Trimethoprim-Sulfamethoxazole–Induced Psychosis Culminating in Catastrophic Self-Injury: A Case Report

To the Editor: Although trimethoprim-sulfamethoxazole (TMP-SMX) seldom causes psychosis, the side effect of visual and auditory hallucinations has been described previously, principally among immunocompromised persons and elderly patients.[1] We are aware of only a single case report of psychosis in an immunologically competent teen[2] and of no suicides or attempts attributed to TMP-SMX. Here, we report a case of catastrophic self-injury resulting from TMP-SMX–induced psychosis.

Case report. An 18-year-old white, male, high-school senior was admitted to the hospital in January 2015 for a self-inflicted gunshot to the face. Seven days before admission, the patient initiated a course of TMP-SMX for an infected toenail. He began to feel depressed and moody and withdrew to his room. His family said he appeared agitated and was uncharacteristically rude. On the day of admission, the patient "saw" his deceased paternal uncle, himself a victim of suicide. The vision audibly reassured him, "It is okay to shoot yourself." Shortly afterward, the patient did so, leaving a photograph of his uncle on the floor nearby. He denied past psychiatric treatment but recalled experiencing mood changes and hallucinations when treated with TMP-SMX 8 months earlier. To minimize psychiatric symptoms, he had taken the medication every other day rather than as prescribed. Medical and substance use history was insignificant. Family history was noteworthy for suicide in a paternal uncle and possible depression in the father.

At admission, the patient displayed extensive facial injuries. His mandible was missing and a gaping cavity assuming the dimensions of a large pear or small gourd replaced his nose, mouth, and much of the maxilla. The narrow part of the wound created a wide chasm separating the laterally displaced though still functional eyes. He was conscious and had limited capacity to communicate. Results from the urine toxicology screen were negative, and electrolytes were within normal limits. The computerized tomography scan showed extensive facial fractures, a small anterior subdural bleed to the left of the falx cerebri, a left inferior frontal gyrus contusion, and punctate air pockets in the left inferior frontal fossa. TMP-SMX was discontinued while critical care and surgical teams stabilized the patient. The brain lesions did not require neurosurgical intervention.

On the 10th hospital day, the patient could be interviewed; he denied, through nods and hand signals, that he had experienced any symptoms of depression or psychosis since coming to the hospital. He was lucid and as cheerful as one could hope under the circumstances. The diagnosis of TMP-SMX–induced psychotic disorder (*DSM-5*) was made on the basis of hallucinations, which developed during both of 2 courses of treatment with TMP-SMX, a drug that can cause these symptoms. The condition is not explained by the presence of another psychotic disorder, reveals no evidence of delirium, and caused extreme distress and impairment. The patient and his family were referred for counseling to aid their adjustment to the new circumstances.

The mechanism for TMP-SMX psychosis is unknown. Both component drugs inhibit metabolism of folic acid, deficiencies of which have long been associated with neuropsychiatric symptoms. Trimethoprim irreversibly inhibits dihydrofolate reductase (DHFR), thereby limiting the conversion of dihydrofolate to tetrahydrofolate, the active form of folic acid. DHFR is also critical for reducing dihydrobiopterin to tetrahydrobiopterin (BH_4) in a BH_4 salvage pathway. Deficiency of BH_4, a cofactor in the biosynthesis of the biogenic amines,[3] has been linked to schizophrenia.[4]

This case highlights the importance of alerting patients about a rare TMP-SMX side effect. Although the mechanism of toxicity is unknown, putative impairments in folate- and biopterin-synthetic pathways warrant further research.

References

1. Lee KY, Huang CH, Tang HJ, et al. Acute psychosis related to use of trimethoprim/sulfamethoxazole in the treatment of HIV-infected patients with Pneumocystis jirovecii pneumonia: a multicentre, retrospective study. *J Antimicrob Chemother*. 2012;67(11):2749–2754.
2. Saidinejad M, Ewald MB, Shannon MW. Transient psychosis in an immune-competent patient after oral trimethoprim-sulfamethoxazole administration. *Pediatrics*. 2005;115(6):e739–e741.
3. Crabtree MJ, Tatham AL, Hale AB, et al. Critical role for tetrahydrobiopterin recycling by dihydrofolate reductase in regulation of endothelial nitric-oxide synthase coupling: relative importance of the de novo biopterin synthesis versus salvage pathways. *J Biol Chem*. 2009;284(41):28128–28136.
4. Richardson MA, Read LL, Reilly MA, et al. Analysis of plasma biopterin levels in psychiatric disorders suggests a common BH_4 deficit in schizophrenia and schizoaffective disorder. *Neurochem Res*. 2007;32(1):107–113.

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