Case Report

Medication-associated Depersonalization Symptoms: Report of Transient Depersonalization Symptoms Induced by Minocycline

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Abstract: Patients with depersonalization disorder experience episodes in which they have a feeling of detachment from themselves. Symptoms of depersonalization may occur in individuals who have other mental disorders, or who have various medical conditions, or who have taken certain medications. A woman developed depersonalization symptoms after initiation of minocycline therapy. Her symptoms ceased after treatment was stopped and recurred when she restarted the drug. Medications that have been associated with causing symptoms of depersonalization are presented and the postulated pathogenesis by which some of these drugs induced depersonalization symptoms is discussed. Medication-associated depersonalization symptoms typically resolve once the inducing drug has been withdrawn.

Key Words: depersonalization, detachment, minocycline

Psychiatric syndromes that consist of disruptions of aspects of consciousness, environmental awareness, identity, memory, or motor behavior are classified as dissociative disorders.[1] Depersonalization disorder is a dissociative disorder characterized by persistent or recurrent episodes in which the individual has a feeling of detachment or estrangement from one's self. Although their reality testing remains intact, the person may feel like they are living in a dream or like an automation. Depersonalization disorder cannot be diagnosed if it is part of another psychiatric condition or if it is secondary to a medical disorder or if it is caused by a drug.[1–7] In contrast, transient depersonalization symptoms may occur in association with several mental disorders, medical conditions, or medications.[1–42]

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Minocycline is a semisynthetic tetracycline derivative that is well absorbed after oral administration.[43–45] Since it penetrates well into sebum, secondary to its high lipid solubility, it is commonly used in the treatment of acne vulgaris.[46] The potential profile of minocycline-associated adverse sequelae has been established.[43–51] Central nervous system-related side effects that may occur in patients treated with this medication include headaches, light-headedness, pseudotumor cerebri (also referred to as benign intracranial hypertension, which clinically presents with blurred vision and headache), and vestibular disturbances (such as ataxia, vertigo, and dizziness).[43–46,52–54]

A young woman with minocycline-induced transient depersonalization symptoms is described. Her symptoms began after initiating treatment with minocycline, ceased after stopping the medication, and recurred after restarting the drug. Other medications that have been associated with causing symptoms of depersonalization are summarized and some of the postulated mechanisms for the pathogenesis of these drug-related symptoms are discussed.

Key Points

- Symptoms of depersonalization, such as persistent or recurrent episodes in which the individual has a feeling of detachment or estrangement from one's self, may occur in association with several medications.
- Hypersensitivity of the serotonin system, drug-related metabolic encephalopathy, panic disorder-related etiology, and substance-induced temporal disintegration possibly secondary to increased levels of brain activity have been hypothesized as possible mechanisms of pathogenesis for some of the medications associated with inducing depersonalization symptoms.
- Medication-associated depersonalization symptoms typically resolve once the inducing drug has been withdrawn.

Case Report

A 24-year-old woman presented for evaluation and treatment of acne. Her current medications included an oral contraceptive (norethindrone acetate and ethinyl estradiol tablets [Estrostep, Warner Chilcott, Rockaway, NJ]) and weekly immunotherapy (SC antigen injection) for allergies. Her medical history was unremarkable and there was no history of psychiatric disorder.

Cutaneous examination showed red papules on the chin and perioral areas of her face. Closed comedones were present on her forehead and open comedones were present on her nose. Random open comedones and postinflammatory lesional scarring were noted on her back. She weighed 140 lb. The diagnosis of moderate (inflammatory and comedonal) acne vulgaris was made. Treatment was initiated with oral minocycline (100 mg each morning and 50 mg each evening), topical adapalene (Differin; Galderma Laboratories, Forth Worth, TX) 0.1% gel each evening to her face, and benzoyl peroxide (Triaz; Medicis Pharmaceutical Corp., Phoenix, AZ) 10% cleanser topically to her back for 3 to 5 minutes during her daily shower. Use of an additional form of contraception while taking the oral antibiotic was also recommended.

Within a few days after starting the minocycline, she began to feel detached from her surroundings, as though she was part of a movie in which she was watching herself perform her daily activities. She remained alert and oriented, realizing that these sensations were not real. For example, she could see herself doing each motion when driving her car, such as lifting her foot and placing it on the gas pedal and pressing it down. Also, she had become apathetic with regard to her graduate studies and was not able to study for examinations, yet she was aware that there were consequences if she did not study. The feelings of depersonalization progressively worsened as she continued to take the minocycline. She felt tired and lethargic. Occasionally, she would have headaches. She discontinued the minocycline after the seventh day; within 48 hours, all of her depersonalization symptoms resolved. After being symptom-free for an additional 5 days, she decided to restart the minocycline; her depersonalization symptoms recurred and she stopped taking the medicine after 2 days. The symptoms again cleared after the minocycline was stopped. There have been no further episodes of depersonalization symptoms.

Table 1. Medications associated with depersonalization symptoms

Alcohol[2,14–16]
Antihistamines[a2]
Antipsychotics[a1,17–19]
Anxiolytics[a1,17–19]
Benzodiazepine[20]
Caffeine[2,21]
Carbamazepine[b21]
Drugs[a2,22]
Fluoxetine[23–25]
Fluphenazine[1,17–19]
Hallucinogens[a2,17–19]
Indomethacin[26,27]
Lysergic acid diethylamide (LSD)[2,28]
Marijuana (tetrahydrocannabinol [THC])[b2,14,19,29–37]
Meta-chlorophenylpiperazine (*M*-CPP)[38]
Metyrapone[39,40]
Minocycline[2,41] (current report)
Nitrazepam[b42]
Sodium pentothal[c16]

[a] *For some of the medications associated with depersonalization symptoms, the reports did not list the specific agents.*

[b] *Depersonalization symptoms occurred after the reduction or the withdrawal of carbamazepine[21] or nitrazepam.[42] In some of the patients who had used marijuana, depersonalization symptoms began either after the drug was discontinued[29,30] or during abuse and peristed after the drug was stopped.[30,36]*

[c] *The investigators postulated that the general anesthetic that was administered to the patient presumably initiated the episode of depersonalization that he experienced following appendectomy.*

Discussion

Depersonalization symptoms have been reported in association with several medications (Table 1).[1,2,14–42] The onset and resolution of this patient's depersonalization symptoms temporally correlated with her starting and stopping minocycline; indeed, her symptoms recurred when she rechallenged herself with the medication. In 1977, Gump et al[41] reported "a feeling of disassociation (a 'spaced out' feeling)" in normal women volunteers who were taking either 75 mg (15 of 30 women) or 100 mg (14 of 30 women) of minocycline twice daily for 5 days. More recently, minocycline has also been listed as an exacerbating factor of depersonalization disorder in Simeon et al's[2] study of the phenomenology, associated psychopathology, and treatment history in 30 consecutively recruited adults with this condition. However, neither "dissociation feelings" nor "exacerbation of depersonalization disorder" are listed as potential adverse reactions to minocycline in either the *Physician's Desk Reference*[55,56] or several extensive reviews of the medication.[43–46,52–54]

Hypersensitivity of the serotonin system has been postulated as a cause of medication-induced depersonalization symptoms.[3,23,25,38] Simeon et al[38] suggest that serotonin dysregulation may in part be responsible for symptoms of depersonalization. They demonstrated that the partial serotonin agonist meta-chlorophenylpiperazine induced depersonaliza-

tion significantly more than the placebo in a double-blind, placebo-controlled study that included normal volunteers and patients with psychiatric disorders (such as obsessive-compulsive disorder, social phobia, and borderline personality disorder).[38]

Precipitation of depersonalization has also been observed during the initiation of treatment with fluoxetine, a serotonin reuptake blocker, in a woman with bipolar disorder and an acute depressive episode.[23] Hollander et al[25] commented that this patient's acute medication-associated depersonalization symptoms were consistent with the induction of depersonalization symptoms secondary to serotonin hypersensitivity. They also speculated that there would be improvement of depersonalization after chronic treatment of the patient with a serotonin reuptake blocker, since they expected that the serotonin hypersensitivity would diminish following the therapy-related down-regulation of serotonin receptors.[25]

Alcohol, caffeine, and marijuana are other drugs for which the mechanism of pathogenesis for associated symptoms of depersonalization has been hypothesized. Recurrent episodes of alcohol-induced depersonalization were described in a 23-year-old man.[16] Serial quantitative electroencephalographic studies were performed during his most recent episode. An abnormal amount of slow wave activity, suggestive of a metabolic encephalopathy, was found on his initial electroencephalogram that was recorded when he was symptomatic. The second and third electroencephalograms, after the depersonalization episode had resolved clinically, revealed a progression toward normalization. The investigators commented that metabolic encephalopathy is a condition that likely contributes to the manifestations of depersonalization and suggested that the cause of alcohol-related depersonalization may be secondary to a metabolic encephalopathy induced by the drug.[16]

Stein and Uhde[21] described a 28-year-old woman with a 6-year history of depersonalization whose symptoms were exacerbated by the oral administration of caffeine. They noted that their patient's exacerbation of depersonalization symptoms in response to caffeine was consistent with the experience of patients with panic disorder. Since both disorders are exacerbated by caffeine administration, Stein and Uhde[21] hypothesized that depersonalization disorder might share a common pathophysiology with panic disorder.

The temporal relationship between marijuana use and depersonalization symptoms is variable. Most investigators describe patients whose onset of symptoms occur either during or shortly after acute intoxication with marijuana.[31–35,37] Less commonly, marijuana-associated depersonalization symptoms first occurred while the patients were using the drug and subsequently continued in the absence of continued exposure to marijuana.[30,36] Rarely, patients whose depersonalization symptoms have begun and persisted after termination of their marijuana abuse have been observed.[29,30]

Mathew et al[34] monitored depersonalization and other behavioral and physiologic indices before and after the administration of high-potency marijuana cigarette, low-potency marijuana cigarettes, and placebo cigarettes in 35 physically and mentally healthy men who had a history of exposure to marijuana. Depersonalization increased significantly after marijuana—but not placebo—smoking, peaking 30 minutes after smoking and returning to baseline within 120 minutes. More severe depersonalization was induced after smoking the high-potency marijuana cigarette. Other behavioral changes after marijuana smoking were anxiety, tension, confusion, and increased temporal disintegration. Several physiologic variables increased after marijuana smoking: regional cerebral blood flow, respiratory rate, pulse rate, and systolic blood pressure. These observations prompted the investigators to postulate that marijuana-associated depersonalization was possibly related to the following drug-induced changes: increased levels of brain arousal and impairment of temporal lobe function secondary to temporal disintegration.[34]

Conclusions

Individuals may develop depersonalization symptoms after medication administration. Depersonalization symptoms appeared in a woman after starting minocycline therapy and resolved once the drug was stopped; subsequently, the symptoms promptly recurred when she rechallenged herself with minocycline and permanently resolved after the medication was discontinued. The pathophysiology of minocycline-associated depersonalization symptoms remains to be established. However, alternative mechanisms of pathogenesis—not necessarily mutually exclusive—have been hypothesized for some of the other medications associated with inducing depersonalization symptoms: hypersensitivity of the serotonin system, drug-related metabolic encephalopathy, panic disorder-related etiology, and substance-induced temporal disintegration possibly secondary to increased levels of brain activity. Medication-associated depersonalization symptoms typically resolve once the inducing drug has been withdrawn.

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