

Antimicrobial-induced cognitive side effects

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Abstract

Introduction: Antimicrobial-induced cognitive side effects are often overlooked or underreported. Literature often reports symptoms of antimicrobial-induced cognitive impairment under more general blanket terms, such as neuropsychiatric side effects, neurotoxicity, or drug-induced delirium or encephalopathy.

Methods: A PubMed search using terms including antibiotics, antifungals, antivirals, antimalarials, side effects, cognitive, neurotoxicity, encephalopathy, and delirium was conducted. Respectively, symptoms of cognitive impairment were teased out of the multiple neurologic complications presented for each case and reported based on antimicrobial class. Articles were excluded if they focused solely on neuropsychiatric side effects such as seizures, psychosis, hallucinations, or mood disturbances, were conducted in animals, or involved antiretroviral medication therapies.

Results: Of over 50 case reviews, case reports, retrospective chart reviews, and prospective cohort studies analyzed, 25 were deemed appropriate for purposes of this review. Common antimicrobial-induced cognitive side effects for all antimicrobial classes included confusion, delirium, encephalopathy, and impaired concentration or attention. Recurring risk factors included, but were not limited to, older age and renal impairment. Mechanisms of cognitive impairment were relatively specific to each antimicrobial class.

Discussion: Awareness of the potential for antimicrobial-induced cognitive side effects, including the general time frame of symptom onset and symptom presentation, is critical in challenging patient cases. This review article aims to summarize the risk factors, clinical symptoms, mechanisms, and management of antimicrobial-induced cognitive side effects. Pharmacists can play a key role in prevention through adjustment of medications for renal or hepatic dysfunction, avoidance of polypharmacy, and knowledge of critical drug interactions that may precipitate cognitive decline.

Keywords: antibiotics, antifungals, antivirals, antimalarials, side effects, cognitive, neurotoxicity, encephalopathy, delirium, penicillin, beta-lactam, cephalosporin, macrolide, fluoroquinolone, metronidazole

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Introduction

In 2011, outpatient providers prescribed 262.5 million courses of antibiotics, equating to more than 5

prescriptions for every 6 people in 1 year in the United States.^{1,2} Additionally, approximately half of patients admitted into the hospital setting receive antibiotic therapy for at least 1 day during their hospital stay.³ Although case series, case reports, and review articles have described antimicrobial-induced cognitive side effects, the incidence may still be underreported as acute changes in cognition are oftentimes under recognized or misdiagnosed by health care providers, especially in the elderly population.⁴ This review details the literature of antimicrobial-induced cognitive side effects, mechanisms, and management according to



antimicrobial classes including antibiotics, antifungals, antivirals, and antimalarials. Antiretrovirals are not addressed in this review.

Drug-induced cognitive side effects are vast and often reported within the umbrella of neuropsychiatric side effects. Neuropsychiatric side effects commonly reported in the literature include, but are not limited to, anxiety, behavioral changes, mood disturbances, psychosis, and seizures.⁵ This review article focuses specifically on the cognitive side effects of antimicrobial agents, which oftentimes present as psychomotor slowing, poor memory recall, reduced concentration, and severe confusion, or delirium. Medication-induced delirium and encephalopathy are broader terms frequently reported in the literature to describe overall changes in cognition. Although these terms differ diagnostically, references to antimicrobial-induced delirium or encephalopathy throughout this review focus on the presentation of general cognitive symptoms outlined above. Multiple studies have shown that severe confusion, or delirium, can lead to increased mortality rates, prolonged hospital stays, increased complications during hospital admissions, and an increased number of discharges to long-term care facilities.^{6,7} This review article aims to summarize the risk factors, clinical symptoms, mechanisms, and management of antimicrobial-induced cognitive side effects. Increased awareness of risk factors and presentation of antimicrobial-induced cognitive impairment, as well as appropriate judicious monitoring, can enhance patient safety.

Risk factors for medication-induced cognitive side effects can include underlying neurologic disorders, advanced age, polypharmacy, kidney impairment, and medical comorbidities.⁸ Underlying neurologic disorders such as epilepsy or cerebrovascular disease may increase the risk of neurotoxicity as a result of increased blood-brain barrier (BBB) permeability.⁹ Elderly patients are at an increased risk of drug-induced cognitive side effects because of alterations in neurotransmission and signal transduction, changes in pharmacokinetics and pharmacodynamics, and increased medication burden.¹⁰ Multiple medications predispose individuals to more drug interactions. Since many medication side effects are dose related, side-effect profiles of multiple medications can be synergistic.¹¹ Kidney impairment can prevent medication excretion, leading to toxic levels. Additionally, uremia can increase medication BBB penetration, and decreases in albumin can increase the free fraction of drugs.¹² Comorbidities that lead to a change of oxygen and nutrient delivery to the central nervous system (CNS), such as myocardial infarction, heart failure, or respiratory failure, may predispose to delirium.¹²

Two main factors accounting for drug-induced cognitive side effects have been proposed: pharmacodynamic and pharmacokinetic effects.^{8,13} Pharmacodynamic mechanisms can be described by medication interactions with neurotransmitters or the sensitivity of an individual to a medication, and are generally correlated with age.^{8,13} Pharmacokinetic mechanisms can be defined by absorption, distribution, metabolism, and excretion of drugs. Blood flow, volume of distribution, phases I and II metabolism, and glomerular filtration rate are just several mechanisms contributing to medication efficacy, inefficacy, or toxicity.^{10,14} In addition to basic pharmacodynamic and pharmacokinetic principles of medications, side effects are oftentimes caused by drug interactions that potentiate medication toxicity.¹¹ Drug interactions may also be pharmacokinetic or pharmacodynamic in nature.¹⁰ Many common drug interactions are known to affect phase-I drug metabolism, involving the cytochrome P450 (CYP) enzyme system.¹⁰ Although drug interactions can occur through various mechanisms, the ultimate effects involve either enhancement or antagonism of a medication's effects. Specific mechanisms of medication-induced cognitive side effects are reviewed within each antimicrobial class.

Methods

A PubMed search using terms including antibiotics, antifungals, antivirals, antimalarials, side effects, cognitive, neurotoxicity, encephalopathy, and delirium was conducted. Respectively, symptoms of cognitive impairment were teased out of the multiple neurologic complications presented for each case and reported based on antimicrobial class. Articles were excluded if they focused solely on neuropsychiatric side effects such as seizures, psychosis, hallucinations, or mood disturbances, were animal studies, or if they involved antiretroviral medication therapies.

Results

Of over 50 case reviews, case reports, retrospective chart reviews, and prospective cohort studies analyzed, 25 were deemed appropriate for purposes of this review. Common antimicrobial-induced cognitive side effects for all antimicrobial classes included confusion, delirium, encephalopathy, and impaired concentration or attention. Recurring risk factors included, but were not limited to, older age and renal impairment.

Antibiotics

Penicillin Antibiotics

Reports of penicillin antibiotic-induced encephalopathy have been documented, including symptoms of disori-

entation and confusion.^{15,16} The time to development of encephalopathy after piperacillin or piperacillin/tazobactam administration can range from 1.5 days to 7 days, with resolution within hours to days.¹⁵ As documented in the Table, Ye et al¹⁶ details piperacillin/tazobactam-induced confusion in a 63-year-old woman with stage 5 chronic kidney disease, estimated creatinine clearance (CrCl) of approximately 8 mL/min, who was administered nonrenally adjusted doses, whereas another case report¹⁵ documents piperacillin/tazobactam-induced encephalopathy in an 87-year-old man despite appropriate dose adjustment for estimated kidney function. The mechanism of penicillin antibiotic-induced cognitive side effects may be related to the serum concentrations of the drug and to inhibition of gamma-aminobutyric acid (GABA) transmission because of the similarities between the β -lactam ring structure and GABA.^{17,18} Penicillin antibiotics may also reduce benzodiazepine (BZD) receptors via a direct binding to the BZD receptor itself.¹⁹ This reduction in BZD receptors may reduce inhibition and alter neuronal excitability, playing a role in penicillin-induced encephalopathy.¹⁹ Both cases reported resolution of encephalopathy after drug removal and high-flux hemodialysis. Measured serum piperacillin levels also markedly declined after hemodialysis; a concentration of 86.9 $\mu\text{g/mL}$ (more than double the therapeutic range of $26 \pm 15 \mu\text{g/mL}$) declined to 22.2 $\mu\text{g/mL}$ after 4 hours in the first patient described and dropped from 56.9 $\mu\text{g/mL}$ to approximately 16 $\mu\text{g/mL}$ in the second patient case, demonstrating a possible link between drug concentration and toxicity.^{15,16} Given that elevated penicillin antibiotic levels have been associated with penetration of the CNS at toxic levels, measuring serum trough concentrations may aid in prevention of toxicity²⁰; however, therapeutic drug monitoring of β -lactam antibiotics has not been extensively investigated due to their wide therapeutic window.

Cephalosporins

Cephalosporin antibiotics have been associated with confusion, aphasia, and encephalopathy.^{21,22} The general time frame for cephalosporin-induced encephalopathy ranges from 1 to 10 days after medication initiation, with resolution in 2 to 7 days after discontinuation.²¹ A retrospective review of 8 patients with acute renal failure (CrCl ≤ 17 mL/min in 7 patients; CrCl 50 mL/min in remaining patient) and a case series of 5 patients with acute renal failure revealed that each patient developed cognitive side effects subsequent to nonrenally adjusted cefepime initiation, as referenced in the Table.^{21,22} Conversely, appropriately dosed cefixime has induced encephalopathy and delirium in a patient without renal impairment.²³ There may be an association between elevated cefepime plasma concentrations and neurologic toxicity.^{21,22} Furthermore, patients with renal impairment may show accumulation of the drug,

predisposing to neurotoxic effects; serum trough concentrations ranging from 15 to 20 mg/L may suggest a neurotoxic threshold.²⁴ It is proposed that cephalosporin therapy may release endotoxins, leading to release of cytokines, such as tumor necrosis factor- α (TNF- α), which may in turn induce neurotoxic properties.²⁵ Additionally, medication-induced suppression of inhibitory postsynaptic responses, mainly regulated by neurotransmitter GABA_A, may also play a role in the alteration of cognitive function.^{18,19,21} Cephalosporins with higher affinities for GABA_A receptors and increased BBB penetration, such as cefazolin, ceftazidime, and cefepime, are proposed to be more neurotoxic.^{17,26} Cephalosporin antibiotic removal and hemodialysis have led to reversal of symptoms.^{22,23}

Fluoroquinolones

Altered mental status, disorientation, and decline in attention and concentration have been reported with gemifloxacin, levofloxacin, and ciprofloxacin.²⁷⁻³⁰ Additionally, Karagoz et al³¹ reported impaired memory recall and loose association in 1 patient receiving moxifloxacin, requiring administration of low-dose quetiapine. Symptoms may manifest anywhere from 1 to 2 days after fluoroquinolone initiation of therapy, with resolution within 2 to 9 days.^{27,28,30} It is postulated that GABA_A inhibition plays a role in CNS side effects.^{18,32} The degree of fluoroquinolone inhibitory effects on the GABA receptor are likely correlated to neurologic and cognitive side effects.^{18,32} Compromise of the BBB allows exposure to increased drug concentrations, and therefore, possibly neurotoxic effects.³³ Alternatively, fluoroquinolones may induce the excitatory effects of N-methyl-D-aspartate via direct activation.³¹ Case reports, presented in the Table, have shown complete symptom resolution and restored cognition after drug withdrawal.^{27,28,30}

Macrolides

Clarithromycin and azithromycin use have been linked to delirium, disorientation, and impaired concentration.³⁴⁻³⁶ Time to symptom presentation may range from 3 to 10 days after drug ingestion, with resolution within approximately 3 days.^{34,35} As noted in the Table, 1 patient on highly active antiretroviral therapy was diagnosed with a neuropsychiatric reaction secondary to clarithromycin and treated with diazepam and temazepam.³⁴ The CYP3A enzyme system drug interaction between clarithromycin and nevirapine, a non-nucleoside reverse transcriptase inhibitor, may have contributed to the neuropsychiatric reaction.³⁴ Nevirapine has been shown to increase the area under the curve of the active 14-OH metabolite of clarithromycin, which may be correlated to neuropsychiatric side effect development.³⁴ However, the exact mechanism for this reaction in macrolide antibiotics is unknown.³⁴ Drug discontinuation has been shown to aid in symptom resolution.³⁵

TABLE: Study information of antimicrobial-induced cognitive side effects, interventions, and presence of renal impairment

Study, Year	Study Design	Patient Population	Intervention	Renal Impairment/ Dose	Antimicrobial Class	Cognitive Effects
Huang et al, ¹⁵ 2009	Case report	87 y/o M	High-flux HD	Yes; dose adjusted, pip/tazo 2.25 mg q12h	Penicillins	Disorientation, confusion
Ye et al, ¹⁶ 2011	Case report	63 y/o F	Drug D/C; high-flux HD	Yes; no renal adjustment, pip/tazo 2 g q6h	Penicillins	
Capparelli et al, ²⁴ 2005	Case report	85 y/o M	Drug D/C	No	CPN	Confusion, aphasia, encephalopathy
Chatellier et al, ²² 2002	Case series	Two 73 y/o F, 16 y/o M, 65 y/o M, 75 y/o M	Antiepileptic drugs and HD	Yes; no renal adjustment, cefepime 2-9 g daily	CPN	
Sonck et al, ²¹ 2008	Retrospective chart review	8 patients	Drug D/C	Yes; no renal adjustment, cefepime 1-8 g daily	CPN	
Barrett et al, ²⁷ 2009	Case report	67 y/o F	Drug D/C	No	FQ	Delirium, AMS, disorientation, decreased attention and concentration
Slobodin et al, ²⁸ 2009	Case report	83 y/o M	Drug D/C	No	FQ	
Raj et al, ²⁹ 2013	Case report	13 y/o F	Drug D/C	No	FQ	
Karagoz et al, ³¹ 2015	Case report	60 y/o F	Quetiapine, drug D/C	No	FQ	
Al-Ghamdi, ³⁰ 2002	Case report	46 y/o M, 67 y/o F, 39 y/o F, 30 y/o F	Drug D/C	Yes; no renal adjustment, ciprofloxacin 250-500 mg bid	FQ	
Prime et al, ³⁴ 2001	Case report	58 y/o M	Diazepam, temazepam, drug D/C	No	Macrolides	Delirium, disorientation, impaired concentration
Ozsoylar et al, ³⁵ 2007	Case report	87 y/o M	Drug D/C	No	Macrolides	
Cone et al, ³⁶ 2003	Case report	2 geriatric males	Drug D/C	No	Macrolides	
Papathanasiou et al, ³⁷ 2013	Case report	62 y/o M	Drug D/C	No	Other ABX, anaerobic agents	Cognitive decline, slow response to verbal commands
Kim et al, ³⁸ 2011	Case report	71 y/o M	Drug D/C	No	Other ABX, anaerobic agents	
Denholm et al, ⁴⁰ 2014	Prospective cohort study	Data on first 100 patients reported	N/A	No	Other ABX, antimycobacterials	Cognitive impairment
Winn et al, ⁴⁵ 1979	Case report	28 y/o M	Medication rechallenge	No	Antifungals	Confusion, disorientation
Ellis et al, ⁴⁴ 1982	Clinical and autopsy studies	14 patients treated with AME	N/A	No	Antifungals	

TABLE: Study information of antimicrobial-induced cognitive side effects, interventions, and presence of renal impairment (continued)

Study, Year	Study Design	Patient Population	Intervention	Renal Impairment/ Dose	Antimicrobial Class	Cognitive Effects
Hansen et al, ⁴⁸ 1996	Case report	43 y/o M, HIV (+)	Drug D/C	No	Antivirals	Disorientation, confusion, incoherent phrases
Sharathkumar et al, ⁴⁹ 1999	Case report	11 y/o M, with ALL	Drug D/C	Yes; drug withdrawal, ganciclovir 5 mg/kg bid	Antivirals	
Asahi et al, ⁵⁰ 2009	Case series presented in review article	12 M, 8 F; with ARF or CRF	N/A	Yes; 57.1% had excessive dosages, valacyclovir 500-3000 mg/d	Antivirals	
Davis et al, ⁵¹ 1990	Case report	CMV-antibody negative male status post renal transplant	Haloperidol, drug D/C	Slight impairment; ganciclovir 5 mg/kg bid	Antivirals	
Hikaru et al, ⁵² 2013	Case report	55 y/o M	Drug D/C, hemodialysis	Yes; no renal adjustment, ganciclovir 150 mg/d	Antivirals	
Gilbert, ⁵⁴ 1977	Case report	72 y/o F	Drug D/C	No	Antimalarials	Confusion, memory and attention impairment, slowed psychomotor speed, altered mental manipulations
Javorsky et al, ⁵⁵ 2001	Case report	52 y/o F	Olanzapine, lorazepam, fluoxetine, trazodone	No	Antimalarials	

ABX = antibiotics; AME = amphotericin B methyl ester; AMS = altered mental status; ARF = acute renal failure; CPN = cephalosporin; CRF = chronic renal failure; D/C = discontinuation; HD = hemodialysis; F = female; FQ = fluoroquinolones; HAART = highly active antiretroviral therapy; M = male; pip/tazo = piperacillin/tazobactam; SCr = serum creatinine; q = every; bid = twice daily dosing; y/o = year-old.

Other Antibiotics, Anaerobic Agents

Several case reports describe metronidazole-induced encephalopathy, including symptoms of confusion, disorientation to time and place, and slowed response to commands.^{37,38} Time to onset of metronidazole-induced encephalopathy can be months after treatment start, with resolution within days to weeks.^{37,38} Papathanasiou et al³⁷ detail rapidly progressive decline in cognition in one individual after self-medicating with metronidazole for febrile gastroenteritis for roughly 6 months. Infectious Diseases Society of America guidelines recommend metronidazole treatment duration for 7 to 10 days for this indication.³⁹ This incident highlights the necessity of antimicrobial stewardship to promote appropriate antimicrobial use. Possible mechanisms for metronidazole neurotoxicity may include modulation of GABA within the cerebellar and vestibular areas, and the generation of neurotoxic radicals from reactions with catecholamine neurotransmitters.³⁷ Binding of metronidazole metabolites to RNA instead of DNA may inhibit RNA synthesis, leading to axonal degeneration.³⁷ Prompt discontinuation of metronidazole therapy can reverse symptoms.^{37,38}

Other Antibiotics, Antimycobacterials

A prospective cohort study⁴⁰ documents that 7% of patients treated with a 9-month course of isoniazid preventative therapy for latent tuberculosis experienced cognitive impairment, as shown in the Table. Older age was associated with an increased risk of isoniazid side effects (odds ratio = 1.05/y; confidence interval 1.02-1.08 = 95%).⁴⁰ Although a specific time frame to cognitive impairment induction was not defined, the study concluded that the majority of adverse effects were low grade and transient in nature.⁴⁰ The mechanism of isoniazid-induced neurotoxicity is thought to be related to decreases in GABA concentrations, owing to the inhibition of pyridoxine metabolism, and the accumulation of glutamic acid.⁴¹ In addition, research has shown a potential correlation with isoniazid metabolites and neurotoxicity, particularly the metabolite hydrazine.⁴² Isoniazid removal and the addition of pyridoxine, in doses of 100 mg daily, have been shown to normalize symptoms of neurotoxicity and establish return to baseline functioning.⁴³

Antifungals

Dementia, manifested as mild confusion and disorientation, has been reported with both intravenously and intrathecally administered amphotericin B.^{44,45} Intravenous administration of amphotericin B may not attain adequate levels of drug in the cerebrospinal fluid owing to poor BBB penetration.⁴⁶ However, cognitive side effects of confusion and disorientation have been reported with both intravenous and intrathecal administration, despite poor BBB penetration with the intravenous formulation.^{44,45} Symptom onset has been reported anywhere from hours to weeks after drug administration, with resolution several days after drug cessation.^{44,45} As shown in the Table, an analysis of autopsy reports of 14 patients treated with intravenous and/or intrathecal amphotericin B methyl ester (AME), a methylated derivative of amphotericin B, revealed symptoms of confusion and disorientation in about half of the patients without significant meningitis.⁴⁴ The severity of side effects increased as total AME doses and exposure increased.⁴⁴ Winn et al⁴⁵ describe a patient with a significant decrease in responsiveness, and an electroencephalogram revealing diffuse slowing after amphotericin B intrathecal administration. After medication rechallenge at a reduced dose, tolerability was eventually established, demonstrating a possible dose-related relationship and emphasizing the need to avoid more than recommended initial doses of intrathecal amphotericin B.⁴⁵ Amphotericin B binds to ergosterol, on the cell membrane of fungi, for its antifungal effect. However, when amphotericin B, instead, binds to cholesterol, the membrane-stabilizing sterol for human cells, toxicity develops, leading to the symptoms presented above.⁴⁷

Antivirals

Ganciclovir, acyclovir, and acyclovir's oral prodrug, valacyclovir, have been reported to cause confusion, disorientation, forgetfulness, incoherent speech, and cognitive decline.⁴⁸⁻⁵⁰ Symptoms can occur within several days of drug initiation and tend to subside within days to weeks after drug removal.⁴⁸⁻⁵⁰ Case reports, documented in the Table, have demonstrated cognitive decline in those with and without renal impairment.^{48,49,51,52} Reported cases of valacyclovir-induced cognitive impairment generally involve excessive doses of the antiviral agent and are preceded by acute or chronic renal failure.⁴⁶ Acyclovir can provoke renal impairment via precipitation within the tubular lumen or from development of acute interstitial nephritis.⁵⁰ Therefore, once valacyclovir is converted to acyclovir, renal impairment can ensue and increase the risk of neurotoxicity.⁵⁰ Both acyclovir and ganciclovir cross the BBB; however, the mechanism for cognitive impairment is unknown as neurologic side effects and systemic drug concentrations have remained inconsistent.^{52,53}

However, it is hypothesized that increased concentrations of 9-carboxymethoxymethylguanine, the main metabolite of acyclovir, may contribute to neurologic side effects. The 9-carboxymethoxymethylguanine levels have been shown to be higher in chronic kidney disease (CrCl of approximately 15-30 mL/min) compared with normal renal function, 2.9 μ M versus 12 μ M, respectively.⁵³ Drug discontinuation as well as hemodialysis may hasten recovery time.^{50,52}

Antimalarials

Quinidine and mefloquine have been suggested to induce confusion, memory and attention impairment, slowed psychomotor speed, and inaccurate mental manipulations of information.^{54,55} Occurrence of cognitive side effects may manifest from a couple of days to years after medication initiation and continue to progress with time.^{54,55} Gilbert⁵⁴ details the hospitalization for confused mental status and worsening memory loss over several years in an individual with a 14-year history of quinidine use. Throughout the course of quinidine treatment, the patient had undergone 2 neurologic evaluations, with no cause of cognitive decline found.⁵⁴ Another patient was hospitalized in an inpatient psychiatric unit for neuropsychiatric symptoms, including cognitive disturbances, shortly after mefloquine ingestion, suggesting drug causation.⁵⁵ The underlying mechanism for mefloquine-induced cognitive impairment is unknown; however, central cholinergic syndrome has been shown to cause other neuropsychiatric side effects of mefloquine administration.⁵⁶ It is possible that this may play a role in cognitive changes induced by antimalarial agents. Furthermore, mefloquine disruption of endoplasmic reticulum calcium homeostasis could be related to in vitro neurotoxicity.⁵⁷ Simple drug removal has been shown to restore baseline functioning over the duration of a month.⁵⁴

Discussion

It is important to note that the majority of antimicrobial-induced cognitive side effects are supported only through limited case reports or case series. Data from large, randomized-controlled studies are lacking. However, despite the deficiency of strong evidence, common trends in the literature are perceived. For example, frequent recurring risk factors in the cases presented include advanced age and renal impairment, emphasizing the importance of attention to these factors with antimicrobial use. Pharmacists can play a pivotal role in prevention by identifying high-risk patients and having an increased awareness of risk factors and presentation of antimicrobial-induced cognitive impairment. As medication experts, pharmacists can improve patient care and safety through

knowledge of extensive pharmacokinetics and application of antimicrobial stewardship practices. Awareness of the potential for antimicrobial-induced cognitive side effects, especially in high-risk patients, can help prevent misdiagnosis, unnecessary treatment, and unwanted direct and indirect costs to the patient.⁵⁸

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