

The inexplicably suicidal patient

Michael B. Murphy, MSIV, Lloyd C. Alcera, MD, Jasmine K. Gill, MD, and Jeffrey Dunn, MD

After becoming confused, Mr. A attempts suicide by jumping off a bridge. He has a history of cognitive developmental delay but no psychiatric history. What prompted his action?

CASE Confused and suicidal

Mr. A, age 39, becomes disoriented while walking and approaches a suspension bridge. He borrows a passerby's cell phone and calls his sister. His sister later states that he was confused and expressed his final goodbyes, saying, "I will see Mom in heaven." He gives back the phone and leaps off the bridge. A nearby boat rescues him almost immediately.

Mr. A is brought to the trauma unit, where he is treated for a lacerated liver. After he is stabilized, Mr. A is awake and answering questions appropriately. He is placed on suicide precautions and direct 24-hour, one-to-one supervision. Our psychiatric team evaluates him.

Mr. A reports no history of diabetes, hypertension, cardiac disorders, or neurologic disorders, but does have a history of cognitive developmental delay. He has no history of psychiatric illness, suicide attempts, or self-injurious behavior. He denies a psychiatric family history or using alcohol, tobacco, or illicit drugs; drug screen is negative. He is unemployed, collects disability, and lives with his sister.

What step would you take next?

a) order neurologic workup

- b) screen for depressive disorder
- c) review history for clues to suicidal behavior
- d) all of the above

The authors' observations

In our initial evaluation, we find no obvious reason for Mr. A's confusion or suicide attempt. We decide to closely review Mr. A's history in the days leading up to his jumping off the bridge.

HISTORY Otitis media treatment

Mr. A has a history of chronic otitis media and sought treatment for ear pain at a local emergency room (ER) 10 days before his suicide attempt. He was prescribed amoxicillin, 500 mg tid for 10 days, and meclizine, 25 mg every 8 hours as needed for dizziness.

Immediately after his first dose of both drugs, the patient told his family he was feeling "weird," but denied being dizzy. Thinking the unusual feeling was from meclizine, Mr. A stopped taking it but continued amoxicillin. On the second day of amoxicillin, he noticed bouts of confusion. He could perform his daily activities, but with difficulty. Mr. A's niece said he had to ask for help with minor tasks, such as opening a can of soup.

On day 3, Mr. A developed prominent auditory hallucinations. He described hearing unrecognizable male and female voices



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Mr. Murphy is a medical student, Drs. Alcera and Gill are residents, and Dr. Dunn is associate professor, department of psychiatry, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Cooper University Hospital, Camden, NJ.

Clinical Point

Several classes of antibiotics have psychiatric side effects that range from minor confusion to psychosis

Table 1

Potential psychiatric effects of antibiotics

Medication	Side effects
Antibacterials	
Penicillins	Encephalopathy, irritability, sedation, anxiety, hallucinations
Cephalosporins	Sleep disturbances, hallucinations
Cycloserine	Dose-dependent side effects, depression, irritability, psychosis
Quinolones	Sleep and mood disorders, psychosis
Nitrofurans	Euphoria, psychosis, sleep disturbances
Tetracyclines	Decreased concentration, mood and sleep disorders
Chloramphenicol	Depression
Trimethoprim, sulfonamides	Depression, psychosis
Antimycobacterials	
Isoniazid	Cognitive impairment, mood disorder, psychosis
Clofazimine	Major depression, suicide
Rifampin	Sedation
Ethionamide	Sedation, irritability, agitation, depression, psychosis
Ganciclovir	Sleep disturbances, anxiety, mood disorders, psychosis
Antifungals	
Amphotericin B	Delirium
Ketoconazole	Decreased libido, mood disorders, psychosis
Flucytosine	Sedation, hallucinations
Griseofulvin	Depression, psychosis, sleep disturbances

Source: Turjanski N, Lloyd GG. Psychiatric side effects of medications: recent developments. *Advances in Psychiatric Treatment* 2005;11:58-70. Reprinted with permission

chattering and mumbling throughout the day. The voices and confusion progressively worsened, but Mr. A continued taking the antibiotic and did not mention the voices to his family.

Mr. A's sister reports that in a phone conversation with her brother on day 7, "he wasn't himself...he was talking about my sister and mother but what he said didn't make sense." She asked a neighbor to check on Mr. A; he reported that Mr. A was "OK." On the final day of amoxicillin—day 10—Mr. A became increasingly agitated. He says us that shortly before wandering onto the bridge and jumping, he was having a difficult time dealing with the voices and confusion.

We suspect amoxicillin might have been responsible for Mr. A's psychotic symptoms.

Potential neuropsychiatric effects of amoxicillin include all of the following except:

- hallucinations
- anxiety
- irritability
- euphoria

The authors' observations

Treatment modalities and pharmaceutical approaches used to treat infectious diseases carry many potential adverse effects. When a patient presents with new-onset psychiatric symptoms, explore whether they are related to an underlying mood disorder or medication side effects. Three important considerations are to:

- determine whether the condition is reversible by discontinuing a drug

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Table 2**Amoxicillin-triggered psychosis: 3 case reports**

Study	Patient	Description
Beal et al ⁷	Woman, age 30	Confusional manic symptoms after 10 days of treatment; symptoms resolved within 12 days of admission; patient had a similar reaction to ampicillin 14 years earlier
Stell et al ⁸	Man, age 55	Auditory, visual, and tactile hallucinations within hours of first dose
Rao ⁹	Woman, age 63	Auditory and visual hallucinations 1 week after taking 250 mg tid; patient had a similar reaction to amoxicillin 5 years earlier; in both cases symptoms resolved within 3 days of discontinuing amoxicillin

Clinical Point

Irritability, sedation, anxiety, and hallucinations are potential psychiatric side effects of amoxicillin

- identify and characterize previously unrecognized adverse drug effects
- avoid inaccurate diagnosis that leads to nonindicated psychiatric treatment.¹

Antibiotic side effects vary, depending on the particular drug and its target bacteria. The most common are gastrointestinal, such as upset stomach and diarrhea. Antibiotics also can induce an anaphylactic reaction ranging from mild (pruritic rash or slight wheezing) to life-threatening (swelling of the throat, difficulty breathing, and hypotension).

Several classes of antibiotics have psychiatric side effects that range from minor confusion and irritability to severe encephalopathy and suicide (*Table 1, page 74*).² Case reports have described psychotic symptoms associated with cotrimoxazole,³ trimethoprim/sulfamethoxazole,⁴ and ciprofloxacin.⁵ An older review found that amoxicillin is among the top 10 most commonly prescribed medications associated with psychiatric side effects.¹

Amoxicillin is a penicillin-based, broad-spectrum antibiotic (*Box*).^{1,6} Its potential psychiatric side effects include encephalopathy, irritability, sedation, anxiety, and hallucinations.² These symptoms usually are managed by reducing the dosage or discontinuing the medication. In some cases, antipsychotics may be used to control the symptoms.

A literature search reveals 3 cases of amoxicillin-related psychosis (*Table 2*).⁷⁻⁹ A 30-year-old woman with a urinary tract infection (UTI) developed “confusional manic symptoms” after 10 days of amoxicillin.⁷ The patient’s family reported she’d had a similar reaction 14 years earlier following 9 days of ampicillin for a perforated appendix; since then she had received non-aminopenicillins without incident. In both incidents, her psychotic symptoms resolved.

A 55-year-old man developed auditory, visual, and tactile hallucinations within hours of his first dose of amoxicillin for presumed pneumonia. The patient “was able to describe what he had experienced clearly with evidence of subjective terror.”⁸

Most recently, a 63-year-old woman taking amoxicillin, 250 mg tid, for a UTI developed sleep disturbance after 1 day and auditory and visual hallucinations after 4 days. She had a similar episode that required hospitalization 5 years earlier. In both episodes, psychotic symptoms resolved within 3 days of antibiotic discontinuation, with no psychotropic drug treatment.⁹

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Mechanism of psychiatric effects

The mechanisms of antibiotic-related neuropsychiatric sequelae are uncertain and vary with drug class and patient factors.

Hoigné's syndrome—an acute psychotic reaction to intramuscular procaine penicillin first reported around 1950—is characterized by psychiatric symptoms, predominantly anxiety and hallucinations, almost immediately following injection. Anxiety is marked by a fear of imminent death as well as autonomic hyperactivity. This “pseudoanaphylactic reaction” persists for 5 to 30 minutes and has been noted for its resemblance to temporal lobe and limbic seizures (perceptual disturbance, sympathetic hyperactivity, and “doom anxiety”).

The underlying pathophysiology remains unclear; the reaction was originally attributed to microembolization of procaine crystals to the lungs and brain, later to direct procaine neurotoxicity, and most recently to temporolimbic kindling—the appearance of physiologic and behavioral responses to repetition of a stimulus (procaine) that initially is without effect.¹⁰

A potential mechanism for amoxicillin's neuropsychiatric effects is less clear. Because amoxicillin is an oral medication, hypotheses regarding Hoigné's syndrome seem inapplicable. In addition, amoxicillin is largely excreted unchanged by the kidneys; the lack of significant P450 metabolism argues against mechanisms mediated by polypharmacy or altered metabolite levels. Furthermore, penicillins are polar molecules with poor CNS penetration.⁶ Penicillins demonstrate known neurotoxicity, however, most often causing convulsions or myelopathy. Identified risk factors for penicillin neurotoxicity include:

- intravenous/theocal administration
- high doses
- CNS disease
- renal insufficiency
- advanced age
- use of drugs that block antibiotic export from the CNS

Box

Amoxicillin: Well-tolerated, broad spectrum

Beta-lactam compounds inhibit bacterial growth by interfering with cell wall synthesis. As a beta-lactam antibiotic, amoxicillin's chemistry, mechanism of action, pharmacologic and clinical effects, and immunologic characteristics are similar to those of cephalosporins, monobactams, carbapenems, and beta-lactamase inhibitors.⁶

Amoxicillin is an aminopenicillin. These antibiotics retain the antibacterial spectrum of penicillin but have a broader spectrum against gram-negative organisms because of their enhanced ability to penetrate the gram-negative outer membrane. Amoxicillin causes less gastrointestinal (GI) irritation than penicillin and is stable in an acidic environment.

Amoxicillin is administered 250 to 500 mg every 8 hours for adults and 20 to 40 mg/kg of body weight every 24 hours for pediatric patients.¹ Amoxicillin is more stable and better absorbed in the GI tract than most penicillins, so amoxicillin 3 times a day is as effective as 4 daily doses of other penicillins.

- conditions that increase blood-brain barrier permeability.

One hypothesis focuses on penicillin's inhibition of both the GABAA receptor-chloride ionophore complex and the benzodiazepine receptor, yielding CNS disinhibition and decreasing the seizure threshold. Notably, GABA antagonism is considered a primary facilitator of CNS kindling. Penicillin also has been reported to cause delirium related to allergy-mediated cerebral edema.¹¹ Beal et al⁷ argue for an immune-mediated cerebritis.

Psychiatric symptoms secondary to antibiotics—particularly penicillins—are likely multifactorial, suggesting certain individuals may be predisposed to “Hoigné's syndrome” from amoxicillin. In the 3 case reports of amoxicillin-related psychosis, there is variation in duration of exposure until symptom onset, medical

Clinical Point

A potential mechanism for amoxicillin's neuropsychiatric effects is unclear

Clinical Point

Some individuals may be predisposed to developing psychiatric symptoms from antibiotics use

indication for the antibiotic, and patient age and gender. Any or all of these factors may be clinically significant. None of these patients, however, had a psychiatric history.

It is not clear whether a single 25-mg dose of meclizine—an H1-receptor antagonist—played a role in Mr. A's psychotic symptoms. Meclizine overdose can cause extreme drowsiness, seizures, hallucinations, and decreased breathing. This anticholinergic has a half-life of only 6 hours and a duration of action of up to 24 hours, although anticholinergic toxicity from overdose can last for days.¹⁰ Mr. A ingested a single 25-mg dose of meclizine, however, and his auditory hallucinations persisted for 9 days. Furthermore, Mr. A's previous well-tolerated meclizine use and lack of other signs and symptoms of anticholinergic toxicity do not support a substantial role for meclizine in his psychotic symptoms.

OUTCOME Symptoms resolve

Mr. A's confusion and auditory hallucinations resolve approximately 36 hours after he completed amoxicillin treatment. When transferred to the psychiatric unit, he denies auditory hallucinations or suicidal ideation. He also denies ear pain, tinnitus, vertigo, or ear tenderness; physical examination of the ear is unremarkable. Throughout the hospital admission, Mr. A experiences no confusion or changes in mental status and he continues to adamantly deny suicidal ideation.

He does not require treatment with antipsychotics or other psychotropic medications and is discharged in stable condition.

Bottom Line

Consider antibiotic-induced psychosis in the differential diagnosis of a patient with new psychotic symptoms and no history of psychiatric disorders, particularly if the patient is taking amoxicillin. Symptoms typically resolve within days of discontinuing antibiotics. Treatment with psychotropics usually is unnecessary.

Related Resource

• Levenson JL, Schneider RK. Infectious diseases. In: Levenson JL, ed. *The American Psychiatric Publishing textbook of psychosomatic medicine*. Washington, DC: American Psychiatric Publishing; 2005:577-98.

Drug Brand Names

Amoxicillin • Amoxil, Trimox, others	Flucytosine • Ancobon
Amphotericin B • Amphotin, Abelcet	Ganciclovir • Cytovene
Ampicillin • Principen	Griseofulvin • Fulvicin U/F, Grifulvin V
Chloramphenicol • Chloromycetin	Isoniazid • Nydravid
Ciprofloxacin • Cipro	Ketoconazole • Nizoral
Clofazimine • Lamprene	Meclizine • Antivert, Bonine, others
Cycloserine • Seromycin	Rifampin • Rifadin, Rimactane
Ethionamide • Trecator	Trimethoprim/sulfamethoxazole • Bactrim, Septra

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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