

# The Question of Therapy Continuation in the Light of Dependence on Short-Acting Opioids in Long-Term Cancer Patient

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## Abstract

**Introduction:** The risk of addiction in cancer patients with a relatively good prognosis is a challenge for modern medicine. As the number of therapies increases, so do patient survival and, consequently, the risk of inappropriate use of opioid drugs, especially the short-acting ones. The aim of the present study is to evaluate the decision to continue therapy with a short-acting fentanyl preparation and suggest possible alterations in the treatment plan of an addicted patient.

**Methods and materials:** The present study concerns a 49-year-old male patient with an advanced neuroendocrine tumour in the pre-sacral region. The tumour infiltrates the rectal wall and has formed metastases to the liver, lungs and bones. The patient is under the care of the Palliative Medicine Clinic due to the reported severe pain, assessed as 7-10 on the Numeric Rating Scale (NRS). In the course of the therapy with opioid analgesics, the patient has developed an addiction to the prescribed short-acting intranasal fentanyl preparation. The attempts to modify the treatment have not produced the desired effects due to aggravation of the symptoms and a lack of compliance. The patient remains pleased with the therapy and considers the prescribed fentanyl preparation to be the only effective drug. The research method includes the medical history and physical, an analysis of the patient's medical record and a self-designed questionnaire to assess the degree of dependence on opioid drugs. The questionnaire consists of 19 questions divided into the major and minor criteria.

**Conclusion:** The analysis of the results of the survey results confirmed the patient's dependence on opioid drugs. He gave positive answers to 16 out of 19 questions in the survey. The history and physical revealed that the patient was pleased with the instituted therapy as it allowed him to remain physically fit and maintain a high quality of life. Because of the advanced stage of the neoplastic process as well as the significantly increased pain, the improvement of life quality is of the utmost importance. Therefore, it seems justified to continue the intranasal fentanyl preparation therapy since it is both well-tolerated by the patient and able to produce a highly satisfactory analgesic effect.

**Keywords:** Addiction; Short-acting opioid; Intranasal fentanyl; Cancer pain; Life quality

## Introduction

Dependence on psychoactive substances can be defined as a primary, chronic disease with an underlying neurobiological causation, characterized by loss of self-control leading to compulsive drug use fuelled by a desire to obtain and use the addictive substance despite being aware of the adverse consequences [1]. Opioids, especially in the short-acting form, are a group of potentially addictive substances. Dependence on them is a growing problem in medicine. In the USA, 21-29% of patients reporting chronic pain abuse prescription opioids [2]. 70% of advanced stage cancer patients complain of moderate or severe pain [3].

Pharmacological guidelines for pain treatment in cancer were created and updated by the European Association for Palliative Care in 2012 [3], and in Poland by the Polish Association for Palliative Care in 2014 [4]. It can be observed that just as the number of possible oncological therapies increases, so does the survival of patients and the risk of misuse of opioid drugs, particularly the short-acting ones [5]. As a rule, short-acting opioid analgesics, such as intranasal fentanyl, should be used in the treatment of breakthrough pain [6,7]. In addition, the analysis of pharmacokinetic properties proves that intranasal sprays have the most rapid onset of action and a high bioavailability. Also, they do not undergo the first pass effect [8,9].

The effects of opioids, especially the result of the stimulation of the reward system i.e., euphoria are particularly conspicuous in the case of rapid drug absorption and delivery to the brain. This explains their increased addictive potential, which is even greater when the drugs are used with poor compliance. The present study describes the

case of a patient who developed an addiction to an intranasal fentanyl preparation due to non-compliance.

## Methodology Adopted

The present study concerns a 49-year-old advanced cancer patient undergoing analgesic therapy. It involves the medical history and physical, an analysis of the patient's medical record and a self-designed survey to assess the degree of dependence on opioid drugs (Table 1). The survey consists of 19 questions divided into the major and minor criteria. The 15 questions address the issues of the patient's physical and mental condition as well as behavioural patterns connected with the use of opioids. The other 4 questions concern addiction susceptibility. All the 19 points are Yes/ No questions. A minimum of 3 positive responses in the major criteria group suffice to diagnose an addiction. The minor criteria are complementary and therefore not required to establish a diagnosis but may prove useful in borderline cases.

## Case Presentation

The patient is a 49-year-old male with an advanced neuroendocrine

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tumour in the pre-sacral region. The tumour infiltrates the rectal wall and has formed metastases to the liver, lungs and bones. The patient is under the care of the Palliative Medicine Clinic due to the reported severe pain. In 2008 the patient underwent an anterior resection of the rectum as well as sacrectomy. In 2011 he had a retroperitoneal recurrence removed. In the late 2012 and early 2013 he received three courses of palliative chemotherapy. Since 2013 he has been treated in the Department of Endocrinology with a somatostatin analogue, presenting monthly to receive injections. Between April and November 2017, he was administered 4 doses of a beta-emitter-labelled somatostatin analogue. Due to a severe episode of depression the patient was hospitalized at the Department of Psychiatry and remains under psychiatric care. The patient has a history of COPD and recurrent bronchitis and is a chronic smoker.

The patient has been undergoing treatment at the Palliative Medicine Clinic since July 2015. Before 2015 he received analgesic treatment at

other departments, already showing symptoms of addiction to short-acting transmucosal opioid analgesics. At each appointment the patient reported pain in the lower part of the body which he assessed as 7 on the NRS. The pain, present mostly in the hypogastric and perineal regions, radiated to both thighs and was aggravated by motion. In 2015 the patient's analgesic therapy comprised intranasal fentanyl 400 µg qid into each nostril, morphini sulfas 20 mg (Figure 1) prn, oxycodone 80 mg q8h, pregabalin 120 mg q12h. In the patient's medical record, the doctor in charge noted that the patient's compliance was low and thus there was a considerable risk of developing and addiction to the intranasal fentanyl preparation. The doctor observed that the patients used 10 packs of the preparation between appointments. On the following appointments the patient reported exacerbation of pain to 8 or even 10 on the NRS during motion. As a result, the therapy was modified, and the patient was administered 100 mg q8h and ketoprofen 100 mg prn. Also, an unsuccessful attempt to replace intranasal fentanyl with sublingual fentanyl was made. In later stages, methadone was also included in the therapy.

In 2016 and 2017 the patient was hospitalized at the Palliative Medicine Department in order to have his analgesic treatment optimized as the symptoms were becoming difficult to manage. At subsequent follow-ups the patient reported pain rated as 8 on the NRS. According to the medical record from late 2016 and early 2017, the patient repeatedly exceeded the prescribed overall dose of fentanyl and failed to comply with the regimen, despite being instructed how to use the analgesic on a number of occasions.

The patient described his condition as good but remarked that the pain worsened whenever he had run out of fentanyl, which he considered to be the only effective drug. Despite having all the other prescribed analgesics, the patient frequently presented to the Clinic before the scheduled appointment to obtain an intranasal fentanyl prescription. It thus seemed doubtful whether the patient used the long-acting analgesics at all. According to the medical record, the patient may have abandoned therapy with methadone and pregabalin and used only short-acting drugs, believing them to be the only effective treatment. In late

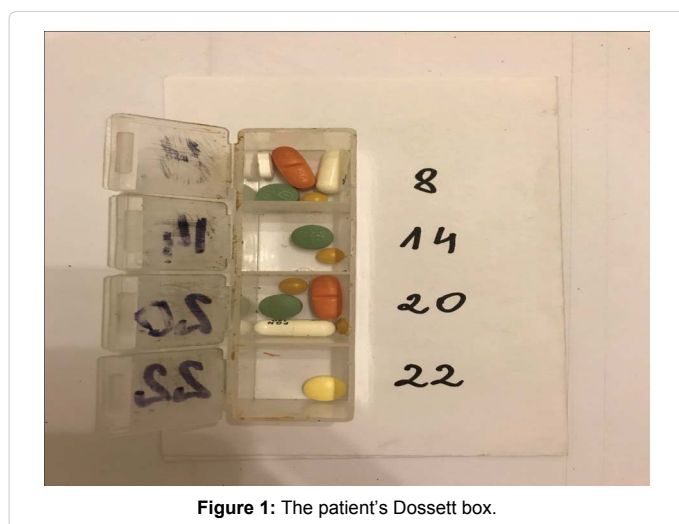


Figure 1: The patient's Dossett box.

Major Criteria			
1	Have you ever had to take a larger dose of the drug to cause the same effect as before?	Yes	No
2	Have ever experienced symptoms such as anxiety, sleeplessness, profuse sweating, sneezing or watery eyes when you tried to discontinue the drug?	Yes	No
3	Do you ever take larger doses than those prescribed by the doctor?	Yes	No
4	Would decreasing the dose or discontinuing the drug cause any difficulty?	Yes	No
5	Have you ever felt the need to take an opioid drug despite having no pain?	Yes	No
6	Have you ever tried to obtain an opioid drug from more than one source to increase the recommended dose?	Yes	No
7	Do you feel you have lost control over the drug you are taking?	Yes	No
8	Do you feel the need to take the drug despite the adverse effects you are perfectly aware of?	Yes	No
9	Have you ever neglected your duties/ missed a social event because of drug use?	Yes	No
Minor Criteria			
1	Do you feel anxious when your drugs are about to run out?	Yes	No
2	Have you ever taken your drug first thing in the morning?	Yes	No
3	Do you feel you are taking larger doses of the drug than you should?	Yes	No
4	Have you ever felt remorse caused by drug use?	Yes	No
5	Have people around you observed that you are taking larger doses of the drug than you should?	Yes	No
6	Do you ever wonder how you will feel after you take the drug?	Yes	No
7	Have you ever abused other drugs?	Yes	No
8	Are you addicted to alcohol/cigarettes/illegal drugs?	Yes	No
9	Has anyone in your closest family ever been addicted to anything?	Yes	No
10	Are you or have you ever been treated psychiatrically?	Yes	No

**Note:** The survey contains a screening question, a positive answer to which qualifies the responder for the next stage of the test; Each question should be answered 'Yes' or 'No.' The survey encompasses the previous 12 months. Have you ever taken opioid drugs? Yes/No.

Table 1: A self-designed opioid dependence assessment survey.

2017 the patient managed to photocopy an intranasal fentanyl prescription and succeeded in obtaining twice the prescribed amount.

In 2018 the patient was readmitted to the Palliative Medicine Department to have his pain assessed and drug doses titrated. The modified therapy included oxycodone 80 mg q8h, fentanyl 100 µg/h 1 patch q72h, pregabalin 150 mg bid, intranasal fentanyl 400 µg qds or Servedol 20 mg T in the case of breakthrough pain. The patient was still under psychiatric care and was prescribed: carbamazepine CR 400 mg bid am and pm, amitriptyline 10 mg qid, paroxetine 20 mg qd am, cholprothixine 15 mg qd pm, pregabalin 150 mg tid.

At that time the patient usually scored 7 on the NRS. At one of the appointments the patient produced his Dossett box containing all the drugs he used, which confirmed his failure to comply and proved that he created drug administration patterns himself (Figure 1). The patient is still treated at the Palliative Medicine Clinic and the Psychiatric Clinic and has been scheduled for further injections of a somatostatin analogue.

## Results

From the taken history it transpired that the patient's main complaint was a pelvic pain radiating to the lower limbs. The pain was typically rated as 7-8 on the NRS. It frequently affected the patient's daily life and made him unable to work. The patient attended all the appointments unaided. Despite his health problems, he assessed his life quality as good and believed his analgesic therapy to be very effective. He admitted being an addict, but frequently emphasised that intranasal fentanyl was the only drug that could help him manage the pain sufficiently. The patient also explained that the increased demand for the drug was due to the death of a parent, who had passed away a few months before.

The results of the self-designed questionnaire unequivocally confirm the diagnosis of opioid drug dependence. The patient gave a positive answer to 7 out of 9 questions concerning the major criteria and to 9 out of 10 questions verifying the minor criteria. The patient admitted to the need for increased doses of the drug and the presence of drug withdrawal syndrome occurring at attempts to discontinue it. Also, the patient acknowledged poor compliance, confirming low control over the use of intranasal fentanyl and admitting that discontinuation or even dose reduction would be incredibly difficult. He confessed that he often neglected his duties and devoted time to thinking about the drug and the feelings that its use would trigger. At times, he used short-acting fentanyl despite experiencing no pain for purposes other than analgesia. The patient denied obtaining opioids from other sources, although a successful attempt to photocopy and reuse an opioid prescription was well-documented in the record. He also denied abusing any other drugs. Both the patient and his kin noticed that he had been using larger amounts of opioid drugs than he should have. The patient admitted occasional remorse and a sense of shame resulting from drug abuse. He felt anxious whenever the drug was about to run out but was not positive whether he feared potential pain or the perspective of restricted drug access. The patient fulfilled the criteria for increased risk of dependence, namely chronic nicotine dependence, alcohol addiction in the past, psychiatric treatment and a history of addiction in the family.

## Discussion

There are several therapeutic options for patient's dependent on opioid analgesics. One of them is withdrawal treatment, which is not possible in the case of advanced cancer patients because of the

accompanying pain. Another possibility is opioid replacement therapy, in which one analgesic is replaced with another [10].

Given the fact that the risk of developing an addiction in cancer patients who take long-acting opioids is relatively low (>10%), increasing the doses of controlled release drugs could be effective [11].

In the present case, such measures had been taken several times, even in the form of inpatient care. The main indications for hospitalisation at the Palliative Medicine Department were inappropriate pain management and limited control over the amount of the used intranasal fentanyl preparation. As the patient has advanced, progressive cancer, it seems reasonable to continue treatment with short-acting intranasal opioid. The preparation is well-tolerated by the patient and the analgesic effect is rated as highly satisfactory. Discontinuation of a drug that the patient deems to be the only effective one would be morally dubious. Moreover, taking into account factors such as the presence of other addictions, a mental disease and a positive family history of addiction, the chance of patient cooperation in overcoming the addiction is slim. The patient persistently failed to comply with the regimen and the attempts to alter the therapy did not bring the desired effects. Given the advanced stage of the cancerous process and significantly increased pain, life quality improvement seems to be of overriding significance while the question of addiction should be seen as one of secondary importance. In the light of the above, it is recommended that treatment with the short-acting fentanyl preparation should be continued [12].

## Conclusion

To prevent similar cases in other patients, it may be useful to perform drug abuse screening tests. However, it is necessary to design uniform, systemic addiction risk assessment strategies for patients using transmucosal opioids such as REMS for TIRF (Risk Evaluation and Mitigation Strategy for transmucosal immediate-release fentanyl) in the USA. Approved by FDA in 2011, the system aims to prevent abuse and dependence. Patients reporting severe pain with a predicted long-term survival ought to be assessed more carefully in terms of addictions, comorbidities, including mental disorders, as well as social and family history. To conclude, intramucosal short-acting opioids are an important group of drugs that should be used for the benefit of patients. Yet, due care and thorough assessment both before and during treatment are highly recommended.

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