European Review for Medical and Pharmacological Sciences 2019; 23: 6315-6320

Psychotic symptoms following oxycodone withdrawal, case report and update

N.M. CASADO-ESPADA[1,2], C. MARTÍN[1,2], J.I. DE LA IGLESIA-LARRAD[1,2], R. DE ALARCÓN[1,2], C.I. FOMBELLIDA[1,2], L.C. FERNÁNDEZ-MARTÍN[1,2], C. RONCERO[1,2,3]

[1]University of Salamanca Healthcare Complex, Psychiatry Service, Salamanca, Spain
[2]University of Salamanca, Institute of Biomedicine of Salamanca, Salamanca, Spain
[3]University of Salamanca, Psychiatry Department, Salamanca, Spain

Abstract. – Opiate withdrawal-induced psychosis is an uncommon clinical manifestation. We present a 36-year-old male patient, with no prior personal or familiar psychiatric history, in treatment with several analgesic drugs (including oxycodone) for non-inflammatory chronic rachialgia. The patient is hospitalized after exhibiting psychotic symptomatology (delusions of harm and contamination, olfactory hallucinations, and aberrant behavior). This psychotic symptomatology first manifested after abruptly interrupting his prescribed oxycodone intake. It had a fluctuating course over time (alternating between lucid states and delusional ones) and eventually subsided after the prescription of antipsychotic drugs. In this case report, we describe the follow-up of the patient and discuss the influence and relevance of oxycodone withdrawal on the psychotic symptomatology.

Key Words:
Opioid withdrawal, Psychosis, Oxycodone, Dual disorder, Schizophrenia, Chronic pain, Delusion, Hallucination, Aberrant behavior, Pain killers.

Introduction

In the last few years, the prescription of opiates has increased significantly. One of the main causes is thought to be the publication in 1986 of the WHO analgesic ladder, which indicated the use of opiates in cases of moderate and severe pain, as a result of the principle that promoted pain control as a fundamental human right. We can find a clear example of the remarkable use of opiates as a treatment for chronic pain in the study taken by Checchia et al[1], where it is shown that a considerable amount of cases (19%) required opioids as treatment of chronic sciatic pain. We present a case of a 36-year-old male who was taking opioids for years as treatment of a chronic back pain.

Case Report

We report a case of a 36-year-old male patient who was admitted for the first time in the psychiatric short-stay unit with a diagnosis of unspecific psychiatric disorder on arrival, probably associated to the withdrawal of opioid analgesics (oxycodone). He did not have a previous history of treatment or monitoring from psychiatry services. With regard to his personal record, he had been monitored by the Departments of Traumatology and Rheumatology and the Pain Treatment Unit for "rachialgia without signs of inflammatory disease", a condition that had been treated with diazepam 5 mg every 8 h; pregabalin 75 mg every 12 h; baclofen 5 mg every 8 h, and oxycodone 5 mg/naloxone 2.5 mg every 12 h. Also, he had undergone surgery multiple times over the last years due to a traumatic fracture of the fifth metacarpal of the left hand that had taken place 12 years earlier. On admission, the patient lived with his parents and had been granted permanent total incapacity for work 5 years earlier. Prior to the fracture, since age 18, the patient had emancipated; he had lived in shared flats, worked as an aircraft mechanic and been economically independent, with a completely normal familiar, social and labor functioning.

In this context, 10 days prior to his admission, and in parallel with the sudden withdrawal of oxycodone 10 mg/day (prescribed as an analgesic for his rachialgia), the patient started to show persecutory delusions of being harmed and drugged, with possible olfactory and kinesthetic hallucinations,

Corresponding Author: Carlos Roncero, MD; e-mail: croncero@saludcastillayleon.es

delusions of reference and a tendency towards social isolation. The patient reported inability to think clearly, memory loss, and multiple physical problems (dyspnea, nonspecific dizziness, gum bleeding, oppressive headache, vomiting, and urinary problems) that he attributed to "the gases with which were trying to poison me"; he stated that "they wanted to kill me" and that "the television and radio were talking about me". These symptoms were accompanied by a significant behavioral and emotional change: he placed towels over his mouth like a mask, he boiled water before drinking it, and he put cloth at the bottom of closed doors to "prevent gases from entering". In addition, the patient suffered "bursts of rage" and he expressed suicidal thoughts. Given this clinical picture, urine samples were analyzed for drugs of abuse (including opioids, benzodiazepines, amphetamines, cocaine, and cannabinoids), but the substances were undetectable. The treatment was started with risperidone 3 mg every 24 h, diazepam was maintained with 5 mg every 8 hours, and oxycodone/naloxone 5/2.5 mg every 12 h were reintroduced (after a recommendation from the Pain Treatment Unit). However, the patient only received half a dose of oxycodone/naloxone 5/2.5 mg on that night because 1 h later he presented a picture of severe hypotension and the staff of the Department of Internal Medicine decided to stop that medication together with risperidone.

The patient was referred to the Department of Internal Medicine with suspicion of septic shock, with the corresponding empirical therapy, and fluctuations of the psychiatric symptoms which alternated with episodes of psychopathological stability. A fluctuation in his ability to properly apply rational judgment to the reality of his psychotic symptoms was also observed, as well as acute episodes of agitation and the expression of delusional ideas. After one week of analysis and study in which an extensive battery of diagnostic tests was performed (complete blood count, coagulation, biochemical analysis, thyroid function, lipid metabolism, vitamin B12, folic acid, urine analysis, brain CT scan, CSF, serology tests for HIV, HBV, HCV, *Treponema pallidum*, abdominal ultrasound, EEG, and echocardiogram), no abnormalities were found. The patient was then referred again to the Department of Psychiatry with a clinical assessment of "hypotension probably related to oxycodone withdrawal" made by the Internal Medicine Team upon discharge from their Unit.

In the first days after the referral, the patient was calm, collaborative and stable, both physically and psychopathologically, without any psychotic symptoms; however, on the fifth day, a new episode took place where the patient was suspicious and defiant. He stated that he "perceived gas and the water was not normal" and refused to cooperate. Consequently, the security staff was summoned and 10 mg intramuscular haloperidol was administered. In view of the atypical nature of the symptoms, further organic screening was necessary and more autoimmunity tests were requested, together with a brain NMR. The remaining hospitalization time passed without incidences, with good clinical evolution and therapeutic outings. At the time of the discharge, the patient reported feeling pain and claimed to feel "flat", which he attributed to the medication, "but not sad". The diagnosis on discharge was "nonspecific psychotic disorder, probably related to the withdrawal of opioid analgesics (oxycodone)", with a treatment consisting of risperidone 3 mg/day; diazepam 30 mg/day in three daily doses; ranitidine 150 mg at dinner time and paracetamol or ibuprofen if required for pain.

After discharge, the patient was referred to the psychiatric day hospital to work on his insight and adherence to treatment, close monitoring, improvement of social skills, schedule organization, activation for daily life, and a program for improving his mechanisms for coping with pain. During the follow-up period, these objectives were worked out and the doses of medication were gradually reduced (risperidone 1.5 mg/day and diazepam 7.5 mg/day in two daily doses). Upon discharge from this unit, after seven weeks of follow-up, the patient was more active, with an organized schedule and a remarkable decrease in the number of somatic complaints, apart from an improvement in the general self-efficacy scale (GS), with an initial score of 45 and a final score of 55; and in the short-form 36 questionnaire (SF 36), with an initial score of 70 and a final score of 70.55. However, although no psychotic symptoms were observed, almost no changes were found in the Health of the Nation Outcome Scales (HoNOS; punctuation at admission was 28 out of 48 and at discharge was 13 out of 48) and the Drug Attitude Inventory (DAI-10; 15 out of 20, the same at admission and discharge), which came together with the assessment of an emotional flattening and a tendency to social isolation.

The patient was monitored again by the Department of Traumatology and the Pain Treatment Unit, where he asked for the opioids to be reintroduced as part of his medication. He attended his

follow-up consultation appointments with his psychiatrist only once, when he refused any variations in the prescribed medication and rejected the proposal to continue visiting mental health professionals. At the time of that visit and evaluation, he was psychopathologically stable, although barely aware of his condition. We made sure that, two months later, the patient abandoned the monitoring routine established by the Department of Psychiatry.

Discussion

Although the appearance of psychosis after a sudden withdrawal of opioids is not common as part of a withdrawal syndrome, there are cases of psychotic symptoms that have been described in literature[2-6] related to a withdrawal of buprenorphine, morphine, tramadol, and methadone.

In the clinical case reported in this article, at least six factors may be listed that support the clinical suspicion of withdrawal from oxycodone/naloxone. First, the patient lacked any personal or family history of psychiatric disorders, with an unusual age of onset for a first psychotic episode (36 years). Similarly, the evolution of the symptoms fluctuated, alternating between acute episodes showing abundant psychotic symptoms and episodes of psychopathological stability in which he could adequately discuss those same, previously irreducible psychotic symptoms; he perfectly remembered such episodes and he admitted that, during those episodes, "he lived them as if they were real". On the other hand, the onset of these symptoms coincides in time with the sudden withdrawal of oxycodone, a medication he had been using for years as an analgesic for his back pain and which he abruptly decided to interrupt. Furthermore, the antipsychotic treatment with risperidone does not seem to be related to the evolution of symptoms since the fluctuations described before persisted with a stable dose of this drug. Finally, intoxication caused by drugs of abuse was ruled out (no trace of such drugs of abuse were detectable in urine), together with any other organic pathology which could account for an organic mental disorder.

Nevertheless, despite these arguments in favor of an oxycodone/naloxone withdrawal syndrome that may be responsible for his clinical symptoms, the fact that the drug was not reintroduced to verify whether the symptoms subsided prevents us from being completely certain that the withdrawal was indeed the cause. It also needs to be taken into account that the patient was also treated with baclofen, an antispastic drug which was also associated with a sudden interruption, on the one hand, with psychotic symptoms[7] and, on the other hand, with the worsening of withdrawal syndromes related to other substances (alcohol)[8]. Similarly, as we mentioned above, the patient presented an impairment in his work, social and family life over the last 10 years after an accident where he fractured his left hand, which might suggest a primary psychiatric entity. However, this case does not follow the usual clinical structure and the response to the antipsychotic drugs is not what may be expected in a primary or an induced psychosis. Although Lu et al[9] point out that specific findings suggesting Schizophrenia can be found in magnetic resonance, there are still no determining markers for the diagnosis of schizophrenia in neuroimaging. In any case, the Brain Magnetic Resonance did not show any alterations in our patient that could suggest a primary psychosis, being then unsupportive of a diagnose in that direction. Therefore, the evolution and degree of functional recovery[10] of the patient are key elements in the differential diagnosis to establish the nature of clinical symptoms, as often happens in the field of psychiatry.

The case we describe is the first one of a psychotic syndrome secondary to the withdrawal of oxycodone/naloxone, although there are references of psychosis secondary to withdrawal from other opioids, which are described below.

The case described here establishes a time relation between the withdrawal of oxycodone and the appearance of the psychotic symptoms. The patient did not report previous psychotic symptoms. Therefore, they must be associated with the opiate withdrawal rather than with a potential antipsychotic effect of the same agents that "controls" the symptoms. In this regard, according to Maremmani et al[11], even though there is a causal relation between most drugs of abuse and psychosis, this connection is unclear in the case of opioids. These are the only central nervous system depressants that have shown an antipsychotic effect. Consequently, they have even been considered potentially useful for the treatment of mental diseases[11,12]. For its part, maintenance therapy with methadone prevents relapses in patients with a previous history of psychosis. This theory is supported by the fact that its progressive withdrawal is associated with relapses (which may be attributed to its antidopaminergic activity). Shreeram et al[6] describe the case of a 45-year-old woman who, while receiving maintenance thera-

py with methadone with doses of 100 mg/day, underwent ultra-rapid detoxification. One day later, with a urinary positive screen for methadone, she became agitated during extubation and presented psychotic symptoms (she believed that members of the staff were trying to kill her and the anesthesiologist was attempting to choke her, as well as experiencing auditory hallucinations) and significant anxiety, despite being fully aware and oriented. 24 h later the symptoms receded and the patient remained asymptomatic within the next three months.

Weibel et al[2] and Karila et al[3] discuss two different cases of psychotic symptoms following buprenorphine withdrawal. The first[2] presents a 37-year-old man who consumed marijuana regularly and showed mystical and paranoid delusions, auditory hallucinations, suicidal thoughts, and intense anxiety, with a sudden onset two weeks after the withdrawal of buprenorphine at a dose of 8 mg/day. The patient was hospitalized and treated with risperidone up to 8 mg, without any clinical response. Then, buprenorphine was restarted at the initial dose and the symptoms subsided completely. Two months later, buprenorphine was gradually discontinued over 4 months. 18 months later he remained asymptomatic despite his continued use of marijuana. The second case[3] presents a 32-year-old man who received buprenorphine 6 mg/day and who, during a gradual decrease of his dose, presented a typical withdrawal symptom and psychotic symptoms (with buprenorphine 2 mg/day). The psychotic symptoms remained in spite of the treatment until the initial dose of buprenorphine was reintroduced.

Aiyer et al[4] present the case of a 57-year-old man who had an intrathecal morphine pump for chronic lumbar pain for several years and suddenly started showing psychotic symptoms including auditory and visual hallucinations, disorganized thinking, paranoia, and persecutory delusions. The neurology team evaluated the patient and recommended to stop baclofen, which the patient received as part of his treatment. A brain CT scan and an EEG were performed, with results within normal values. The patient showed a limited response to treatment with antipsychotics. Given the slow evolution of the symptoms, further examinations were performed and it was determined that there was a mechanical failure in the intrathecal pump. Treatment started with oral oxycodone which led to a remission of psychotic symptoms in a few days. This indicated the withdrawal from morphine as a cause of symptoms.

Finally, in a report with 422 patients treated with tramadol carried out by Senay et al[5], 1 in 8 patients (55 in total) showed atypical symptoms for opioid withdrawal (hallucinations, paranoia, extreme anxiety, panic attacks, and confusion), apart from the typical symptoms after the sudden tramadol withdrawal.

There might be an antipsychotic effect in some opioids[3,4,11-13]. In a study with 10 patients, the remission rate of psychotic symptoms after a single dose of buprenorphine was of 70%, with an average duration of 4 h. This potential antipsychotic effect of buprenorphine might be attributed to its kappa antagonist activity[3]. Also, Gold et al[13] compare in their research the effect of morphine and FK 33-824 (a synthetic *d*-alanine methionine-enkephalin derivative) on serum prolactin in primates. In their discussion they state that "opiate agonists stimulate opiate receptors in the brain to modify dopamine impulse flow and release, thereby interfering with the postsynaptic action of dopamine. Endogenous opioid peptides, endorphins, may act as an inhibitory neuromodulator of dopamine activity so that an endorphin deficiency could result in increased dopamine release and turnover and possibly psychosis"[13].

Despite the fact that baclofen does not belong to the family of opioids, it must be mentioned since it was part of patient's treatment in the case, and it is been shown to have an impact on a different kind of substance withdrawal syndrome[8]. First, Calvo et al[8] present the case of a 46-year-old male, alcohol-dependent, and a cannabis user, who stopped drinking a week after intrathecal baclofen (ITB) pump implant due to a cervical spinal cord injury because "he did not feel the urge anymore". According to this work, baclofen can be useful in the acute treatment of alcohol withdrawal syndrome (AWS), thereby reducing diazepam requirements and in long-term alcohol abstinence. Furthermore, Calvo et al[8] suggest that in the presence of AWS, while on chronic baclofen, no dose reduction should be attempted, as it can worsen the AWS. Second, there is a report by Rivas et al[7] which presents and analyzes three clinical cases in which, after the sudden withdrawal of baclofen (prior to urological surgery), the patients developed neurological symptoms (seizures, diplopia, and other visual disorders) in addition to the psychotic symptoms (hallucinations, paranoia), unlike the case presented here in which no neurological symptoms were observed. However, psychotic symptoms related to the pharmacological treatment are not exclusive to the drugs men-

tioned above. The literature includes other drugs that can be accompanied by psychotic symptoms, such as the dopaminergic agonists used in the treatment of Parkinson's disease[14,15].

Regardless of the reasons that caused the psychosis, a common clinical priority for the health professionals is to ensure that their patients reach an optimal level of functional recovery[10].

Conclusions

We present the first description of psychotic symptoms after an oxycodone withdrawal. Even though the patient was also receiving baclofen, the symptoms were not related to its withdrawal and no neurological symptoms appeared. The sudden withdrawal of oxycodone seems to have triggered the psychotic syndrome, with an atypical evolution and the characteristics of an acute confusional syndrome (fluctuating ability to discuss his episodes). However, the fact that the patient responded well to the antipsychotics, and did not need opioid reintroduction to stop the symptoms, does not allow us to establish an unequivocal cause-effect relationship between the symptoms and the withdrawal from the drug. Consequently, a further monitoring of the patient is required. In this regard, there are researches that describe how the sudden withdrawal from different opioids (methadone[4], buprenorphine[2,3,4], morphine[4], tramadol[4,6]) triggers an atypical withdrawal syndrome with psychotic symptoms (alterations of consciousness and perception, delusions, disorganized behavior), anxiety crises and panic attacks. This psychotic syndrome generally shows little or no response to antipsychotics; however, it completely subsides after reintroducing the opioid that was withdrawn or an analogue[2-4,6,7]. Since all the published studies are case reports or series of cases, it is necessary to continue observing and reporting all cases of psychotic symptoms after an opioid withdrawal, as well as the potential antipsychotic effect of the drugs.

Conflict of Interests

Dr. Carlos Roncero has received fees to give lectures from Janssen-Cilag, Ferrer-Brainfarma, Pfizer, Indivior, Lundbeck, Otsuka, Servier, GSK, Rovi, Astra, Gilead, MSD, Sanofi, and Exceltis. He has received financial compensation for his participation as a board member of the Janssen-Cilag, Lundbeck, Gilead, MSD, Mundipharm, INDIVIOR, Exceltis, and Martindale board. He has participated in the PROTEUS project, which was funded by a grant from Reckitt-Benckisert/Indivior. He received two medical education grants by Gilead. Dra Carmen Martín has received fees to give lectures from Janssen and Lundbeck. Dra Clara Fombellida has received fees to give lectures from Astra, Zéneca, and Lundbeck. Dra Nerea M. Casado-Espada has received an economic award from Janssen in an oral communication contest.
The other authors declare that they have no conflict of interests.

Acknowledgements

In the name of the authors, we wanted to thank David González-Iglesias, translator of the Official College of Doctors of Salamanca, for his work and dedication.

References

1) Checchia GA, Letizia Mauro G, Morico G, Oriente A, Lisi C, Polimeni V, Lucia M, Ranieri M; Management of Peripheral Neuropathies Study Group. Observational multicentric study on chronic sciatic pain: clinical data from 44 Italian centers. Eur Rev Med Pharmacol Sci 2017; 21: 1653-1664.
2) Weibel S, Mallaret M, Bennouna-Greene M, Bertschy G. Case report: a case of acute psychosis after buprenorphine withdrawal. J Clin Psychiatry 2012; 73: e756.
3) Karila L, Berlin I, Benyamina A, Reynaud M. Psychotic symptoms following buprenorphine withdrawal. Am J Psychiatry 2008; 165: 400-401.
4) Aiyer R, Jain V, Bhatia A, Mekinulov B, Gungor S. Rare presentation of intrathecal morphine withdrawal psychosis. Pain Manag 2017; 7: 171-173.
5) Senay E, Adams E, Geller A, Inciardi JA, Muñoz A, Schnoll SH, Woody GE, Cicero TJ. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. Drug Alcohol Depend 2003; 69: 233-241.
6) Shreeram SS, McDonald T, Dennison S. Psychosis after ultrarapid opiate detoxification. Am J Psychiatry 2001; 158: 970.
7) Rivas DA, Chancellor MB, Hill K, Freedman MK. Neurological manifestations of baclofen withdrawal. J Urol 1993; 150: 1903-1905.
8) Calvo ME, Gunnarsson T, Smith L, Hao M. Delirium tremens in an AUD patient after an intrathecal baclofen pump induced total alcohol abstinence. Eur Rev Med Pharmacol Sci 2018; 16: 5371-5376.
9) Lu XB, Zhang Y, Yang DY, Yang YZ, Wu FC; Ning YP, Wu K. Analysis of first-episode and chronic schizophrenia using multi-modal magnetic resonance imaging. Eur Rev Med Pharmacol Sci 2018; 22: 6422-6435.

10) Lahera G, Pérez-Fuster V, Gálvez JL, Martínez M, Sánchez P, Roca M. Is it possible to achieve functional recovery in schizophrenia? A qualitative and quantitative analysis of psychiatrist's opinion. Actas Esp Psiquiatr 2016; 44: 97-106.

11) Maremmani AGI, Rovai L, Rugani F, Bacciardi S, Dellosso L, Maremmani I. Substance abuse and psychosis. The strange case of opioids. Eur Rev Med Pharmacol Sci 2014; 18: 287-302.

12) Maremmani A, Pallucchini A, Rovai L, Bacciardi S, Spera V, Maiello M, Perugi G, Maremmani I. The long-term outcome of patients with heroin use disorder/dual disorder (chronic psychosis) after admission to enhanced methadone maintenance. Ann Gen Psychiatry 2018; 17: 14.

13) Gold MS, Redmond E Jr, Donabedian RK, Goodwind FK, Extein I. Increase in serum prolactin by exogenous and endogenous opiates: evidence for antidopamine and antipsychotic effects. Am J Psychiatry 1978; 135: 1415-1416.

14) Maremmani AGI, Bacciardi S, Rovai L, Rugani F, Dell'Osso L, Maremmani I. Natural history of addiction in psychotic heroin-addicted patients at their first agonist opioid treatment. Addict Disord Treat 2013; 12: 31-39.

15) Bertolín JM, Sáez R, Morant Y. Delusional psychosis induced by dopamine agonists in the treatment of Parkinson's disease: four clinical cases. Actas Esp Psiquiatr 2017; 45: 79-88.