The woman who wasn't there

Ahmed Janjua, MD, Daniel Rapport, MD, and Gina Ferrara, MD

How would you handle this case?

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Since a night of heavy drinking 4 years ago, Ms. A has felt detached from reality and confused. Various antidepressants and anxiolytics have not helped. What would you try next?

CASE Feeling detached

Ms. A, age 23, presents to our clinic complaining of feeling detached for the past 4 years. She says she feels "fuzzy all the time, like I lost touch with reality 4 years ago and really miss it." She complains of "confused thinking," excessive tiredness and weakness, depression, and anxiety. She says, "It feels like I'm watching my life on television; I don't feel any emotions." These symptoms began immediately after a college party, which the police stopped because of underage drinking. She says, "I don't know why, but that party set it off, and it feels like I am in a dream all the time."

For the last 4 years, Ms. A has been working as a waitress and is now engaged. She presents to our clinic because the treatments she has been receiving are ineffective and she wants to feel her emotions again, especially before her wedding.

Ms. A has no history of mania, depression, or psychosis. She says she was an anxious child and suffered from anorexia nervosa between age 13 and 14. She experienced occasional panic attacks beginning in high school that were triggered by feeling overwhelmed or frustrated with not feeling normal. During these panic attacks, Ms. A experienced tightness in her chest and dizziness. She denies suicidal or homicidal ideation or attempts.

At age 18, she was sexually assaulted. Ongoing stressors include living in a dangerous neighborhood, having her car broken into, her father's disapproval of her fiancé, and wanting to get married. She drank heavily in college, but has used alcohol infrequently since then.

Ms. A's father has a history of anxiety. She describes him as domineering and her mother as very emotional and always wanting to be her friend. Ms. A says she struggles with relationships, employment, and plans for advancement, all of which are moderately to severely affected by her depersonalization symptoms. During the initial appointment, we diagnose Ms. A with generalized anxiety disorder, panic disorder, and major depressive disorder (MDD).

Which diagnoses would you include among the differential diagnosis?

a) posttraumatic stress disorder (PTSD)
b) MDD with psychotic features
c) depersonalization disorder
d) schizophrenia, undifferentiated type
e) psychosis not otherwise specified

The authors' observations

Depersonalization symptoms can occur in a variety of situations, including:

Dr. Janjua is a third-year psychiatry resident, University of Toledo Medical Center, Toledo, OH. Dr. Rapport is associate professor of psychiatry and director of the consultation-liaison service, University of Toledo Medical Center, Toledo, OH. Dr. Ferrara is second-year child/adolescent psychiatry fellow at the University of Southern California, Los Angeles, CA.

Table 1

Assessing for depersonalization: 3 rating scales

Scale	Description
Cambridge Depersonalization Scale[5]	29-item, self-report questionnaire meant to capture frequency and duration of depersonalization symptoms over the previous 6 months
Depersonalization Severity Scale[6]	Covers a range of axis I and II psychopathology
Dissociative Experiences Scale[7]	28-item, self-report instrument to measure dissociation

- mentally healthy persons suffering from acute stressors, fatigue, or drug use
- neuropsychiatric conditions such as epilepsy
- migraine
- anxiety disorders
- depressive disorders
- schizophrenia.[1]

Transient depersonalization symptoms are common and have been found in 2.4% of the general population.[2] Community surveys using standardized diagnostic interviews reveal 1-month prevalence rates of 1.6% to 1.9% in 2 UK samples.[3,4] Depersonalization symptoms are brief and less debilitating than depersonalization disorder.

Depersonalization rarely presents as a primary disorder, when symptoms persist chronically. Rating scales (***Table 1***)[5-7] and DSM-IV-TR criteria (***Table 2, page 64***) can help assess symptom severity and differentiate transient symptoms from a disorder. Psychiatric conditions that commonly are comorbid with depersonalization disorder appear in ***Table 3 (page 71)***.[8] Triggers for a first episode of depersonalization disorder include:

- psychological stressors (31%)
- substance abuse (25%)
- physical stressor (12%)
- situational stressor (17%)
- social and/or relationship problems (10%)
- trauma (6%)
- panic/anxiety (2%).[8]

Although Ms. A experiences depersonalization—constant numbness and emptiness—when she thinks about the sexual assault, she does not meet criteria for PTSD because she denies re-experiencing the assault, hyperarousal, and avoidance behaviors.

Ms. A meets all 4 DSM-IV-TR criteria for depersonalization disorder (***Table 2, page 64***). She experiences persistent feelings of detachment, which cause her considerable distress. Her reality testing is intact and these experiences are not due to a general medical condition, another mental disorder, or direct physiological effects of a substance.

Which medications would you consider for Ms. A?

a) benzodiazepine plus a tricyclic antidepressant (TCA)
b) selective serotonin reuptake inhibitor (SSRI) plus a benzodiazepine
c) trazodone plus bupropion
d) atypical antipsychotic plus a benzodiazepine and a TCA

TREATMENT Insufficient response

Ms. A's previous psychiatrist prescribed various SSRIs and selective serotonin-norepinephrine reuptake inhibitors, including sertraline, escitalopram, citalopram, paroxetine, and venlafaxine, for depression and anxiety with little or no benefit. When she presented at our clinic, Ms. A was taking clonazepam, 0.25 mg as needed, and fluvoxamine, 50 mg/d, which she said helped her anxiety a little, but not depersonalization symptoms. She received supportive psychotherapy provided during biweekly 30-minute medication management visits.

We add aripiprazole, 2.5 mg/d, to augment fluvoxamine's antidepressant effect and reduce

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Rating scales and DSM-IV-TR criteria can help differentiate transient symptoms from a disorder and assess severity

Table 2

DSM-IV-TR criteria for depersonalization disorder

A. Persistent and recurrent experiences of feeling detached from oneself and as if one is an outside observer of one's mental processes or body.

B. During the depersonalization experience, reality testing remains intact.

C. The depersonalization causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The depersonalization experience does not occur exclusively during the course of another mental disorder, such as schizophrenia, panic disorder, acute stress disorder, or another dissociative disorder, and is not due to the direct physiological effects of a substance (eg, a drug of abuse or a medication) or a general medical condition (eg, temporal lobe epilepsy).

Source: Diagnostic and statistical manual of mental disorders, 4th ed, text revision. Washington, DC: American Psychiatric Association; 2004

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Depersonalization disorder is associated with HPA axis dysregulation and lower basal cortisol levels

her anxiety and dissociative symptoms. At the next visit 5 weeks later, she reports her depersonalization symptoms gradually lessened from 10 to 6 on a 10-point self-report scale.

We discontinue fluvoxamine after 5 weeks because it no longer significantly contributes to her recovery. We add amantadine, 100 mg/d, based on the belief that dopamine augmentation might help reduce her symptoms. Ms. A reports improved depersonalization symptoms over the next 4 weeks (5/10). However, a week later she says she feels her anxiety is worsening the depersonalization symptoms. We start buspirone, 7.5 mg/d titrated to 15 mg/d over 4 weeks, Ms. A reports feeling worse so we discontinue the drug.

Next Ms. A complains of excessive sleepiness, which seems to be related to amantadine, so we discontinue it. We start bupropion, 150 mg/d and titrate it to 450 mg/d, which we hope will reduce her fatigue, anxiety, depersonalization, and depression. Bupropion's effect on norepinephrine and dopamine reuptake and a study of autonomic blunting in depersonalization[9] justify our selection.

After 3 months, Ms. A stops taking aripiprazole because it is too costly. The following month she presents with severe anxiety and low-to-moderate depression. Clonazepam and bupropion are discontinued and replaced with diazepam, 20 mg/d, and clomipramine, 25 mg/d at bedtime titrated to 75 mg/d. Our decision is guided by a study on the efficacy of clomipramine in treating depersonalization[10] and our desire to aggressively treat her anxiety and depression. After 2 weeks, Ms. A says her anxiety and depression have resolved completely but the depersonalization symptoms persist. We restart amantadine, 100 mg as needed, for anorgasmia.

Because of her persistent complaints of depersonalization, after discussion with Ms. A, we decide to return to what had helped her at the beginning of treatment and restart aripiprazole, 2.5 mg/d. Four months later, she reports her depersonalization symptoms have resolved completely. At this time, her regimen consists of clomipramine, 50 mg at bedtime, diazepam, 10 mg at bedtime, and aripiprazole, 2.5 mg/d.

Which neurotransmitter systems have been implicated in depersonalization disorder?

a) HPA axis
b) serotonin system
c) norepinephrine-dopamine system
d) dopamine-serotonin system
e) all of the above

The authors' observations

The neurobiology of emotion processing is still unclear but some evidence indicates that the amygdala, anterior cingulate cortex, and medial prefrontal cortex might be involved in emotion regulation and integration.

Depersonalization disorder is associated with HPA axis dysregulation and patients with depersonalization disorder have a lower basal cortisol level compared

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with patients with MDD.[11,12] Simeon et al[9] found a marked basal norepinephrine decline with increasing depersonalization severity.

Various SSRIs,[13,14] TCAs,[10,15,16] citalopram-olanzapine combination, naltrexone, citalopram-clonazepam combination,[17] and fluoxetine-buspirone combination[18] have been studied as treatment for depersonalization disorder. We present the first case report of aripiprazole to treat depersonalization disorder. A previous study[19] of quetiapine—a low potency blocker of dopamine D2 receptors, which also has a high affinity for serotonin 5-HT2A receptors—suggested a potential role in improving emotional numbing symptoms in depersonalization/derealization disorder. The authors hypothesized that quetiapine may facilitate dopamine and serotonin neurotransmissions in the anterior limbic cortex and prefrontal cortex, which are involved in emotional experiences.

Other treatment options

The kappa opioid system also is implicated in depersonalization. Enadoline, a selective k-opioid agonist, has been shown to cause depersonalization symptoms in healthy subjects.[20] High doses of opioid antagonists, such as naltrexone, have been used successfully to treat depersonalization symptoms in patients with borderline personality disorder,[21] PTSD,[22] and depersonalization disorder.[23]

Ketamine—which can produce depersonalization—increases glutamate transmission, which suggests that drugs that affect the glutamate system might be targets for future investigation. Similarly, smoking marijuana can induce depersonalization, which indicates that cannabinoid receptors might be another area for research. Hallucinogens, such as lysergic acid diethylamide, psilocybin, and dimethyltryptamine, can produce temporary depersonalization. These drugs are 5-HT2 agonists (HT2A, HT2C), which gives weight to using 5-HT2 antagonists to treat depersonalization.

Table 3

Depersonalization comorbidity: Common disorders

Disorder	Percentage of depersonalization patients reporting comorbidity
Anxiety	45%
Major depressive disorder	41%
Panic disorder	22%
Agoraphobia	11%

Source: Reference 8

Psychodynamic approaches based on self-constancy—cohesiveness and stability of self-representation—may be helpful, especially in patients with acute symptoms.[24] Cognitive-behavioral therapy may be effective and could be divided into 2 phases:

- nonspecific interventions such as activity scheduling, graded exposure to avoidance behaviors, and negative automatic thought charts
- techniques to facilitate controlled re-experiencing of emotions and refocusing of attention away from the self and the depersonalization experience.[25]

Measures such as relaxation techniques, breathing exercises, yoga, tai chi, and meditation also might help decrease anxiety.

OUTCOME Why did it work?

Ms. A responded partially to the diazepam-clomipramine combination but experienced a full response only after we added aripiprazole. We are not certain whether her response was caused by aripiprazole, a delayed action of clomipramine, or a spontaneous remission. Aripiprazole, 2.5 mg/d, was the first medication we added when Ms. A presented to our clinic and she had reported a partial response to the drug. Aripiprazole was also the last medication added before she experienced response, which lasted for at least 5 months, after which Ms. A was lost to follow-up.

continued

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High doses of opioid antagonists, such as naltrexone, have been used successfully to treat depersonalization symptoms

Clinical Point

Aripiprazole might rebalance serotonin/dopamine neurotransmission for some patients with depersonalization disorder

Related Resource

- Simeon D. Feeling unreal: Depersonalization disorder and loss of self. New York, NY: Oxford University Press; 2006.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Bupropion • Wellbutrin
Buspirone • BuSpar
Citalopram • Celexa
Clomipramine • Anafranil
Clonazepam • Klonopin
Diazepam • Valium
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Ketamine • Ketalar
Naltrexone • ReVia
Olanzapine • Zyprexa
Paroxetine • Paxil
Quetiapine • Seroquel
Sertraline • Zoloft
Trazodone • Desyrel
Venlafaxine • Effexor

Disclosure

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

The authors' observations

We believe that aripiprazole might rebalance serotonin/dopamine neurotransmission for some patients with depersonalization disorder. We theorize that aripiprazole's blockade of serotonin 2A receptors may enhance dopamine release in certain areas of the brain, possibly improving cognitive and affective symptoms. Depersonalization may be a symptom of worsening psychiatric illness and justifies the use of intensive pharmacologic and psychological therapy.

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Bottom Line

Although common as a symptom—even in healthy individuals—depersonalization is rare as a primary disorder. Frequently comorbid with anxiety disorders and major depressive disorder, depersonalization often is treated with antidepressants and anxiolytics; however, aripiprazole and quetiapine might be promising options.