

# The frequency of agitation due to inappropriate use of naltrexone in addicts

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## Abstract

**Background:** There is a high tendency among specialists to treat the addicts with naltrexone; withdrawal symptoms are frequent after taking naltrexone along with opioids. This study investigated the frequency of agitation due to inappropriate use of naltrexone in addicts.

**Materials and Methods:** This was a cross-sectional study, conducted in Noor and Aliasghar hospitals in Isfahan city. The study population included the addicts who were agitated as a result of naltrexone abuse. Scores of patients with agitation were measured with Richmond Agitation Sedation Scale (RASS). Patient outcomes including recovery without complications, recovery with complications (rhabdomyolysis), and mortality were recorded.

**Results:** All the patients with agitation caused by naltrexone abuse during 1 year were 40 people, of whom nine were excluded due to their comorbid diseases (diabetes or cardiovascular disease). Among the remaining 31 patients, 30 were male. The patients' mean age was 29.93 (5.24) years. The most common symptoms observed besides agitation was midriasis (41.9%), and vomiting (41.9%). A 38.8% of the patients scored 3 or 4, and, 61.2% scored 1 or 2 for agitation. The mean time for patients' restlessness scores to reach zero was 9.30 (3.71) h (min: 3 h, max: 18 h). All the patients in both groups were discharged with recovery without complication.

**Conclusion:** Considering the high prevalence of agitation in the poisoning emergency department due to inappropriate use of naltrexone, more accurate planning for administration of naltrexone in addicts seems necessary.

**Key Words:** Drug abuser, naltrexone, restlessness score, Richmond agitation sedation scale

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## INTRODUCTION

Naltrexone is a competitive antagonist of opioid receptors, which blocks  $\mu$  and  $\kappa$  receptors and is used in addiction control programs.<sup>[1-3]</sup> Before using naltrexone, the opioid abusers should have participated in detoxification programs, and their bodies would be cleared of drugs. So in the case that an

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addicted person uses naltrexone before the complete detoxification, it leads to acute blocking of opioid receptors and development of opioid acute withdrawal symptoms.<sup>[4,5]</sup>

These symptoms may be caused 5 min after using naltrexone and may remain for 48 min. Symptoms include agitation, confusion, hallucinations, sweating, hyperthermia, tachycardia, abdominal pain, vomiting, diarrhea, increased creatine kinase (CPK), and rhabdomyolysis.<sup>[6]</sup>

At present, the treatment of symptoms of drug withdrawal is supportive and includes intravenous fluids, analgesics, and antispasmodic drugs. However, one of the acute symptoms of drug withdrawal syndrome following the use of naltrexone is restlessness or agitation, which has no effective treatment so far, and sometimes requires general anesthesia in severe cases.<sup>[5-7]</sup>

There are only a few case reports available regarding the agitation caused by naltrexone misuse in addicts. In 1999, two cases were reported in Italy; one related to injecting heroin and the other one to ex-heroin, and both cases were restless due to the use of naltrexone and were hardly controlled with anesthetic drugs. Also, three similar cases, one in Australia and two in England were reported. In all of the above cases, supportive measures and heavy sedation were taken to control restlessness, but they were not quite satisfactory.<sup>[6,8-11]</sup>

Because there is a high tendency among specialists to treat the addicted patients with naltrexone, and this drug may be abused by addicts, and also high easily accessible of this drug, there may be observed more cases of withdrawal symptoms after using naltrexone in detoxification program. Furthermore, their agitation is sometimes so severe that the patients may hurt themselves or the healthcare staff. So, this study was aimed to investigate the frequency of agitation due to inappropriate use of naltrexone in addicted patients.

## MATERIALS AND METHODS

This was a cross-sectional study conducted in Noor Hospital in Isfahan city during 1 year. It was approved by the ethics committee of Isfahan University of Medical Sciences (Research Project Number: 387454). The study population included the drug addicts (of any opioids other than alcohol) who were agitated due to naltrexone abuse. The exclusion criteria were having underlying diseases (diabetes, renal stones, renal failure, dialysis, and cardiovascular diseases),

being restless due to using a substance other than naltrexone (eg, naloxone) and pregnancy.

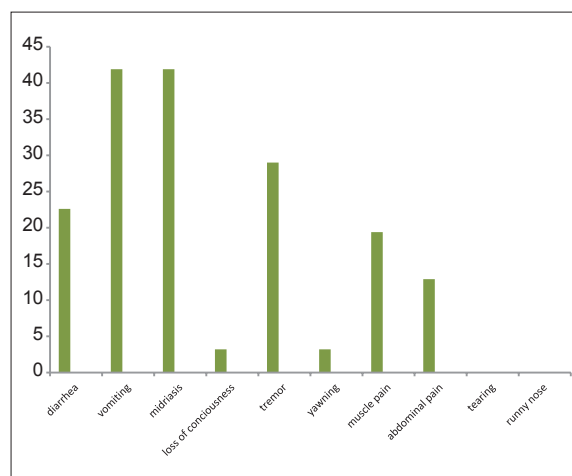
Before the patients entered the study, a written consent was obtained from them or their companion. The patients were admitted to the poisoning emergency department. At the beginning, the patient's agitation scores were measured by Richmond Agitation Sedation Scale (RASS).<sup>[12,13]</sup> The restlessness score was measured at the beginning of the study and every hour until the patient's agitation score reached zero. Patients' vital signs including arterial blood pressure, heart rate, respiratory rate, and peripheral body temperature were recorded hourly by nurses. After treatment, the outcomes of patients including recovery without complications, recovery with complications (rhabdomyolysis), and mortality were recorded. For data analysis, SPSS 17.0 software was used.

## RESULTS

All the patients with the agitation caused by naltrexone abuse during 1 year were 40 people, but nine of them were excluded due to associated diseases (diabetes or cardiovascular diseases). From the remaining 31 patients, 30 were males and 1 was female. Their mean age was 29.93 (5.24) years (min: 20 years, max: 40 years). Of the patient's, 9.7% had a history of mental illness.

In our study, the most common symptoms associated with agitation were midriasis (41/9%), vomiting (41/9%), tremor (29%), and diarrhea (22%) [Figure 1].

No hypothermia or hyperthermia was observed in any of the patient's. Patient's vital signs were normal during hospitalization.



**Figure 1:** Cumulative frequency of accompanying symptoms in patients with agitation

For the purpose of checking the patient's agitation scores, the RAAS scale was used upon admission and every hour until it reached zero upon admission, 38.8% of the patients scored 3 or 4 and 61.2% scored 1 or 2 [Figure 2].

The mean time it took patients' agitation score to reach zero was 9.30 (3.71) h (min: 3 h, max: 18 h).

The patients' outcomes including recovery without complications, recovery with complications (rhabdomyolysis), and mortality were recorded, and all the patients in both groups were discharged without complications.

## DISCUSSION

Naltrexone is easily accessible in some communities. There are only a few case reports regarding the use of naltrexone in addicts and treating its subsequent agitation, whereas in Noor and Ali Asghar hospitals, we had 40 cases of withdrawal symptoms during a year following the inappropriate use of naltrexone with drug abuse.

In a study conducted in 2003, by Boyce *et al.*, a 39-year-old man who was addicted to heroin had used three 50 mg tablets of naltrexone, he became so restless that when he arrived at the hospital, he was held by four police officers. Physicians' early efforts for controlling restlessness by intravenous midazolam and droperidol were not satisfactory. Consequently, the patient was anesthetized and ventilated.<sup>[6]</sup>

In 2008, a study was conducted by Pinelli *et al.*, whose results showed that using naloxone for drug users increased malondialdehyde or MDA, and MDA

and antioxidants were able to reduce the effects of naloxone.<sup>[14]</sup>

In a review on a case report by Ruan *et al.* in 2010,<sup>[15]</sup> a new compound called Embeda was introduced. It is a combination of slow-release morphine plus naltrexone that has been introduced recently as a pain killer. Introducing such pain killers containing naltrexone increases the potential of having more withdrawal syndromes in opioid abusers.

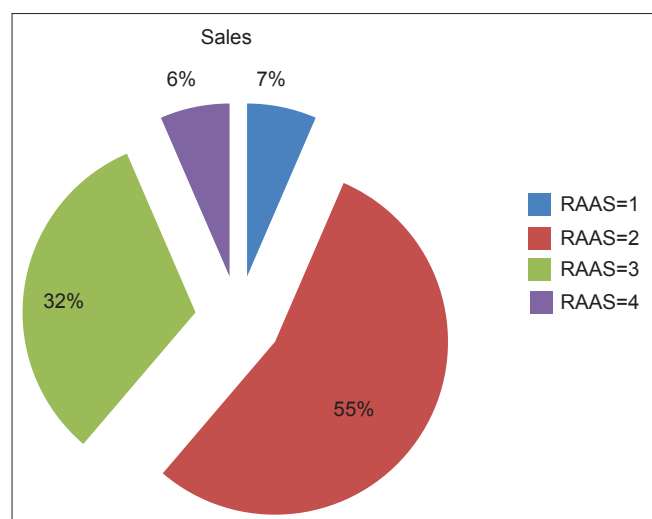
Naltrexone abuse in addicted patients can cause drug withdrawal symptoms, which include symptoms of agitation, confusion, hallucinations, sweating, hyperthermia, tachycardia, abdominal pain, and periods of vomiting and diarrhea that cause dehydration. It also can increase phospholipids, creatine kinase (CPK), rhabdomyolysis, or even lead to death. These signs and complications of the patients were studied. In our study, the most common symptoms included midriasis (41.9%), vomiting (41.9%), chills (29%), and diarrhea (22%). Patient outcomes including recovery without complications, recovery with complications (rhabdomyolysis), and mortality were recorded, and all patients in both groups were discharged without complications.

One limitation of the study was ignoring the interval between the last drug use and naltrexone use as an antagonist. The authors believe it may be involved in the severity of withdrawal symptoms, and due to the lack of a detailed drug history, it was impossible to determine such a relationship.

Considering the high prevalence of agitation in the poisoning emergency department due to inappropriate use of naltrexone, more accurate planning for administration of naltrexone in addicts seems necessary.

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**Figure 2:** Agitation score on admission in patients. , Richmond Agitation Sedation Scale

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