Initiation of Illusions After Combination of Zolpidem and Paroxetine in a Young Woman: A Case Report

To the Editor: We report a case of possible interaction between the non-benzodiazepine hypnotic zolpidem and the selective serotonin reuptake inhibitor (SSRI) paroxetine in a young woman diagnosed with panic disorder and then summarize the current relevant literature as identified via PubMed, EMBASE, and PsycINFO as well as reference sections of selected articles.

Case report. Ms A, a 24-year-old woman, visited the outpatient clinic in a state of crisis and reported experiencing illusions after the addition of zolpidem to her daily paroxetine regimen.

She had been diagnosed with panic disorder, per *DSM-IV-TR* criteria, 2 years earlier and was stabilized on a dosage of oral paroxetine 30 mg daily. The results of all necessary blood tests, including complete blood cell count, biochemical analysis, and thyroid function tests, were unremarkable at that time. Recently, during her regular follow-up visit to the outpatient psychiatric department, she complained of insomnia consisting of difficulties in the initiation of sleep with additional nighttime awakenings mainly during the first half of the night. After discussion of her problem with her psychiatrist, she was given detailed advice on how to improve her sleep. Despite following sleep hygiene advice, she returned, continuing to complain of disordered sleep. The clinician prescribed zolpidem 10 mg at bedtime.

After the first dose of zolpidem, she experienced disturbance of perception, specifically an illusional state, when watching herself in the mirror (an illusion is a temporary distortion or misinterpretation of a real perception, in contrast to a hallucination, which is a perception in the absence of a real stimulus). In this case, the illusions took the form of a frightening distortion of her perceived appearance that triggered a panic attack in the patient. When levels of anxiety decreased, she understood that this phenomenon was not real, but the symptom did not fully resolve until after approximately 1 hour.

Paroxetine is an SSRI, a drug category that is believed to act through the blocking of the serotonin reuptake transporter; paroxetine additionally desensitizes serotonin (5-HT_{1A}) autoreceptors, resulting in the disinhibition of the serotonergic neuron, increase of serotonin release, and increase of neuronal impulse flow. Panic disorder is characterized by overactivation of amygdala-centered circuits,[1] and SSRIs are thought to act therapeutically by increasing serotoninergic inhibitory input to the amygdala from incoming serotonergic neurons from the raphe nuclei area.[2] Also, paroxetine is thought to have mild noradrenergic as well as mild anticholinergic action. Paroxetine is commonly prescribed for the treatment of panic disorder.[3–6] Zolpidem is a commonly prescribed non-benzodiazepine hypnotic sleep medication, a drug category that is believed to act through binding in the α_1 isoform of the benzodiazepine receptor, consequently enhancing chloride conductance through the γ-aminobutyric acid (GABA) ion channel, leading to increased inhibitory GABA action in brain sleep centers.

To the knowledge of the authors this is the first reported case of a patient with panic disorder stabilized and symptomless with paroxetine that destabilized by the experiencing of fear after the addition of zolpidem. Some authors have reported development of hallucinations in a patient treated with zolpidem[7–12] or with the combination of zolpidem and SSRIs,[13–15] including the combination of zolpidem and paroxetine[16] specifically. Other authors found the combination of zolpidem and SSRIs to be generally effective and safe.[17,18] There is no obvious pharmacokinetic mechanism responsible for this interaction, as paroxetine is thought to be an inhibitor of the cytochrome P450 (CYP) isoenzyme CYP2D6,[19] whereas zolpidem is converted to hydroxylated metabolites principally by the CYP3A4 isoenzyme, with minor contributions of 1A2 and 2C9 isoforms.[20] A pharmacodynamic interaction mechanism has been suggested,[16] based on the fact that both drugs are highly protein bound and could interact through competitive binding with consequent toxic increase of serum zolpidem levels causing symptoms of delirium such as illusions and hallucinations. We suggest that physicians use this 2-drug combination with caution as well as under close supervision in a clinical setting similar to the one described.

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