoroquinolones appear to penetrate the blood–brain barrier, despite having poor lipophilicity profiles.\(^12,13\) The ability to cross the blood–brain barrier may increase the risk of neurotoxicity with agents such as trovafloxacin.\(^12\) Levofloxacin, penetrates the CNS to the lowest degree and, therefore, should be associated with the fewest neurotoxic adverse events.\(^9\) Conversely, a review by Bryskier and Chantot\(^14\) indicates fluoroquinolone CNS penetration does not relate to the prevalence of neurologic ADRs. The conflicting mechanisms could be partially explained by drug interactions. Concurrent administration with products containing xanthine (caffeine and theophylline) derivatives could increase the likelihood of excessive CNS stimulation. Although most fluoroquinolones do not inhibit xanthine metabolism, ciprofloxacin is an exception.\(^15\) NSAID use is proposed to decrease blood flow to the kidneys and increase concentrations of fluoroquinolones, increasing the risk of ADRs. Ciprofloxacin has an unsubstituted piperazinyl ring in the seventh position of the quinolone ring, which puts patients who are concurrently using NSAIDS at a higher risk for neurotoxicity.\(^9\) Levofloxacin and moxifloxacin appear to have the lowest likelihood of an interaction with NSAIDS and have different side chains at this position.\(^16\)

The etiology of fluoroquinolone-induced CNS toxicity is likely multifactorial; an increasing number of case reports and review articles report psychiatric ADRs seen with fluoroquinolone use. A comprehensive review performed by Tomé and Filipe\(^9\) identified 145 individual case reports of neurologic or psychiatric disorders in individuals who received fluoroquinolones. The review reported no statistical difference in the incidence of ADRs with respect to sex and age. Within the 145 reports identified, 206 ADRs were found to be psychiatric (111 ADRs) or neurologic (95 ADRs). Of the 111 ADRs described as “psychiatric,” the most commonly reported presentations included mania (38 cases: ciprofloxacin, ofloxacin, and norfloxacin), insomnia (10 cases total: ciprofloxacin and ofloxacin), acute psychosis (8 cases total: ciprofloxacin), and delirium (8 cases total: ciprofloxacin, pefloxacin, and levofloxacin). Concomitant medication use with fluoroquinolones was associated with development of neuropsychiatric ADRs in 25 case reports. The onset of most psychiatric events occurred within 1 week of therapy initiation. Discontinuation of therapy led to resolution of the presentation; however, a mean time recovery is not elucidated. The review was not designed to determine the significance of drug–drug interactions precipitating fluoroquinolone-induced CNS toxicity. Tomé and Filipe\(^9\) noted that although their findings indicate increased occurrences of psychiatric ADRs with agents including ciprofloxacin and ofloxacin, the observed pattern may be related to common use of these agents worldwide and heightened awareness of these rare, but serious ADRs.

A review of cases reported to a French pharmacovigilance database from 1985 to 2002 analyzed the frequency of psychiatric ADRs with fluoroquinolone use.\(^17\) Five hundred and ninety cases were analyzed and the rates of confusion (51%), hallucinations (27%), agitation (13%), delusion (12%), insomnia (8%), and somnolence (4%) were noted. Mean age of the population was 66 years, and the range was 12–102 years. Data on concurrent medication use, comorbid conditions, onset of ADR, and time to ADR resolution were not examined.

Role of Age

A firm link between increased occurrences of neurotoxicity in elderly populations receiving fluoroquinolones relative to younger populations has not been reported.\(^17\) A review by Stahlmann and Lode\(^15\) noted that, although a lack of data exists on increased frequency of fluoroquinolone-induced ADRs in the elderly, it is possible that an age-related increase might exist. The literature to date neither confirms nor denies this conjecture. However, the geriatric population is at risk for psychiatric disturbances by multiple externalities, including infections, pharmacotherapy, cardiovascular diseases, metabolic conditions, trauma, and surgery.\(^18,19\) For example, urinary tract infection is a common cause of delirium in the elderly.\(^20\) An increasing number of psychiatric ADRs docu-
mented with fluoroquinolone exposure across all ages warrants close monitoring during use, especially in the elderly.

**Macrolides**

Erythromycin and its newer derivatives (azithromycin and clarithromycin) are used extensively in the community and health care settings. Indications include respiratory tract infections, sexually transmitted diseases, *Helicobacter pylori*–associated peptic ulcer disease and Mycobacterium avium complex (MAC) infection. Adverse effects most notably associated with this class include gastrointestinal intolerance, hepatotoxicity, and cardiotoxicity (QT prolongation). CNS toxicity (primarily seizure) is reported with the use of erythromycin and clarithromycin.

CNS events (eg, insomnia, dizziness, light-headedness, or confusion) associated with clarithromycin were first reported in 7 of 13 geriatric patients treated with clarithromycin (1200 mg daily) for chronic MAC infection. Cessation of therapy led to resolution of symptoms. Concurrent medications and comorbid conditions were not identified in the report. Cases were reported by Nightingale et al on 2 men (21 and 33 years of age) who developed mania secondary to clarithromycin use (2000 mg daily) for AIDS-associated MAC bacteremia. Both patients were found to be acutely psychotic after initiation of therapy; symptoms resolved upon discontinuation and occurred again upon rechallenge. Concurrent medications were reviewed; however, in this instance, there was no direct association of drug interactions precipitating these events.

Bandettini di Poggio et al performed a review of the literature from 1994 to 2009 and found 38 cases of psychiatric manifestations associated with use of clarithromycin. Mean age of patients was 51.3 years (range 19–87 years). Sixty-eight percent of cases had reported comorbidity or risk factors independently associated with developing altered mental status (eg, psychiatric illness, aging, cardiopathy, arterial hypertension, respiratory disease, or chronic renal failure). In the 38 cases reviewed, 12 patients were diagnosed with delirium (31.5%), 11 with acute psychosis (29%), 10 with mania (26%), 3 with hallucinations (8%), and 1 patient with a major depressive episode. Two patients received clarithromycin at 2000 mg daily (for MAC infection), and 9 patients (24%) received <1000 mg daily. Most indications for use included treatment of respiratory infections (58%) or gastric ulcer disease (18.4%). Mean onset of symptoms occurred within 5 days after clarithromycin initiation (range 1–10 days), with resolution occurring upon discontinuation (4 patients required 6 or more days for recovery). Twenty-two patients (58%) required use of antipsychotic or anxiolytic agents during the initial symptomatic presentation. The authors reported potential factors for precipitation of psychiatric events, including dosage and drug interactions. Concomitant use of agents with affinity to the cytochrome P450 3A oxidizing enzymes is affected by macrolide inhibition (erythromycin>>clarithromycin>>azithromycin) of enzyme activity. Notable interactions with anticonvulsants, selective serotonin reuptake inhibitors, and highly active antiretroviral therapy are reported in macrolide-induced neurotoxicity. Authors suggest cytochrome P450 inhibition by macrolides may contribute to serum concentration elevation of these agents, which increases the risk of neurotoxic events. While the importance of drug interactions must not be underestimated, several patients reviewed were prescribed clarithromycin alone. This suggests that elevated serum concentrations of clarithromycin alone can lead to development of psychiatric side effects.

Clarithromycin is more commonly associated with neurotoxicity, however, azithromycin has also been connected with triggering delirium in 2 geriatric patients. The 2 patients (a 78-year-old male and an 88-year-old female) developed psychiatric symptoms within 60 and 84 hours, respectively, after the initiation of azithromycin therapy, with symptoms resolving within 48 to 72 hours after discontinuation. The patients were not reported to have pre-existing psychiatric illness. Comorbid conditions included chronic myelomonocytic leukemia, spinal stenosis, arteriosclerotic heart disease, peripheral vascular disease, and diabetes mellitus. Concomitant medications were not recounted. The authors did note CNS symptoms associated with azithromycin use seem to have a longer time to resolution after discontinuation of therapy. The PK profile of azithromycin, contributing to a prolonged half-life when compared with other macrolides, potentially leads to delayed symptomatic resolution.

The mechanisms of CNS toxicity of macrolides are unclear. Several hypotheses include drug interactions (metabolism through cytochrome P450 3A4), adverse
effects of the lipid-soluble active metabolite of clarithromycin (14-hydroxyclarithromycin) on the CNS, alterations of cortisol and prostaglandin metabolism, as well as interactions with glutaminergic and GABA pathways.\(^{29}\)

**Role of Age**

There is no direct association between macrolide neurotoxicity and age. However, given the alterations in PK and pharmacodynamic properties with advanced age, neuropsychiatric events may be more likely to occur in geriatric patients receiving macrolide. The cases of azithromycin delirium have been in elderly patients, whereas clarithromycin neurotoxicity, albeit rare, occurs irrespective of age. The incidence of disease manifestation is not clear. Regardless, clinicians should be cognizant of this potential adverse effect.

**Sulfonamides**

The combination of trimethoprim and sulfamethoxazole (TMP-SMX) provides a bactericidal effect against many gram-positive cocci and gram-negative bacilli. Its clinical indications include, but are not limited to, skin and soft tissue, urinary tract, and respiratory tract infections. TMP and SMX are also utilized in the prophylaxis and treatment of several opportunistic infections associated with immunodeficiency, including HIV and AIDS. The most common toxicities reported with TMP-SMX are gastrointestinal, hypersensitivity, and dermatologic reactions. In immunocompetent hosts, ADRs occur in 8% of TMP-SMX exposures.\(^{30}\) However, HIV-infected persons are reported to have ADRs in up to 83% of exposures.\(^{31}\)

Reports on psychiatric effects associated with sulfonamides were published as early as 1942.\(^{32}\) Most recently, TMP-SMX has been implicated in acute psychosis. Before 2006, most cases connecting TMP-SMX with psychosis were found in patients being treated for urinary tract infections.\(^{33–37}\) Subsequently, Walker et al\(^{38}\) reviewed TMP-SMX use in immunosuppressed HIV-negative, renal transplantation patients with *Pneumocystis jirovecii* pneumonia. In 20 of these reported patients, 4 were found to have developed acute psychoses after administration of TMP-SMX. The onset of symptoms occurred between 3 and 10 days after initiation of therapy. Resolution of symptoms occurred within 24 hours of therapy discontinuation. Immunosuppressive regimens included prednisolone in 2 patients, with mycophenolate mofetil, sirolimus, tacrolimus, or cyclosporine in 3 patients. All patients except 1 (30 mg/kg/d; adjusted for dialysis use) were exposed to 120 mg/kg/d TMP-SMX. The Naranjo algorithm was utilized by the authors and the events were graded 9/13, indicating a definite ADR due to TMP-SMX. While Walker et al determined a temporal relationship with TMP-SMX use and acute psychosis, several variables were not reported. These factors include comorbid conditions, concurrent medication use (other than immunosuppressants), and severity of presenting illness (*P. jirovecii* pneumonia).

A larger case series performed by Lee et al\(^{39}\) reviewed 135 patient medical records of HIV-infected patients who presented with *P. jirovecii* pneumonia and were treated with intravenous TMP-SMX. They found 16 (11.9%) patients who developed acute psychosis after a mean duration of 5 days of treatment (range 3–11 days). Symptoms resolved after discontinuation of therapy (n = 5), dose reduction of intravenous TMP-SMX (n = 4), change to oral TMP-SMX administration with same dose (n = 1), change to oral TMP-SMX administration with dose reduction (n = 1), or reduction in intravenous TMP-SMX infusion rate (n = 1). The series reported the incidence of psychosis increased from 0% to 23.5% when the trimethoprim dosage was increased from <12 mg/kg/d to >18 mg/kg/d. There are features in the study population, such as underlying psychiatric illness (excluded from this review), concurrent medications (not directly reviewed), hyponatremia (n = 12), use of corticosteroids (n = 13), and intensive care unit admission (n = 7), which may confound the extrapolated results. The clinical characteristics mentioned, along with several others, were analyzed for significance in patient outcomes. Factors statistically associated with psychosis in this population include increasing TMP-SMX dosing and concurrent use of corticosteroids. The authors noted difficulty in determining the incidence of psychosis related directly to TMP-SMX use. Nevertheless, a risk for development of acute psychosis appeared with increasing doses of TMP-SMX.

The mechanism by which sulfonamides cause acute behavioral changes remains unclear. The case reports and series in the literature vary in age, comorbidities, concurrent medication use, dosing, indications for use, route of administration, onset of presentation, and resolution of symptoms. Some literature indicates a correlation between glutathione...
advanced disease presentations. Chronic HIV contributes to diagnosis of chronic HIV infection with inadequate risk assessment often contributing to treatment failure and diagnosis of primary infection. Unfortunately, inadequate risk assessment often contributes to TMP-SMX toxicity. Deficiencies in glutathione can potentially increase the risk of toxic metabolite formation. Populations noted to have glutathione deficiency include HIV-infected and geriatric patients. A secondary mechanism purported to contribute to TMP-SMX toxicity is the interference of TMP-SMX on the synthesis of tetrahydrobiopterin. This co-factor is utilized in the formation of dopamine and serotonin. Deficiencies in these neurotransmitters could potentially contribute to CNS side effects.

Many case reports of psychosis and hallucinations have occurred in the geriatric population. Within this population, several considerations are noted. The likelihood of renal dysfunction in advanced aged could contribute to impaired drug clearance. In patients with uninfamed meninges and normal renal function, TMP and SMX concentrations in cerebrospinal fluid (CSF) are about 50% and 40%, respectively, of concurrent serum concentrations of the drugs. Although temporal relationships between drug concentrations and the development CNS-related side effects are not reported, Lee et al described improvement in acute psychosis in some patients after dose reduction of TMP-SMX. Additional investigations are required to determine the validity of this association.

The Centers for Disease Control and Prevention report an increasing trend in the incidence and prevalence of HIV infection in older adults (aged older than 50 years) due to increased life expectancy on antiretroviral therapy and diagnosis of primary infection. Unfortunately, inadequate risk assessment often contributes to diagnosis of chronic HIV infection with advanced disease presentations. Chronic HIV infection is associated with complications, including renal dysfunction and cognitive impairment. TMP-SMX use in these individuals is more likely to occur, given its utility in opportunistic infection treatment and prophylaxis. With a baseline-increased likelihood of TMP-SMX–induced ADR occurrence in HIV-infected persons, the geriatric subset of this population could be more likely to develop neurotoxicity during TMP-SMX use. Additionally, factors mentioned previously (ie, glutathione and tetrahydrobiopterin deficiencies) could also contribute to TMP-SMX–induced psychiatric adverse effects in the elderly. Additional research is required to determine the factuality of such associations.

β-Lactams

There are numerous reports of neuropsychiatric events in patients receiving β-lactam, although rarely psychosis and delirium. Associated factors increasing the risk of β-lactam neurotoxicity include renal dysfunction, advanced age, excessive dosing, underlying CNS disease, and concomitant administration of nephrotoxic agents. Manifestations of CNS toxicity associated with β-lactam class exposure are primarily linked to the core β-lactam ring seen within members of this class. CNS ADRs described in the literature include seizures, encephalopathy, myoclonus, tremors, and hyperexcitability and hyperactivity. The toxicities reported are noted to involve inhibition of GABA neurotransmission. The β-lactam ring structure shares structural similarities with GABA. Alterations in GABA transmission and its potential role in psychosis have been studied, although a direct link is not yet reported.

Penicillins

Among the penicillin agents, piperacillin and tazobactam appear to be most associated with neurotoxic events. Several reported cases implicate piperacillin and tazobactam in patients with advanced renal insufficiency (creatinine clearance <15 mL/min). Individuals experienced an array of neurotoxic events, including convulsions, myoclonus, hallucinations, drowsiness, disorientation, bizarre behavior, delirium, and confusion. The onset of symptoms occurred within 7 days of therapy initiation. Most patients were initially diagnosed with CNS infection or acute cerebral vascular disease, rather than implicating piperacillin and tazobactam. This led to performance of various radiographic and invasive diagnostic procedures to rule out disease. Of note, elderly patients on dialysis experiencing neurotoxic symptoms improved upon discontinuation of piperacillin and tazobactam and receiving dialysis treatment. Investigation of piperacillin and tazobactam’s PK properties in patients receiving dialysis found serum half-life prolongation (up to 14.1 hours) during nondialysis sessions. Additionally, several predisposing conditions, including advanced age, malnutrition,
hypoalbuminemia, and inflammation, potentially increase the risk of piperacillin and tazobactam accumulation in patients with renal dysfunction. In addition, several published reports also allude to neurotoxicity in patients with advanced renal insufficiency or on dialysis who received excessive piperacillin and tazobactam dose regimes. However, one report illustrated neurotoxicity in a regimen adjusted for renal dysfunction. Substantial evidence is lacking to affirm risk factors associated with increasing piperacillin and tazobactam-induced neurotoxicity.

Ampicillin-induced neurotoxicity is noted primarily in very low birth weight neonates. Mechanisms for increased risk in this patient population include elevated CSF concentrations (due to immature transport mechanisms and renal immaturity) and increased permeability of the blood–brain barrier (possibly due to meningeal inflammation, immaturity of the cerebrovascular system, or underlying CNS disease). Neurotoxic events are sparsely reported in both pediatric and adult patients. Patients were found to be acutely psychotic after exposure to amoxicillin. Onset of presentations varied from hours up to 10 days. Symptoms included auditory, visual, and tactile hallucinations along with mania. Two patients had similar reactions before exposure to either amoxicillin or ampicillin. Several patient characteristics, including comorbidities, concomitant medication use, and renal function, were provided to determine other potential causes for toxicity. Additional accounts are needed before recommendations can be provided for monitoring with agents commonly prescribed to geriatric patients.

Role of Age
Penicillins are generally considered safe for administration in the elderly, although neurotoxicity with piperacillin and tazobactam is more prevalent in the aged. Neurotoxicity, including psychosis and delirium, is rare when the agent is dosed appropriately for renal dysfunction and the patient does not have a CNS infection.

Cephalosporins
Various reports implicate cephalosporins in neurotoxic events. A review by Grill and Maganti illustrates a spectrum of adverse CNS effects, including altered mental status (encephalopathy), myoclonus, coma, seizures, delirium, and status epilepticus, although the incidence is not known. These presentations are reported within all 4 generations of cephalosporins. Neurotoxicity has not been reported, to date, in the new cephalosporin, ceftaroline. The most frequent reports are seen with cefepime, ceftazidime, cefuroxime, andcefazolin.

Numerous publications associate cefepime with development of seizure activity, specifically nonconvulsive status epilepticus (NSCE). NSCE manifests primarily as altered mental status rather than the typical convulsions seen with generalized tonic–clonic status epilepticus. In June 2012, the US Food and Drug Administration released a safety announcement informing providers to dose adjust cefepime in patients with renal impairment because of the possibility of NSCE. The US Food and Drug Administration cited 59 cases of NSCE during administration of cefepime. Of note, 56% of these patients were aged older than 65 years, 69% were female, and 98% had renal dysfunction. Confusion and delirium have also been described with cefepime. The mechanism is GABA antagonism and cefepime is at particularly high risk because of the good penetration into the CNS, combined with the high doses often used for sick patients. The cases available indicate that the delirium is related to high doses in relation to poor kidney function.

At least 12 cases of ceftazidime-associated neurotoxicity have been reported. The majority (75%) of patients were found to have electrophysiologic findings consistent with NSCE, primarily manifesting as confusion (91%) and myoclonus (50%). Symptoms occurred, on average, after 6.5 days on ceftazidime. Mean age was 65 years old, with reported baseline serum creatinine at 6.5 mg/dL. All patients returned to neurologic and electrophysiologic baselines after ceftazidime withdrawal. The median duration of symptoms was 4 days (range 4–6 days).

Risk factors associated with development of cephalosporin-associated neurotoxicity include underlying renal insufficiency, pre-existing neurologic disease, and advanced age. A preponderance of published reports implicates renal insufficiency in potentially contributing to neurotoxic events. The disturbance in renal function would increase the serum concentration of most cephalosporins. Many cephalosporins have a high degree of CSF penetration. The elevated serum concentrations and good CSF penetration
increase the likelihood for adverse neurologic effects. In addition, several laboratory investigations with rats reported increased incidence of seizures, even with lower serum concentrations of cephalosporin. Dose adjustment is recommended with renally eliminated cephalosporins to prevent neurotoxicity in those who are renally impaired. Neurologic diseases (including Parkinson’s disease and stroke) in combination with renal insufficiency were found to escalate the risk of CNS effects. Several reports also found neurotoxic disease in elderly patients without renal insufficiency. Overall, resolution of clinical disease occurred upon discontinuation of the cephalosporin. The mean time to disease resolution is not clearly discerned.

**Role of Age**

Limited information is available on cephalosporin-induced neuropsychiatric events and its prevalence in the elderly.

**Carbapenems**

Like other β-lactams, reports of neurologic adverse events illustrate the carbapenem class’s ability to antagonize the GABA receptor. These agents are primarily associated with generation of seizure and seizure-like activity, however, ertapenem can be associated with a psychosis syndrome and both meropenem and ertapenem have been reported to contribute to delirium. Phase III trials evaluating imipenem-cilastatin (imipenem) report a marked incidence (2%–3%) in seizures with use. Similar to other β-lactams, the investigators of these trials report CNS disease and renal insufficiency (leading to increased drug concentration) to be risk factors for seizure development with imipenem. The FDA labeling actually states that the seizure incidence is 0.4% for imipenem compared with 0.5%–0.7% for meropenem. However, other in vitro and in vivo studies indicate that imipenem has higher seizure potential. Post-marketing reports indicate a seizure incidence with imipenem of 1.5%–2% with predisposing factors of advanced age, history of seizures or stroke, CNS disease or infection, and impaired renal function. Seizures are not as prevalent with newer carbapenems, including meropenem, ertapenem, and doripenem. Doripenem, in animal studies, showed a weak affinity for the GABA receptor leading to it theoretically having little to no seizure potential. Despite this animal model, an open label trial in humans found that the incidence of seizures in the doripenem arm was 1.1%. The carbapenem structure includes a C-2 side chain, which, in conjunction with the β-lactam ring, interacts with the GABA receptor. Imipenem is noted to have a more basic C-2 side chain structure, while newer carbapenems are reported to have less basic structures. Animal studies allude to the increased seizure activity of imipenem compared with meropenem due to the difference in side chain chemical properties. The good penetration of carbapenems into various tissues (including the blood–brain barrier) also increases the risk of neurotoxicity. While many investigations have reported on CSF concentrations of imipenem and seizure activity, scant evidence exists for newer carbapenems. In addition, few clinical publications connect newer carbapenems with seizure incidences similar to imipenem. Published reports of carbapenem-induced neuropsychiatric toxicity are limited.

Carbapenems can cause psychosis syndrome with hallucinations. Cases have been reported of auditory and visual hallucinations and delusions. Duquaine et al reported delirium in 2 elderly men receiving ertapenem. Both patients developed altered mental status within 1 week of therapy initiation. An extensive workup was performed on both patients for other causes of the symptoms. Resolution of disease manifestation occurred upon discontinuation of ertapenem. The authors’ noted one patient developed renal insufficiency without dose adjustment of ertapenem. Decreased elimination and increased serum concentration of ertapenem may have contributed to this patient’s presentation. Wen et al also described neurotoxicity in 2 elderly patients with severe renal dysfunction (Stage 5 chronic kidney disease) not on dialysis who received ertapenem. Both patients were initiated on renally adjusted regimens and subsequently developed symptoms within 4–5 days. Manifestations of the neurotoxicity include hallucinations, asterixis, myoclonic jerks, and cognitive impairment. Comprehensive differential diagnostics workups were performed and discontinuation of ertapenem eventually occurred. Despite the initiation of high-flux hemodialysis in both patients after ertapenem cessation, neurotoxicity persisted for 14 days before resolution. The authors noted renal dysfunction and advanced age as risk factors for neurotoxicity.
Recently, delirium was reported for the first time in a centenarian man being treated with meropenem for a complicated urinary tract infection. The patient’s agitation and confusion resolved immediately upon discontinuation of therapy. Piperacillin and tazobactam were initiated until urine cultures reported *Pseudomonas aeruginosa* resistant to piperacillin and tazobactam. Subsequently, the patient was restarted on meropenem with immediate reappearance of altered mental status. The presentation resolved again upon discontinuation.

**Role of Age**

While information about neuropsychiatric events in patients receiving carbapenem is limited, mental status should be monitored in geriatric patients, especially in those with renal insufficiency. Seizures have been reported with all carbapenems, however, the most prevalent incidence is with imipenem. Advanced age appears to be a risk factor for both neuropsychiatric events and seizure activity.

**Oxazolidinone**

Post-marketing surveillance indicates a growing trend of patients treated with linezolid experiencing neurotoxicity, even though initial reports were low at 0.36%. Manifestations of neurotoxicity include peripheral neuropathy, optic neuropathy, serotonin syndrome, encephalopathy, and delirium.

Peripheral neuropathy appears to be most commonly reported. The incidence of each event in the population is unknown. Neuropathies are more likely to occur during prolonged courses of treatment (>28 days, median 5 months). These neuropathies can take months to resolve and can be permanent. In addition, 3 cases describe peripheral neuropathy and optic neuropathy occurring in patients after 10 and 16 days of treatment, respectively.

Optic neuropathy generally improves or completely resolves after discontinuation, although can occasionally be permanent. All cases of peripheral neuropathy are documented as improving after discontinuation; however, persistent neurologic symptoms or damage are present in patients upon follow-up.

The mechanism of neuropathies associated with use of linezolid is unclear. Given the antimicrobial’s ability to inhibit protein synthesis, it may be associated with mitochondrial injury, contributing to development of toxic neuropathies. In addition, the agent’s ability to penetrate various tissue sites, including the central nervous and ocular systems, may further contribute to toxic events. Several reviews mention risk factors for developing neuropathy associated with use of linezolid, including pre-existing neurologic disease, alcohol abuse, diabetes, chemotherapy, or antiviral therapy. Caution is recommended in patients with the risk factors mentioned.

Serotonin syndrome is reported with a median onset at 4 days. Neuropsychiatric events (encephalopathy and delirium) have limited reporting, although generally occur within 2–9 days after initiation. Catecholamines, including epinephrine, norepinephrine, and dopamine, are reported to be involved in some neurotoxic events (serotonin syndrome, encephalopathy, and delirium) associated with linezolid. Linezolid is a known nonselective inhibitor of monoamine oxidase (MAO). Inhibition of MAO-A can increase levels of serotonin, whereas MAO-B inhibition would contribute to elevation of catecholamines. Concomitant use of therapies increasing catecholamine levels (eg, selective serotonin and norepinephrine reuptake inhibitors and antimuscarinics) increases the risk of these presentations. Two case reports illustrate patients receiving linezolid and antihistamines (hydroxyzine and diphenhydramine) who developed delirium and encephalopathy, respectively. The central antimuscarinics properties of antihistamines, including altered mental status and excitation, compounded with MAO inhibition may potentiate toxicity.

Serotonin syndrome typically resolved after discontinuation of linezolid and providing supportive care. Resolution of neuropsychiatric symptoms occurred within 3 days, in 3 cases, after discontinuation of linezolid.

**Role of Age**

Concern for use of geriatric patients developing neurotoxic events while receiving linezolid is warranted. Many patients in this population have reported risk factors for potentiating the development of toxic neuropathies. Additionally, commonly prescribed medications in this population include agents that contribute to excessive CNS stimulation. Concomitant use with linezolid may exacerbate neuropsychiatric events.
Aminoglycosides

Aminoglycosides are utilized in patients with serious gram-negative infections. Adverse effects attributed to these agents include nephrotoxicity and neurotoxicity. Neurotoxic effects include ototoxicity, peripheral neuropathy, encephalopathy, delirium, and neuromuscular blockade.112

Ototoxicity is seen as cochlear or vestibular organ damage. Agents within this class all have the potential to lead to damage to both organs, however, each agent appears to have slightly different predilections to each organ.113 Gentamicin and tobramycin are primarily vestibulotoxic (results in dizziness, ataxia, or nystagmus), whereas neomycin, kanamycin, and amikacin are mainly cochleotoxic (results in hearing loss).114,115 Symptoms occur within days or weeks after systemic application and are often bilateral in presentation.116 Vestibulotoxicity occurs in up to 15% of patients after administration, whereas cochleotoxicity occurs in 2%—25% of patients.117,118 Proposed mechanisms include uptake of aminoglycosides into the inner ear, formation of reactive oxidative species, involvement of phosphoinositide lipids, epigenetic changes, and cell death pathways.119

This class is implicated in the inhibition of neuromuscular and autonomic transmission blockade in an experimental model. Offending agents include streptomycin, tobramycin, gentamicin, amikacin, tobramycin, neomycin, and kanamycin.120–124 Gentamicin is the most potent neuromuscular blocker, followed by amikacin, followed by tobramycin.124 While reporting is sparse on this adverse event in clinical practice, when administering aminoglycosides in patients with neurologic disease, such as myasthenia gravis, caution should be taken to avoid worsening of disease.

Peripheral neuropathy and encephalopathy were seen in one reported case series of 4 patients administered gentamicin; the neurotoxicity was reversible.125 Nerve biopsy found abnormalities similar to changes seen in gentamicin-induced nephrotoxicity. The mechanism is unknown, however, some reports and animal experiments found formation of lesions in brain tissue after intrathecal administration of gentamicin.120,121 Delirium is reported twice in the available literature for aminoglycosides. McCartney et al126 describe a 66-year-old female being treated with tobramycin for a urinary tract infection. The patient had several risk factors for development of delirium, including advanced aged, active infection, and concurrent use of CNS depressants. These features could have compounded the delirium presentation. Kane and Byrd127 also implicated gentamicin for inciting delirium and neurologic dysfunction (grand mal seizure, abnormal deep tendon reflexes, muscular rigidity, spasticity, and alterations in tonus) after 7 days of treatment. Resolution occurred 6 weeks after onset. The report does not specify details on concurrent medications, kidney function, and comorbid conditions (aside from active intellectual disability and prior depression). Insufficient data directly link aminoglycosides to delirium development.

Role of Age

The aging process is accompanied by various physiologic changes (eg, alterations in body composition, impairments in kidney function), which may affect aminoglycoside PK properties, increasing the likelihood for neurotoxic adverse effects with aminoglycosides.

Nitroimidazole

Metronidazole is frequently used for the treatment of Clostridium difficile—associated diarrhea (CDAD), protozoa infections (eg, amebiasis, giardiasis), anaerobic infections, and bacterial vaginosis. Various reports implicate this agent with neurotoxicity, so much so that the Infectious Diseases Society of America guideline’s on C. difficile do not recommend metronidazole beyond the first recurrence due to risk of neurotoxicity.128 Symptoms of neurotoxicity include paresthesias, peripheral neuropathies, seizures, ataxic gait, dysarthria, and encephalopathy.129–134 Pathogenesis of metronidazole-induced neurotoxicity is not fully elucidated. Animal studies theorize several etiologies, including axonal degeneration by metabolites of metronidazole inhibiting protein synthesis and modulation of GABA receptor within the cerebellar and vestibular systems.135,136 Of note, cerebellar dysfunction is found in magnetic resonance imaging during encephalopathic manifestations in many patients.134,137–139 Lesions are typically found in the cerebellar dentate nuclei and appear to be bilateral and symmetrical.134,137–139 Repeat imaging illustrates these changes are reversible upon symptom resolution.

Reported neuropsychiatric events are predominately seen as psychosis. Psychosis is noted with monotherapy and concurrent with other medications, including other antimicrobial agents and disulfiram.
Most patients presented with psychosis between 2 and 14 days after initiation. Differential diagnostic workups were performed leading providers to implicate metronidazole in most cases.\textsuperscript{140–144} Patients experienced resolution of psychosis between 2 and 14 days after cessation; 2 patients were prescribed antipsychotics for treatment, while all others were given anxiolytics or no medications. Ofloxacin and cefuroxime were given concomitantly and considered contributory to psychosis by the authors in 2 cases.\textsuperscript{140,145} Several publications connect the combination of disulfiram and metronidazole to psychosis. The ability of both agents to inhibit aldehyde dehydrogenase leads to aversive symptoms when taking alcohol. This led to an investigation by Rothstein and Clancy\textsuperscript{143} looking at combination use for treatment of alcohol dependence. Twenty-one percent (n = 6) received the combination of metronidazole and disulfiram, and experienced psychotic symptoms, while patients on disulfiram alone were symptom free. While the onset of symptoms is not noted, resolution occurred within 14 days after discontinuation of both agents. The mechanism of this reaction may be related to inhibition of dopamine metabolism by disulfiram and metronidazole.\textsuperscript{146–149} Disulfiram metabolites appear to inhibit dopamine-β-hydroxylase, an enzyme that converts dopamine to norepinephrine. Metronidazole was found to have in vitro inhibition of bovine MAO, a dopamine-catabolizing enzyme. The combination of both these agents may contribute to elevation of dopamine concentrations, possibly eliciting psychosis.

Schentag et al\textsuperscript{150} reported an association with dose and serum concentration inducing psychosis with metronidazole use. The 65-year-old man was started on metronidazole treatment (2 g daily) for a complicated intra-abdominal infection. After 72 hours of metronidazole, he developed mental confusion, hallucinations, and agitation. Metronidazole was discontinued and the patient’s mental status returned to baseline within 48 hours. The patient was exposed to treatment again during his hospital course. The patient was given a much smaller dose of 500 mg daily without developing neurotoxicity. Serum concentrations were acquired during both treatments. Typical concentrations associated with recommended metronidazole regimens are peak levels <15 μg/mL and trough levels >5 μg/mL.\textsuperscript{151} During the first exposure to metronidazole, when he developed psychosis, concentrations were supratherapeutic at 30–40 μg/mL. As mentation improved, reported levels were <10 μg/mL. The second reduced dose course produced serum levels within the reported range for recommended treatment. The authors recommended close monitoring of mental status in severely ill patients on metronidazole.

The cumulative exposure of metronidazole is implicated in neurotoxic manifestations from 13.2 g to 228 g.\textsuperscript{130,152,153} Exposures adding to >40 g are linked with risk for seizures. Given this consideration, caution should be warranted with using metronidazole in geriatric patients. The cumulative exposure to this agent may be elevated in this group versus the general population. In addition, the potential mechanism of metronidazole causing psychosis could be of concern in a population on medications (eg, dopamine agonists for Parkinson’s disease and restless leg syndrome), which can enhance the levels of dopamine.

There does not appear to be an age predilection with neurotoxicity due to metronidazole, although there has been at least one case reported in the elderly population. A geriatric veteran being treated for CDAD developed confusion and hallucinations 48 hours after initiation with oral metronidazole.\textsuperscript{142} Diagnostic workup ruled out metabolic or infectious causes of disease. Metronidazole was the only new medication; therapy was stopped and the patient’s mental status returned to baseline within 24 hours. The patient was readmitted 1 month later for recurrent CDAD and was inadvertently exposed to metronidazole, resulting in hallucinations and confusion again. Metronidazole was discontinued and symptom-resolution occurred.

**Role of Age**

Metronidazole neurotoxicity occurs across all ages. Acute doses as well as cumulative doses may predispose patients to this ADR. The combination of metronidazole and disulfiram may predispose a patient to psychosis. Caution is warranted in patients on repeated course of metronidazole and those with history of alcoholism or Parkinsonism.

**Polymyxins**

Until recently, the utilization of polymyxins for gram-negative bacteria was limited. Use was restricted due to early reports associated with severe renal and neurotoxicity with administration.\textsuperscript{154} The emergence of multidrug-resistant pathogens along
with limited salvage antimicrobial options has reintroduced polymyxins into the antimicrobial armamentarium. Manifestations of neurotoxicity include dizziness, generalized or muscle weakness, facial and peripheral paresthesia, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia, and neuromuscular blockade. Older reports indicate the most frequently identified neurotoxic event is paresthesias. Paresthesias occurred in approximately 27% and 7.3% of patients receiving intravenous and intramuscular colistimethate sodium (polymyxin E), respectively. Koch-Weser et al illustrated that in patients who experienced neurotoxic events on polymyxin E, 83% developed symptoms during the first 4 days of therapy. The incidence of toxicity is not reported between polymyxin formulations.

The polymyxin chemical structure contains a fatty acid. This may correlate to the interactions of this class with the lipophilic content of neurons. Polymyxin neuromuscular blockade may be specifically related to inhibition of acetylcholine release in the synaptic cleft. One report links active polymyxin metabolite serum concentrations and the development of neurotoxicity. While many authors allude to neurotoxicity as a dose-dependent effect of polymyxins, data are insufficient to draw such conclusions. Risk factors linked to polymyxin-induced neurotoxicity include hypoxia, impaired renal function, and concomitant medication use (nephrotoxic agents, muscle relaxants, narcotics, sedatives, anesthetic drugs, and corticosteroids).

Manifestations are reported to subside after discontinuation of polymyxins. Several reports indicate use of dialysis in patients with coexisting acute renal failure. However, recommendations vary on the modality of dialysis utilized for drug removal. Role of Age

There is no age predilection to the neurotoxicity, which can occur with polymyxins. With the resurgence in use of the polymyxins, various dosing strategies are being studied that may alter the incidence of these toxicities.

Lincosamides

Despite reported associations linking clindamycin with CDAD, this agent still plays a role in various infectious processes, including uncomplicated skin and soft tissue infections and pelvic infections. The majority of publications implicating clindamycin in neurotoxic events illustrate onset of neuromuscular blockade during use. Hypothesized mechanisms of blocking effects include direct action on muscle contractility and decreased sensitivity to acetylcholine release. In vitro models produced neuromuscular blockade with clindamycin when used alone. In addition, some reports found prolonged effects of nondepolarizing neuromuscular blockers, such as vecuronium and pancuronium with use of clindamycin. Less evidence is available on the effects of depolarizing neuromuscular blockers (eg, succinylcholine) being prolonged with use of clindamycin.

One case associates prolongation of the nondepolarizing effects with concurrent use of succinylcholine. This patient received an accidental overdose of perioperative microbial prophylaxis with clindamycin at 2400 mg. Neuromuscular blockade lasted for 9 hours in this instance. Most reported cases indicate partial response to use of anticholinesterase reversal agents (eg, neostigmine) to alleviate blockade.

Best et al reported a lincosamide to be the cause of neuromuscular blockade in 44-year-old women undergoing surgery for nasal fractures. The patient experienced an episode of paralysis after postoperative administration of 600 mg clindamycin. Because the effects of intraoperative succinylcholine were reported to have subsided during recovery in the postoperative recovery area, it was not implicated as a cause of the paralysis. Unlike other reported cases, this patient experienced complete reversal of blockade after administration of neostigmine. The paucity of reports implicating this rare but serious adverse effect with clindamycin should caution physicians on awareness of this presentation during use. There are insufficient data to determine if there is an increased risk in geriatric patients.

Nitrofurans

Nitrofurantoin was first available in 1952 for the treatment of urinary tract infections. Neurotoxic evidence was first reported in 1956. Toole and Parrish reported 137 cases of nitrofurantoin neurotoxicity in 1973. Less evidence has been reported in the literature from 1980 onward. Symptoms of neurotoxicity include peripheral neuropathy, dizziness, vertigo, diplopia, cerebellar dysfunction, and benign intracranial hypertension.
Peripheral neuropathy (large-fiber sensorimotor and small-fiber) is the most prevalent manifestation of neurotoxicity. More cases of neurotoxicity with nitrofurantoin are reported in women and elderly patients. This may be selection bias due to the frequent use of nitrofurantoin in cystitis during pregnancy or for chronic prevention therapy, in the respective populations. Onset of neuropathy appears to be dose and duration independent. Most reports indicate appearance within 3 months of a prolonged course, however, patients can develop symptoms with intermittent treatment. Pathogenesis of neuropathy associated with use of nitrofurantoin is hypothesized to be due to axon loss, although the mechanism for preference for nerve fibers is unknown.

Most reported cases of neurotoxicity have occurred in the elderly, however, an outlier of commonly reported manifestations of nitrofurantoin neuropathy occurred in a 38-year-old female receiving nitrofurantoin intermittently and then continuously for a 7-year period. The patient experienced severe sensory neuropathy initially presenting as thigh and chest pain, which progressed to full body neuropathic pain, paresthesias, and numbness of her genitalia. The patient was given diagnoses including postviral syndrome and then early multiple sclerosis. Eight physicians met the patient before nitrofurantoin was linked and subsequently discontinued. Partial neurologic recovery occurred 21 months after cessation. Persisting symptoms included mild neuropathic pain, numbness, and decreased temperature sensations of the digital extremities.

Although the exact mechanism inciting nitrofurantoin-associated neuropathy is unknown, a majority of patients who developed neuropathy in a literature review had impaired renal function, noted by uremia. Of note, uremic neuropathy typically occurs in patients with advanced renal disease (glomerular filtration rates of <12 mL/min). The combination of uremia along with serum accumulation of nitrofurantoin could potentially contribute to neuropathy.

Role of Age

Given the frequent use of nitrofurantoin in acute and chronic urinary tract infections, caution is warranted in the geriatric population. Underlying renal dysfunction prevalent in older patients could increase the risk for neurotoxicity. Additional investigations are required to support this hypothesis.

Tetracyclines

Tetracycline agents are commonly used in presentations including atypical pneumonias, uncomplicated skin and soft tissue infections, and many tick-borne illnesses. Neurotoxicity associated with this class is limited primarily to vestibular symptoms. These include blurred vision, light-headedness, loss of balance, dizziness, vertigo, and tinnitus. Clinical trials link minocycline to higher incidences of CNS toxicity. Minocycline had higher lipid solubility than tetracycline or doxycycline. Jacobson and Daniel described vestibular reactions that occurred in hospital employees taking minocycline after exposure to meningococcal meningitis. Of the 29 exposed and treated staff, 86% experienced moderate to severe vestibular symptoms. Most (84%) experienced symptoms after 1 or 2 doses. Fifty-two percent of the treated staff reported discontinuation due to these side effects. Reported rates of discontinuation due to vestibular symptoms range from 1.7% to 8.8%. Fanning et al studied the incidence and type of side effect with minocycline use. Patients were given 100-mg capsules of minocycline twice daily by mouth for 5 days. Of the 45 patients being treated with active therapy, 24 experienced vestibular symptoms; a majority were female (n = 19). Serum samples taken after administration were found to illustrate higher concentrations of minocycline in female patients, which may be due to females’ smaller body habitus. The authors hypothesized these findings as one explanation to the increased occurrence of vestibular symptoms in these female patients. Del Rosso et al reported a potential for decreased risk in female patients when utilizing the brand immediate-release formulation rather than the generic immediate-release product of minocycline, through PK models. Extended-release formulations were also suggested to have lower potential risks versus immediate-release through similar models. Initially, the osmotic activity of minocycline potentially inducing changes in liquid volume and ionic concentrations of the vestibular system was thought to be the mechanism for vestibulotoxic events. However, Lannigan and Evans did not find a correlation.
between this pathology and the predilection of vestibular toxicity.

A rare but serious neurotoxic effect associated with all tetracyclines manifest as pseudotumor cerebri, also known as idiopathic intracranial hypertension. \(^ {189-194}\) Reports dispute the severity of disease manifestation and resolution. Some patients are reported to have resolution of elevated intracranial hypertension after discontinuation, while others have permanent visual loss, despite discontinuation. \(^ {189,191,195,196}\) The ability of minocycline to contribute to a decrease in CSF absorption is the proposed mechanism for minocycline-induced pseudotumor cerebri. \(^ {197}\) However, evidence is lacking to support this claim.

**Role of Age**

Minocycline may have a higher likelihood of causing neurotoxicity in the elderly, the mechanism has not been elucidated but may be due to minocycline’s increased lipophilicity and accumulation in patients with lower body habitus. There is insufficient data to determine if there is an increased risk of neurotoxic events with tetracycline and doxycycline use in geriatric patients. However, considering the manifestations of vestibulotoxicity, including loss of balance and dizziness, caution is warranted for a population already at risk for falls. \(^ {198}\)

**Azole Antifungals**

CNS disturbances associated with azole antifungals are rare. Package inserts of systemic azole antifungals (ie, itraconazole, fluconazole, voriconazole, and posaconazole) indicate nonspecific presentations, including headache, asthenia, dizziness, and fatigue. \(^ {199-202}\) A few reports indicate neuropsychiatric toxicities with itraconazole and voriconazole, including delirium and hallucinations, respectively. Itraconazole-induced delirium occurred in an elderly male being treated for disseminated histoplasmosis. \(^ {203}\) Differential diagnostics ruled out organic causes of delirium. The medication profile was reviewed and concomitant therapies were not attributed to the pathology of delirium. Treatment was eventually discontinued after the patient’s mental status continued to decline; discontinuation led to a drastic improvement in cognition. However, the fungal infection recurred, requiring re-initiation of treatment. Despite a dose reduction, cognitive decline reoccurred for the remainder of the treatment period.

Voriconazole use is associated with several neurotoxic events. \(^ {204-207}\) The most common, albeit rare, is CNS toxicity, which manifests as visual disturbances (altered or enhanced visual perception, blurred vision, color vision change, and photophobia). It is typically self-limiting and subsides upon completion or discontinuation of treatment. Reports indicate other presentations, including hallucinations, encephalopathy, insomnia, peripheral neuropathy, agitation, impaired concentration, and anxiety. \(^ {205,207-210}\) All symptoms resolved upon discontinuation of treatment. \(^ {207}\) Associations with serum concentrations of voriconazole and neurotoxic manifestations indicate a potential need for therapeutic drug monitoring. Data from Phase II and III trials associated serum concentrations of \(\geq 3 \mu\text{g/mL}\) with increased risk of visual disturbances. \(^ {211}\) Imhof et al \(^ {207}\) reported neurologic toxicities at serum concentrations \(> 5.5 \mu\text{g/mL}\). Patients typically experience these adverse effects within 2 weeks of therapy initiation. Median onset of symptoms occurred in 7 days (range 3–22 days). In this evaluation, of the 26 patients treated with voriconazole, 6 patients (approximately 23%) developed adverse neurologic effects. Another report by Pascual et al \(^ {208}\) found encephalopathy occurring in one third of patients with serum concentrations \(\geq 5.5 \mu\text{g/mL}\). Levels \(< 5.5 \mu\text{g/mL}\) were not associated with onset of neurotoxicity. Although these findings show increased risk of toxicity with serum concentrations \(> 5 \mu\text{g/mL}\), recommendations for therapeutic drug monitoring with voriconazole do not clearly delineate toxicity manifestations within a specified therapeutic index. \(^ {207,212}\)

**Role of Age**

The mechanisms of neurotoxicity are not yet described for these agents. Some of the case reports for neurotoxicity are present in the geriatric population, but it is unknown if these patients are at risk due to their age. Recommendations for clinical monitoring for at-risk populations are not available.

**CONCLUSIONS**

Various antimicrobial classes are implicated in neurotoxicity. The classes with the most reported cases of neurotoxicity include fluoroquinolones, macrolides, sulfonamides, nitrofurans, and \(\beta\)-lactams. The elderly
are at a higher risk of developing various symptoms of neurotoxicity with piperacillin and tazobactam, cephalosporins, carbapenems, aminoglycosides, TMP-SMX, nitrofurantoin, linezolid, and possibly the fluoroquinolones. Potential mechanisms of neurotoxicity differ between the agents. In some instances, the etiology of neurotoxicity is not fully elucidated and the incidence may increase with reported risk factors, renal dysfunction, or drug interactions. Considerations for evaluating a patient with potential neurotoxicity include drug dosing, concurrent medication use, comorbid conditions, and baseline clinical characteristics. The geriatric population is particularly vulnerable to ADRs, given baselines physical frailties contributing to alternations in drug PK and pharmacodynamics properties.\textsuperscript{213} Utilizing antimicrobial agents without concern for such alterations potentiates the risk of harm to patients. Awareness of antimicrobials contributing to neuropsychiatric events may enhance clinical decisions in diagnosis and management when such incidents occur.

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All authors contributed equally to the literature search, review design, data collection, writing and figure creation.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.09.020.

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187. Weight-based Dosing and Extended-release Formulation of Minocycline Tablets: Is There Clinical
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<tr>
<th>Antimicrobial Agent</th>
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<th>Predisposing Factors</th>
<th>Predisposition in the Elderly</th>
<th>Time to Resolution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolortes: Displacement of GABA from receptor site. But exact mechanism is unknown</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
<td>a) CNS toxicity 09%-7.4% headache, dizziness, ataxia, psychosis, delirium, agitation, depression, hallucinations, nightmares</td>
<td></td>
<td>Possible, but not confirmed</td>
<td>Rapid resolution upon discontinuation</td>
<td>9, 37, 214-219</td>
</tr>
<tr>
<td></td>
<td>b) More likely in patients with history of seizures or those taking theophylline or NSAIDs</td>
<td></td>
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<tr>
<td></td>
<td>C) Seizures</td>
<td></td>
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<tr>
<td></td>
<td>Insomnia, dizziness, headache (0.2%-11%) Psychosis: 1 in 6 million</td>
<td></td>
<td>Possible, but not confirmed</td>
<td>Rapid resolution upon discontinuation</td>
<td>9, 16</td>
</tr>
<tr>
<td></td>
<td>Less risk of interaction with theophylline or NSAIDs compared with ciprofloxacin</td>
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<tr>
<td></td>
<td>Dizziness (2.8%)</td>
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<td></td>
<td>Headache (1.1%)</td>
<td></td>
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<tr>
<td>Macrolides: May inhibit glutamatergic transmission221</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td>Headache (2%) Anxiety, confusion, insomnia, psychosis, tremor, dizziness, vertigo, convulsions, disorientation, hallucinations, mania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dosage and drug interactions</td>
<td></td>
<td>No</td>
<td>Transient; 24 hours until resolution</td>
<td>22, 21, 28, 29, 222-227</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Delirium in case reports</td>
<td>Case reports have been reported in the elderly</td>
<td>Possible, but not confirmed</td>
<td>48-72 hours</td>
<td>28</td>
</tr>
<tr>
<td>Sulfamethoxazole-Trimethoprim: Possible hypersensitivity reaction vs. deficiencies in glutathione. Mechanism unknown</td>
<td></td>
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</tr>
<tr>
<td>TMP/SMX</td>
<td>Aseptic meningitis Encephalitis Rare seizures Delirium Hallucinations</td>
<td>Symptoms are abrupt</td>
<td>Yes</td>
<td>36 hours- 10 days</td>
<td>34, 45, 46, 228-230</td>
</tr>
<tr>
<td>Penicillins: Inhibition of GABA neurotransmission</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ampicillin</td>
<td>Convulsions</td>
<td>- Large doses: serum levels ≥800 mcg/mL</td>
<td>No</td>
<td>Within days of discontinuation</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Predisposition to seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin/ tazobactam</td>
<td>Seizures, convulsions, myoclonus, hallucinations, drowsiness, confusion</td>
<td>- Reported with large doses</td>
<td>Yes, especially combined with renal failure</td>
<td>Resolved rapidly w HD removal</td>
<td>54-58, 232, 233</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- generally occurs in first 7 days</td>
<td></td>
<td></td>
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<tr>
<td>Cephalosporins: Antagonism of the GABA receptor</td>
<td></td>
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<tr>
<td>Cefazolin</td>
<td>Encephalopathy Seizures</td>
<td>- Large doses to patients with renal failure</td>
<td>Insufficient data</td>
<td>Upon discontinuation</td>
<td>12, 234</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Quinolone may increase risk of seizures (mice)</td>
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(continued)
## Supplemental Table I. (continued)

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
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<th>Predisposing Factors</th>
<th>Predisposition in the Elderly</th>
<th>Time to Resolution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>a) Diplopia, headache, tinnitus, ataxia, b) Seizures</td>
<td>Very high serum levels. Serum level for a seizure is 120 mcg/mL</td>
<td>Insufficient data</td>
<td>a) Within 2 weeks of discontinuation, b) Within 1 week</td>
<td>235-237</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Headache and dizziness</td>
<td>&lt; 1% of population</td>
<td>Insufficient data</td>
<td>Within days of discontinuation on</td>
<td>238</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Headache, dizziness, paresthesia, seizures, encephalopathy, coma, asterix, neuromuscular excitation and myoclonus</td>
<td>Large doses to patients with renal failure</td>
<td>Insufficient data</td>
<td>Within 2 after and 2 sessions of HD</td>
<td>239-241</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Confusion, hallucinations, agitation, convulsion (0.2%), tremor, delirium and coma</td>
<td>- Onset is 1–10 days, - Large doses to patients with renal failure</td>
<td>Insufficient data</td>
<td>Within 2–7 days after discontinuation on</td>
<td>65-70, 72, 241-244</td>
</tr>
<tr>
<td>Carbapenems: Antagonism of the GABA receptor</td>
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<tr>
<td>Imipenem-</td>
<td>Seizures (0.4% incidence for seizures in US packaging 1.5%–2% in post market experience)</td>
<td>Risk factors include age, renal failure, pre-existing CNS disease, stroke or history of seizure</td>
<td>Yes, seizures more likely</td>
<td>Upon discontinuation on</td>
<td>79-83, 85, 87, 245-248</td>
</tr>
<tr>
<td>Cilastatin</td>
<td></td>
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<tr>
<td>Meropenem</td>
<td>Seizures, Headache, Delirium (case)</td>
<td>Lower incidence of seizures compares to imipenem. Penetrates the BBB well Seizures in all ages</td>
<td>Delirium case reported in elderly</td>
<td>Upon discontinuation on</td>
<td>88, 93, 249, 250</td>
</tr>
<tr>
<td>Doripenem</td>
<td>Seizures</td>
<td>Animals studies indicated that doripenem lacked convulsive activity, trial: 1.1%</td>
<td>Yes</td>
<td>Upon discontinuation on</td>
<td>84, 85</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Seizures, hallucinations, asterix, myoclonic jerks and cognitive impairment</td>
<td>0.5% incidence, more likely in patients with pre-existing CNS disease</td>
<td>Yes</td>
<td>Upto 14 days</td>
<td>91, 92, 251, 252</td>
</tr>
<tr>
<td>Oxazolidinones: Unknown but may cause mitochondrial injury, contributing to the development of toxic neuropathies</td>
<td>Linezolid</td>
<td>a) Peripheral neuropathy, b) Optic neuropathy</td>
<td>Usually after months of treatment. Preexisting neurological disease, alcohol abuse, diabetes, chemotherapy, or antiviral therapy</td>
<td>Possible, but not confirmed</td>
<td>106-108</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) can take months to resolve and may be permanent b) Can lead to loss of vision (may be permanent).</td>
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</tr>
</tbody>
</table>
## Supplemental Table I. (continued).

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>ADR</th>
<th>Predisposing Factors</th>
<th>Predisposition in the Elderly</th>
<th>Time to Resolution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminoglycosides:</strong> Cochlear and/or vestibular organ damage. Inhibition of neuromuscular and autonomic transmission blockade</td>
<td></td>
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<tr>
<td>Gentamicin</td>
<td>a) Neuromuscular blockade, myasthenia gravis, psychosis, encephalopathy, acute organic brain syndrome</td>
<td>Renal impairment and low serum calcium</td>
<td>Yes</td>
<td>a) Resolves upon discontinuation</td>
<td>44, 120, 125, 254-258</td>
</tr>
<tr>
<td></td>
<td>b) Vestibulotoxic</td>
<td></td>
<td></td>
<td>b) May be permanent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) Psychosis and delirium in case reports</td>
<td>Case report only of psychosis</td>
<td>Yes</td>
<td>a) Resolves upon discontinuation</td>
<td>122, 126, 257</td>
</tr>
<tr>
<td></td>
<td>b) Vestibulotoxic</td>
<td>Rare</td>
<td>Yes</td>
<td>a) Resolves upon discontinuation</td>
<td>121, 259-264</td>
</tr>
<tr>
<td></td>
<td>a) Headache, paresthesia</td>
<td>Neuromuscular blockade- rare</td>
<td></td>
<td>a) Resolves upon discontinuation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) Cochleotoxic</td>
<td></td>
<td></td>
<td>b) May be permanent</td>
<td></td>
</tr>
<tr>
<td><strong>Nitroimidazoles:</strong> Possibly by inhibiting protein synthesis and modulation of GABA receptor within the cerebellar and vestibular system</td>
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<tr>
<td>Metronidazole</td>
<td>a) Peripheral neuropathy</td>
<td></td>
<td>No</td>
<td>a) Full recovery when drug is stopped or dose reduced. Occasionally can persist for months/year</td>
<td>129, 130, 132-134, 137, 138, 140-143, 145, 149, 150, 152, 153, 265-274</td>
</tr>
<tr>
<td></td>
<td>b) Ataxia and dysarthria</td>
<td></td>
<td></td>
<td>b) MRI changes can persist for months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) Optic neuritis</td>
<td></td>
<td></td>
<td>c) 1-14 days</td>
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<tr>
<td></td>
<td>d) Aseptic meningitis</td>
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<td></td>
<td>e) Psychosis</td>
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<tr>
<td><strong>Polymyxins:</strong> Inhibition of acetylcholine release in the synaptic cleft &amp; interference with lipophilic content of neurons</td>
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</tr>
<tr>
<td>Polymyxin</td>
<td>Neurological toxicity: dizziness, vertigo, confusion, muscle weakness, parasthesias, ataxia, headache, partial deafness, visual disturbances, hallucinations, seizures</td>
<td>Generally occurs in the first few days of therapy and may be dose dependent. May also be infusion duration dependent</td>
<td>Insufficient data</td>
<td>Reversible upon discontinuation</td>
<td>123, 154, 155, 159-161, 170, 275-278</td>
</tr>
<tr>
<td><strong>Clindamycin:</strong> Can inhibit neuromuscular transmission and augment neuromuscular blocking agents</td>
<td></td>
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<tr>
<td>Clindamycin</td>
<td>Temporary paralysis, increased tremor in a Parkinson's patient, restless leg syndrome</td>
<td>Limited to case reports</td>
<td>Insufficient data</td>
<td>Resolved in 3 days after discontinuation</td>
<td>164, 166-169, 171, 280, 281</td>
</tr>
</tbody>
</table>

(continued)
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<thead>
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<tbody>
<tr>
<td>Nitrofurans: Hypothesized to be due to axon loss</td>
<td>Nitrofurantoin</td>
<td>Headache, dizziness, drowsiness, depression, confusion, abnormal vision, slurred speech, peripheral neuritis, neuropathy</td>
<td>Peripheral neuritis more common with renal failure Neuritis starts within 45 days of initiation</td>
<td>Yes</td>
<td>Polyneuritis can result in death. Slow recovery</td>
</tr>
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<td></td>
<td>173–175, 177, 282</td>
</tr>
<tr>
<td>Tetracycline: V mechanism unknown</td>
<td>Tetracycline</td>
<td>Benign intracranial hypertension: headache and blurring of vision Weak neuromuscular blockade</td>
<td>Generally in young adults and children</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>170, 255, 283, 284</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td>CNS ADRs (3%–67%): Dizziness, disassociation, vestibular, tinnitus</td>
<td>More likely in elderly and women</td>
<td>Insufficient data</td>
<td>Transient</td>
</tr>
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<td>285, 286</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>CNS-related or dizziness (1%–3%) CNS ADRs more common with minocycline</td>
<td>No</td>
<td>Transient</td>
<td>285</td>
</tr>
<tr>
<td>Azole Antifungals: Mechanism unknown</td>
<td>Voriconazole</td>
<td>Visual disturbances, hallucinations and encephalopathy</td>
<td>Unknown risk factors</td>
<td>Insufficient data</td>
<td>Rapid resolution upon discontinuation</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>204–207</td>
</tr>
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