no longer necessary. Of the cohort of 10 patients, four noted mild sedation as an adverse effect of methadone use. In one case, this resolved spontaneously over days, and in a second patient, this resolved when the background opioid dose was reduced. In the third and fourth cases, patients felt the positive analgesic effect outweighed the mild sedation and opted to continue the same methadone dose.

Combination of opioids is not a practice that the authors have previously advocated or taught. The notion of prescribing methadone as a coanalgesic arose when one of the authors (A. N.) had the experience of using methadone while working in specialist inpatient units (where opioid switching could be managed by a confident staff group familiar with the process) before working in an advisory service in an acute hospital. Seeking to harness the potential benefit from the NMDA-receptor antagonism, but lacking the controlled environment within which to micromanage an opioid switch in the usual manner, the idea of considering the coanalgesic role of methadone arose. The initiation strategy was counter intuitive when considering the pharmacokinetics and pharmacodynamics of methadone, but a cautious introductory schedule was deemed important. Patients were reviewed closely and they and their carers counseled with oral and written information, to seek advice if concerned and to reduce opioid doses if adverse effects prevailed.

We are aware that the described case series is limited by small sample size and the retrospective and uncontrolled design of this study. Furthermore, alternative changes to analgesic regimens may have resulted in beneficial effects, similar to the addition of methadone. However, we propose that this study suggests that low-dose methadone may be safely and successfully used as a coanalgesic. This simpler regimen may be of particular use in an outpatient setting and for palliative care inpatients with severe pain being managed by a specialist palliative care unit. Further research is required to confirm the efficacy of this regimen.

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doi:10.1016/j.jpainsymman.2011.06.005

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Emerging Opioid Abuse in Terminal Cancer Patients Taking Oral Transmucosal Fentanyl Citrate for Breakthrough Pain

To the Editor:

Aberrant opioid-related behaviors have been a very rare event in the palliative care (PC) field in Spain up to very recently (no cases reported in the literature). In accordance with recent studies,[1] prescription of the new rapid-onset fentanyl formulations for the management of cancer breakthrough pain (BTP) has been accompanied in our country with emerging aberrant drug-related behaviors associated with them. Recently, two relatively young terminal cancer patients, each with a history of substance abuse (alcohol and tobacco), developed aberrant behaviors clearly related to the prescription of oral transmucosal fentanyl citrate (OTFC) for the management of BTP.

Case 1

A 52-year-old woman, with a history of heavy smoking and drinking within the last years, presented with severe neuropathic and incidental bone pain as a result of an epidural dorsal mass and vertebral metastases from ovarian cancer. Since her diagnosis seven years earlier, she had been treated with surgery, chemotherapy, radiotherapy, and radiosurgery. For the last two years, before her first consultation, she had been on chronic treatment with opioids: oxycodone for her basal pain and OTFC for her BTP. On arrival at the outpatient clinic of the hospital PC unit, she was taking 55 mg of slow-release oral oxycodone every 12 hours; 200 mcg of OTFC as needed (PRN)—approximately 18 units per day; 60 mg of oral duloxetine per day; and multiple drugs used in complementary and alternative medicine. Screening and monitoring for aberrant behaviors had not been adequately performed by either her primary physician or her hospital specialist. However, suspicion about her drug-related behaviors had already been raised by the PC home care team. A proper assessment disclosed several aberrant behaviors: requests for early renewal of OTFC prescriptions, aggressive complaining about the need for more OTFC, OTFC hoarding, openly acquiring OTFC from different medical sources in spite of warnings from the home care team, unapproved use of OTFC to treat anxiety, reporting seeking euphoria with OTFC, and fear of addiction to OTFC. She was treated as an outpatient with an honest and open discussion of the issues involved, the establishment of a new opioid treatment agreement, and the involvement of our psychologist, the home care team, and her family in her management. In spite of these measures, and opioid rotation to immediate-release oxycodone for her rescue doses plus titration of slow-release oxycodone for her basal pain, the patient went through a period of withdrawal when OTFC was discontinued that lasted for two weeks. She repeatedly requested going back to OTFC, to the point of trying to retrieve her previous hoard from the home care team. Concurrently, there was a crescendo in her basal pain because of the progression of the bone metastases. After several weeks, she finally stabilized on a 280 mg dose of slow-release oxycodone every eight hours plus 80 mg of immediate-release oxycodone every four hours PRN. Six months later, and thanks to a neurosurgical procedure, the doses were reduced to 200 mg every eight hours and 60 mg every four hours PRN, respectively (usually just one rescue dose per day), suggesting a total recovery from her previous psychological dependence on OTFC rescue doses. One year later, the patient was admitted to the hospital PC unit and went through a successful opioid rotation to 1200 mg of intravenous morphine per day plus a course of samarium. She died at home five weeks later because of septic complications.

Case 2

A 45-year-old man, with a history of heavy smoking and drinking within the last years plus chronic treatment with alprazolam for anxiety, presented with severe mixed pain as a result of locally advanced esophageal cancer. Since his diagnosis two years earlier, he had been treated with surgery, chemotherapy, and pleural sclerosis. For the last year before the consultation, he had been on chronic treatment with opioids: oxycodone and transdermal fentanyl for his basal pain and OTFC for his BTP. Screening and monitoring for aberrant behaviors had not been adequately performed by the primary physicians and hospital specialists, although some degree of suspicion toward his drug-related behaviors had already been raised in a preliminary consultation with the PC team. On arrival in the emergency room of the hospital because of a pain crisis, he was found to be using three 100 mcg fentanyl patches simultaneously, clearly in excess of the prescribed dose. The patient also was taking 65 mg of slow-release oral oxycodone every eight hours, 600 mg of gabapentin every eight hours, 75 mg of venlafaxine per day, steroids, nonsteroidal anti-inflammatory drugs, and 1200 mcg of OTFC PRN—approximately eight units per day. A proper assessment by the PC team disclosed several aberrant behaviors: addiction to the opioid, chemical coping, misuse, and self-medication. The patient was admitted to the hospital, and an opioid rotation was made to 250 mg of intravenous morphine per day plus 10 mg of midazolam per day, with 10 mg of intravenous morphine PRN for BTP. In spite of this approach, the patient refused to discontinue OTFC. Again, an honest and open discussion of the issues involved and the

establishment of a new opioid treatment agreement allowed the patient to return home with a schedule similar to the previous one: fentanyl patches 200 mcg every 72 hours, 40 mg of slow-release oxycodone every eight hours, 600 mg of gabapentin every eight hours, 10 mg of diazepam every eight hours, steroids, and 20 mg of immediate-release oxycodone every four hours PRN. A maximum of four units of OTFC were permitted per day, and the patient was warned that any violation of the agreement would not be tolerated. No further aberrant behaviors were detected by the family or the team until his death at home three weeks later, when he needed terminal sedation.

Comment

The likelihood of developing addiction in an animal model, by allowing rats extended self-administered access to fentanyl, has been convincingly demonstrated.[2] There also is ample evidence of fentanyl patch abuse by street users with simple extraction methods that mimic rapid-onset fentanyl formulations.[3] Some authors even suggest that aerosolized fentanyl may cause sensitization and subsequent opioid addiction among anesthesiologists and surgeons.[4] The off-label use of OTFC (well more than 90% of the prescriptions written) and its abuse potential have been the cause of much concern and debate in the management of chronic noncancer pain.[5] Finally, the recent article by Passik et al.[1] has demonstrated that, even within the very structured confines of controlled studies, a significant number of aberrant opioid-related behaviors (11% of the 1160 patients included) still occur when prescribing rapid-onset fentanyl formulations for BTP (fentanyl buccal tablet in this study).

Our two cases were successfully managed with an open discussion of the issues involved, plus a customized opioid treatment agreement accepted by both patients, which included opioid rotation and monitoring performed by a specialist PC team. We believe that in the coming years the PC specialists in our country are going to be exposed, for the first time in their professional lives, to aberrant opioid-related behaviors associated with rapid-onset fentanyl formulations prescribed for BTP. We will certainly need to update our skills to properly screen our patients and perform risk assessments, and then monitor for aberrant behaviors. Tailored specific opioid treatment agreements and new pharmacological abuse strategies will have to be developed.[6]

We are in total agreement with other authors[5] that the solution to this challenging new problem is not to be found in curbing the availability of opioids (and more specifically, the new rapid-onset fentanyl formulations) but in the proper assessment and management of both pain and addiction.

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doi:10.1016/j.jpainsymman.2011.07.006

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