

# Naltrexone-associated Visual Hallucinations: A Case Report

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Naltrexone is a competitive antagonist of  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors. Naltrexone has been investigated for use as an anti-obesity agent in both the general population and in patients with severe mental illness, including schizophrenia. In patients with schizophrenia, however, potential psychotic symptoms due to adverse effects of naltrexone have not been investigated. Our case study, a relevant case report, and some related articles suggest that naltrexone might be associated with the emergence of visual hallucinations, which clinicians should be aware of.

**KEY WORDS:** Naltrexone; Narcotic antagonists; Hallucinations; Drug-related side effects and adverse reactions.

## INTRODUCTION

Naltrexone is a competitive antagonist of  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors. It has usually been used for the treatment of alcohol dependence and opiate addiction.<sup>1)</sup> Recently, the naltrexone-bupropion combination pill for obesity treatment was approved by the US Food and Drug Administration and the European Medicines Agency.<sup>2)</sup> Currently, naltrexone has been studied as an anti-obesity agent for general populations and patients with severe mental illnesses, including schizophrenia. In schizophrenia, however, naltrexone-induced visual hallucinations (VHs) are not well known as an adverse effect. We report a case which a patient with schizophrenia experienced VHs after taking naltrexone.

## CASE

A 24-year-old female patient suffering from persecutory delusions, auditory hallucinations (AHs), and aggressive behavior was admitted to the Department of Psychiatry,

Yeouido St. Mary's Hospital, in November 2013. She had no history of substance use disorder. She met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-IV. Antipsychotics were started and her psychotic symptoms gradually decreased. After the last discharge, she was maintained on aripiprazole 25 mg, amisulpride 800 mg, procyclidine 20 mg, propranolol 80 mg, lorazepam 1.5 mg, and valproic acid 250 mg per day, for several years. She had no psychotic symptoms except intermittent AHs (3-4 times/week). In April 2016, the frequency of the AHs increased, and amisulpride was increased to 1,000 mg/day. Two weeks later, AHs were substantially reduced but the patient complained of increased appetite and weight gain. She was prescribed naltrexone 50 mg once a day for 2 weeks. Two weeks later, the patient reported that she had started to see a blurred black object passing by after 2 to 3 days of taking 50 mg of naltrexone, which occurred several times a day. She reported that VHs occurred almost every day while taking naltrexone. The ophthalmic consult was recommended to exclude organic causes for presenting symptoms, but refused by her. Naltrexone was ceased. At the next visit, she reported that the VHs had completely disappeared 3 to 4 days after stopping naltrexone.

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## DISCUSSION

Psychotic symptoms are not well known as an adverse effect of naltrexone, especially in schizophrenia. This report describes a case of VHs associated with naltrexone use. The VHs appeared 2 to 3 days after taking naltrexone, lasted for the duration of the dose, and completely disappeared 3 to 4 days after stopping the medication. The patient of this report had never experienced any perceptual disturbance other than AHs during the period in which she received regular outpatient treatment for more than 2 years. These points support that the VHs were actually associated with the use of naltrexone. Because naltrexone is likely to have triggered new or worsening psychotic symptoms within days, it is necessary to consider stopping naltrexone instead of increasing the dose of antipsychotic drugs or adding new antipsychotic agents.

Until the 1990s, in contrast to our case, opioid receptor antagonists including naltrexone were presumed to have an antipsychotic effect. There have been a few studies reporting use of naltrexone to treat schizophrenic patients, although all of them showed that the drug was ineffective.<sup>3-5)</sup>

There was one case report in which there was an association between naltrexone and psychotic symptoms, such as delusions and hallucinations. A 44-year-old healthy female without schizophrenia reported AHs and VHs, as well as paranoid delusions. She developed acute psychotic symptoms about 3 days after taking naltrexone 50 mg/day to prevent recurrence of alcohol dependence. The psychotic symptoms were completely resolved after 48 hours of naltrexone withdrawal.<sup>6)</sup> This case supports our case in terms of there being a temporal relationship between the use of naltrexone 50 mg per day and psychotic symptoms. Interestingly, the VHs which our patient experienced also stopped after 3 to 4 days of naltrexone discontinuation, similar to this case.

Naltrexone is a opioid antagonist with a half life of 3.9 hours.<sup>7)</sup> It is metabolized to produce active metabolites by the liver.<sup>7)</sup> The quantitatively major metabolite, 6 $\beta$ -naltrexol,<sup>8)</sup> has a half-life of 12.9 hours.<sup>7)</sup> Considering that the short half-life of plasma naltrexone, 6 $\beta$ -naltrexol might be related to the the duration of psychotic symptoms.

The mechanisms by which naltrexone use results in hallucinations in patients with schizophrenia are unclear. Of the  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors, the kappa opioid re-

ceptor (KOR) is known to be involved in regulating the release of several neurotransmitters, such as dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT), in certain brain regions.<sup>9-11)</sup> In the striatum, the mechanisms by which KORs affect presynaptic striatal DA dynamics include a direct inhibitory action on presynaptic DA release, up-regulation of DA transporter function, and possible regulation of presynaptic D2 DA receptors that mediate DA tone.<sup>12)</sup> KOR antagonists can disinhibit DA release,<sup>13,14)</sup> such that there is a possibility of psychotic symptoms occurring. In addition, KOR activation can reduce 5-HT efflux<sup>11)</sup> and decrease ventral tegmental area glutamate release.<sup>15)</sup> These findings suggest that KOR antagonists may be directly or indirectly related to the development of psychotic symptoms.

In conclusion, we suggest that naltrexone might be associated the emergence of VHs. Although the pathophysiology of naltrexone-associated VHs remains unclear, clinicians should be aware of the potential emergence of VHs associated with naltrexone.

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