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Psychosis following Tramadol Withdrawal

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| Background: | Abstract Tramadol is a centrally acting opioid analgesic used to treat moderate to severe pain. It has more advantage and less opioid adverse effects than conventional opioid analgesia. |
| Case Report: | This article reports a patient with tramadol dependency that had psychosis after tramadol withdrawal. |
| Conclusion | By the increase of tramadol usage for relief of chronic pain, tramadol abuse and dependency is increased. Some of tramadol withdrawal symptoms are not related to opioid, for example when the effectiveness is not only on opioid receptors, but on catecholamine and serotonin receptors. So, together with typical symptoms of withdrawal, atypical symptoms had been reported. Psychosis is one of tramadol atypical withdrawal symptoms which subsided a few days after suppression of withdrawal symptoms. In such cases, the diagnosis is substance withdrawal instead of psychotic disorder due to substance withdrawal and treatment is based on this diagnosis. |
| Key words: | Tramadol, Psychosis, Atypical withdrawal |

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Introduction

Tramadol was first suggested for the treatment of post operative and chronic pain in 1970 in Germany.¹ It was approved in 1994 in UK and entered the markets of the United States after the Food and Drug Administration (FDA) approved it in 1995.^{2,3} It is used both orally and in injection form to treat mild to severe pain.⁴ An oral dose of 50-100 mg every 4-6 hours with maximum 100 mg per day and a single 50-100 mg IM or IV in 2-3 minutes for treatment of post operative pain is suggested.⁵

Tramadol Hydrochloride is a centrally acting opioid analgesic that affects μ receptors and increases central nervous system (CNS) catecholamine and serotonin^{2,5-7} and as a result has serious interactions with mono amine oxidase (MAO) reuptake inhibitors, serotonin reuptake blockers and tricyclic antidepressants.⁵

Tramadol's side effects include nausea, vomiting, drowsiness, dry mouth, perspiration, dizziness, tremor, confusion, hallucination, blood pressure instability, and exacerbation of convulsions. Most side effects develop in the first seven days of treatment and the interesting point is that only 10% of reported reactions are psychological.⁵

Tramadol has less respiratory suppression and constipation comparing to opioids⁵ and there is even a belief that it does not have respiratory suppression like morphine.^{8,9} A study in the US reported tramadol abuse to be one in a hundred thousand people.¹⁰ At first, dependency risk of tramadol was assumed to be very low,³ but following its extensive use for chronic pain relief and also in drug abuse cases, dependency was observed.¹¹ In Iran, tramadol has been used as an analgesic for several years and there is no restrictions to its sale and distribution. However, concerning the high number of drug addicts, tramadol abuse is also increasing. Some drug addicts even use it for opium cessation without prescription, which increases its dependency prevalence. Also in some addicts tramadol dependency is added to the opiate dependency. On the other hand, tramadol is one of the few strong analgesics in Iran's drug market and the cultural tendency towards quick and symptomatic pain relief increases its usage. As a result, we are facing more cases of tramadol dependency followed by symptoms of withdrawal in clinics.

Because tramadol affects catecholamines and serotonin as well as μ receptors, some of its withdrawal symptoms are not related to opioid.¹² It is therefore necessary to determine tramadol withdrawal symptoms.

Tramadol withdrawal symptoms are in two forms of natural (typical) and unnatural (atypical). There are rare atypical symptoms reported with the tramadol withdrawal so far.

This case report presents psychotic symptoms as a tramadol atypical withdrawal symptom in a person referred with no history of any drug or opioid dependency.

Case Report

Patient was an unemployed 30-year-old single male with high school diploma from Kerman and was admitted in Beheshti Hospital for the first time. The reason for his referral was severe agitation and anxiety in past week following sudden tramadol cessation. He said that the cause of his agitation and anxiety was fear of the security police force that had been following and threatening him and wanted to kidnap him. He also believed that some black points were formed in his memory and he could see god in television and could see some tiny creatures around him. He also had some severe withdrawal symptoms as rhinorrhea, epiphora, nausea, diarrhea, musculoskeletal pains, tremors, tic in his shoulders and head, agitation, headache, and sleeplessness.

He had a history of heroin and opiate addiction for several years and during cessation started using tramadol. After complete heroin and opiate cessation about 2 years ago, he was taking 300mg of tramadol per day until a week ago when he suddenly stopped taking tramadol and was referred to this center with the above mentioned symptoms. In his history there was no evidence of opioid abuse in past 2 years. He had no family history of any specific mental or physical illness.

In psychological examination, he was well alert and had time, place and person orientation. His concentration and attention was reduced. He was anxious and had normal affection. Restlessness was revealed in his psychomotor examination.

He had persecutory delusion, delusional mood, and first stage of tremor,¹³ and had Lilliputian hallucinations.

Neurological examination was normal and EEG, brain CT scan, and MRI showed no organic abnormalities. Based on DSM-IV, tramadol withdrawal syndrome was considered at the admission and psychosis following drug cessation was the differential diagnosis.¹⁴ The patient was treated with analgesic, sedative, and hypnotic drugs but antipsychotic was not prescribed. After 3 days all physical and mental symptoms including hallucinations and delusions completely subsided. Therefore tramadol cessation diagnosis was confirmed and psychosis following drug withdrawal syndrome was ruled out.

Discussion

Since tramadol binds to opioid μ receptors, it is expected that its cessation after chronic use cause withdrawal symptoms and signs. However, in some cases tramadol withdrawal symptoms are similar to serotonin reuptake blockers withdrawal symptoms rather than opioid blockers and this may be related to tramadol mechanism of action as a serotonin and epinephrine reuptake blocker.

Tramadol withdrawal symptoms and signs include typical and atypical types. Symptoms normally seen in tramadol withdrawal according to their prevalence are as follows: gastrointestinal pain, anxiety, bone pain, depression, diarrhea, insomnia, epiphora, nausea, agitation, rhinorrhea, excessive perspiration. Atypical symptoms include severe anxiety, panic attacks, unusual CNS symptoms such as confusion, delusion, derealization, depersonalization, paranoid thoughts (2.27% prevalence), unnatural sensory experiences such as numbness, tingling, prickling, tinnitus (4.25% prevalence) and hepatic, visual, and auditory hallucinations (20% prevalence). It should be mentioned that typical symptoms are usually seen during the withdrawal period and just in one out of eight cases, atypical symptoms appear.¹²

According to a case report, administration of a therapeutic dose of tramadol to control cancer

pain caused auditory hallucinations in a 74-year-old man.¹²

Yates et al¹⁰ presented a 29-year-old female who was first used tramadol to control her pain due to carpal tunnel syndrome and became dependent to a daily 30-50mg dose for three years while she took no other drugs or opioids. During tramadol withdrawal, she developed severe symptoms including vertigo, diarrhea, headaches and insomnia.

Recently, high rate of tramadol abuse has been noticed¹² and even though in most cases, it is associated with opioid dependency, there are some cases of only tramadol dependency.¹⁰

There are evidences that only a few patients with tramadol dependency are susceptible to atypical withdrawal symptoms; Senay et al¹² reported no relation between age, sex, drug intake duration and history of accompanying drug dependency and it was not predictable, but many patients who experienced atypical symptoms were taking more than 400mg tramadol per day.

Senay et al,¹² in their recommendations, ask physicians and other health authorities to pay attention to tramadol withdrawal atypical symptoms such as hallucinations and delusions and do not justify them with drug withdrawal psychosis or delirium. In our reported patient, tramadol withdrawal psychosis was ruled out because the symptoms subsided in a few days without any antipsychotic prescriptions and the definite diagnosis was atypical symptoms of tramadol withdrawal. Regarding the high rate of tramadol usage as an analgesic drug, and the fact that it is marketed without scheduling under the Controlled Substances Act while it causes various side effects, drug interactions, dependency risk and unusual withdrawal symptoms, physicians and health care professionals as well as public need to be aware of the unusual symptoms as well as quick recovery of its psychotic symptoms after controlling withdrawal symptoms. In order to avoid unnecessary medications, diagnosis for psychotic disorder following tramadol withdrawal should be considered just in cases that controlling withdrawal symptoms do not lead to recovery.

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