CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 6-2019: A 29-Year-Old Woman with Nausea, Vomiting, and Diarrhea

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PRESENTATION OF CASE

Dr. John A. Weems (Medicine): A 29-year-old woman was evaluated at a primary care clinic affiliated with this hospital because of nausea, vomiting, and diarrhea.

The patient had been in her usual state of good health until the day before presentation, when nausea, vomiting, diarrhea, fever, muscle aches, and a mild nonproductive cough developed suddenly. She had no sinus congestion, sore throat, shortness of breath, or abdominal pain. Over the telephone on the morning before presentation, she reported that her symptoms were severe and had prevented her from attending work. However, when she was evaluated later in the day by a provider at her primary care clinic, she reported that she had had spontaneous improvement in the morning and felt well on arrival at the clinic.

The patient had a history of exercise-induced asthma, gastroesophageal reflux disease, vitiligo, and genital warts. Two years before presentation, she had had negative screening tests for hepatitis C virus and human immunodeficiency virus. Fifteen months before presentation, she had received a diagnosis of influenza. During the months that followed, she had reported persistent bouts of fatigue and excessive sleepiness that had resulted in two motor vehicle accidents.

During the first event, which had occurred 13 months before presentation, the patient fell asleep while driving and her car crossed into the other lane, over the curb, and into an open space beside the road. She did not collide with any other vehicles or structures and had no trauma. During the second event, which had occurred 7 months before presentation, the patient collided with a turning vehicle. She did not lose consciousness, and the airbags did not deploy. After the crash, she had intermittent painful episodes of muscle spasms in her neck and low back that limited her range of motion. She was too fatigued to seek medical attention until the day after the collision.

The patient subsequently underwent evaluation at her primary care clinic. Her score on the Epworth Sleepiness Scale was 20, with scores ranging from 0 (low-

normal daytime sleepiness) to 24 (excessive daytime sleepiness). She was referred for a formal sleep study. In addition, she received prescriptions for naproxen and cyclobenzaprine and completed outpatient physical therapy, and her muscle spasms diminished.

The patient had not undergone any surgical procedures. Medications included omeprazole, varenicline, naproxen, and cyclobenzaprine. Hydrocodone–acetaminophen had caused nausea. The patient was adopted, and her family history was unknown. She lived in an urban neighborhood in New England with her daughter, brother, and sister. She worked two full-time jobs, as a school counselor and a bartender. She smoked one pack of cigarettes weekly and had done so for 17 years, and she reportedly drank two to three alcoholic beverages weekly.

On physical examination, the temperature was 36.8°C, the pulse 106 beats per minute, and the blood pressure 117/91 mm Hg. The weight was 63.5 kg, the height 170 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 21.9. The patient appeared to be well. She had no diaphoresis or rashes, needle marks, or scars. The pupils were equal and reactive, the mucous membranes were moist, and the abdomen was soft, with no tenderness on palpation. Results of liver-function tests were normal, and testing for urinary human chorionic gonadotropin was negative.

Just before the conclusion of the office visit, the patient reported a history of use of nonprescribed oxycodone–acetaminophen tablets and requested initiation of therapy with injectable intramuscular naltrexone. Urine toxicology screening was ordered, and oral naltrexone was prescribed. A follow-up visit was planned for 6 days later, but the patient did not complete the urine toxicology screening or return to the clinic for her scheduled follow-up. However, 2 months later, she requested a referral for psychotherapy because of increased symptoms of stress.

Four months after she requested the referral and 6 months after presentation, the patient was seen in the outpatient psychology clinic of this hospital, where additional history was obtained. She reported poor sleep, low energy, loss of interest in enjoyable activities, feelings of guilt, increased appetite, and a sensation that her legs were heavy and difficult to move. She also reported intermittent episodes of heightened energy, pressured speech, racing thoughts, and excessive spending. She had no history of hallucinations or thoughts of harming herself or others.

At the psychology clinic, the patient reported that she had begun to use illicit drugs — including marijuana, oral opioids, cocaine, and 3,4-methylenedioxymethamphetamine — when she was in middle school. She had continued to use multiple substances for 5 years but had abruptly discontinued when she became pregnant, at 19 years of age. She did not use illicit drugs for 8 years after the birth of her daughter but then resumed regular use of oral opioids 3 years before presentation, when she began to work at a bar where drugs were frequently available. Since then, she had used escalating amounts of oral oxycodone to satisfy increased cravings and prevent withdrawal symptoms.

The patient reported that she used 120 mg of oxycodone per day and spent approximately $3000 per month on oxycodone. She had missed work because of withdrawal symptoms, and she worried that she would lose custody of her daughter because of her drug use. She had never been hospitalized for opioid use or had an overdose. On several occasions, she had used nonprescribed buprenorphine, which had alleviated her withdrawal symptoms and cravings, but she had never tried buprenorphine treatment that had been prescribed by a health care provider. In addition, on several occasions, she had tried to initiate treatment with injectable intramuscular naltrexone but had been unable to abstain from opioid use long enough to receive the treatment. A plan was made for the patient to continue with outpatient cognitive behavioral therapy and mindfulness exercises, and a follow-up visit with her primary care physician was scheduled.

One month later, the patient was seen by her primary care physician. Oral-fluid toxicology screening was positive for oxycodone, buprenorphine, benzoylecgonine, and cocaine; testing of the saliva was negative for fentanyl. A diagnosis and management decisions were made.

DIAGNOSIS AND MANAGEMENT

Dr. Alexander Y. Walley: I am aware of the diagnosis in this case. This 29-year-old woman presented to her primary care clinic after she had symptoms

Table 1. Diagnostic Criteria for Opioid Use Disorder.*

Criterion	Characteristics of This Patient
Impaired control	
Patient has taken opioids in larger amounts or over a longer period than intended.	She used escalating amounts of oxycodone.
Patient has a persistent desire or has made unsuccessful efforts to cut down or control opioid use.	She made multiple attempts to cut down or stop oxycodone use by treating herself with diverted buprenorphine and seeking treatment with naltrexone.
Patient has spent a great deal of time on activities necessary to obtain and use opioids and recover from their effects.	She spent a substantial portion of her income on oxycodone and missed work because of withdrawal symptoms.
Patient craves or has a strong desire to use opioids.	She used escalating amounts of opioids in association with increased cravings.
Social impairment	
Patient's recurrent opioid use has resulted in failure to fulfill major obligations at work, school, or home.	She worried that she might lose custody of her daughter.
Patient continues to use opioids despite having persistent or recurrent social or interpersonal problems caused or exacerbated by their effects.	Unknown
Patient has given up or reduced participation in important social, occupational, or recreational activities because of opioid use.	Unknown
Risky use	
Patient has used opioids recurrently in situations in which it is physically hazardous.	She had multiple motor vehicle crashes that most likely occurred while she was intoxicated or in withdrawal.
Patient continues to use opioids despite having knowledge of persistent or recurrent physical or psychological problems most likely caused or exacerbated by their effects.	She had worsening mood disorder and physical injury from motor vehicle crashes.
Pharmacologic dependence†	
Tolerance, as defined by either of the following: a need to use a markedly increased amount of opioids to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of opioids.	She used escalating amounts of opioids in association with increased cravings.
Withdrawal, as manifested by either of the following: the characteristic opioid withdrawal syndrome, or use of the same (or a closely related) substance to relieve or avoid withdrawal symptoms.	She missed work because of withdrawal symptoms, and her current presentation is consistent with withdrawal.

* The criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5).[1] The presence of two or three criteria indicates a mild disorder, four or five criteria a moderate disorder, and six or more criteria a severe disorder.

† Persons who are receiving prescribed opioids may meet these criteria but would not necessarily be considered to have opioid use disorder.

consistent with opioid withdrawal syndrome, which had spontaneously resolved in less than 1 day. At the end of the visit, she requested injectable intramuscular naltrexone, and she later described a history that fulfilled criteria for severe opioid use disorder (Table 1).[1] The patient reportedly used approximately $100 worth of nonprescribed oxycodone per day and thus was at high risk for use of heroin and illicitly manufactured fentanyl, which are more potent, widely accessible, and less expensive. However, according to the history and results of urine toxicology screening, her opioid use disorder was limited to use of illicit oxycodone. Although the patient requested naltrexone treatment, she did not complete the urine toxicology screening or return to

the clinic for 6 months. I suspect that the patient had some ambivalence about treatment, which is common among patients with substance use disorder. Despite any ambivalence, the high mortality associated with opioid use disorder makes it imperative to find an effective treatment for this patient.

TREATMENT FOR OPIOID USE DISORDER

First-line treatment for this patient would be one of the three medications approved by the Food and Drug Administration (FDA) for the treatment of opioid use disorder: naltrexone, methadone, or buprenorphine. These medications lead to longer retention in treatment and decreased opioid use and opioid cravings. In a meta-analysis, methadone and buprenorphine were strongly associated with decreased rates of overdose and death from any cause.[2] In choosing the best medication for this patient, it would be necessary to have an understanding of not only the treatment-program requirements for each medication but also the patient's preferences and previous experience with these medications.

Naltrexone

This patient indicated a preference for naltrexone (an opioid antagonist). Oral naltrexone is available in generic form and is administered once daily as a tablet. However, meta-analyses have shown that oral naltrexone is no more effective than placebo in lowering the rate of opioid use or increasing the rate of retention in treatment.[3] Injectable intramuscular naltrexone is administered every 28 days by a health care provider and is effective in reducing opioid cravings and illicit opioid use. Prescribing naltrexone does not require special training or licensing, although prescribing injectable intramuscular naltrexone often requires prior authorization from an insurance company or collaboration with a specialty pharmacy.

The initiation of either injectable or oral naltrexone treatment precipitates withdrawal symptoms if the patient has not abstained from opioid use for several days before initiation. Of course, abstinence also causes withdrawal symptoms, which are a potent driver of continued substance use. Achieving the abstinence that is necessary to initiate naltrexone therapy is a major challenge; this explains the patient's unsuccessful attempts at treatment with naltrexone. If she again attempts to undergo treatment with naltrexone, how can she and her provider work together to increase the likelihood that she will continue to take the medication? Before the initiation of naltrexone treatment, the patient's withdrawal symptoms should be treated either in an inpatient detoxification unit or at home on an outpatient basis, with comfort medications, social support, and close follow-up.

Methadone

In contrast with naltrexone, methadone (a full opioid agonist) is not associated with a risk of precipitated withdrawal, so abstinence before the initiation of methadone treatment is not necessary. However, because methadone has a relatively long and unpredictable half-life, the treatment must be initiated carefully. An initial low dose and slow approach helps to ensure that the patient is not oversedated during the first several weeks. As a treatment for pain, methadone can be prescribed and dispensed in a manner similar to any other opioid pain medication, but as a treatment for opioid use disorder, methadone can be administered to patients outside the hospital only through an opioid treatment program that is licensed and regulated at the federal and state levels.

If this patient were hospitalized for a reason other than addiction, she could be treated with methadone for opioid withdrawal, and if on discharge from the hospital she were linked to an opioid treatment program, she could be treated with methadone for opioid use disorder.[4] Regulations for opioid treatment programs require patients to receive methadone daily at the clinic and to undergo weekly counseling, random toxicology testing, and medical and psychiatric assessment. Patients may earn "take home" doses after 60 days of documented abstinence and with perfect attendance of dosing and counseling appointments. Methadone treatment through an opioid treatment program is one potential option for this patient to consider.

Buprenorphine

Buprenorphine (a partial opioid agonist) can precipitate withdrawal if the patient has not abstained from opioid use for several hours before the first dose and has not begun to have with-

drawal symptoms. Like naltrexone, buprenorphine can be prescribed in any clinical setting, although to prescribe buprenorphine in an outpatient setting, a waiver must be obtained from the Drug Enforcement Agency after completion of additional training (8 hours for physicians and 24 hours for nurse practitioners and physician assistants). Buprenorphine is typically combined with naloxone in a sublingual or buccal formulation to reduce the potential for injection or diversion. A long-acting injectable buprenorphine formulation was approved by the FDA in 2018.

This patient had some experience with use of buprenorphine that had been obtained by illicit means. I would ask the patient whether she had any withdrawal symptoms, sedation, or dysphoria when she took buprenorphine; whether it was helpful in reducing her oxycodone use; and how well she functioned while she took it. If buprenorphine had worked well for her, then I would ask why she requested naltrexone rather than buprenorphine during her primary care visit. As agonist treatments, buprenorphine and methadone are often stigmatized as "trading one drug for another." This stigma undermines the clear evidence from multiple clinical trials that buprenorphine and methadone therapies can break the addiction cycle of compulsive use.

RISK FOR RELAPSE

Adherence to treatment is a major challenge for patients who receive any of these three medications. It is worth noting that patients who take methadone may have longer retention in treatment than those who take buprenorphine,[5-7] and patients who take buprenorphine have longer retention than those who take naltrexone.[7] In the first 4 weeks after discontinuation of these medications, there is a surge in overdose mortality,[2] which is driven by the high likelihood of relapse coupled with reduced tolerance. Before the initiation of naltrexone, methadone, or buprenorphine treatment in this patient, it would be crucial to explain to her that she is at very high risk for relapse and overdose if she discontinues the medication.

Regardless of the treatment that is chosen, this patient will need a strategy to reduce the risk of overdose in the event of relapse. Key elements of an overdose risk-reduction plan include use of opioids in the presence of others who are equipped with naloxone and can respond if overdose occurs; avoidance of additional sedative substances, such as benzodiazepines and alcohol; and administration of the opioid at the lowest possible dose and slowly to test its potency. In accordance with guidance from the Department of Health and Human Services, a naloxone rescue kit should be prescribed to this patient so that she can be prepared to respond to any overdose that she witnesses and can ensure that naloxone is available to anyone who is with her if she relapses.[8]

OPPORTUNITIES FOR IMPROVING CARE

This case shows several ways in which the care of patients with opioid use disorder can be improved. During the patient's previous encounters with the health care system, there were missed opportunities to discuss and diagnose her opioid use disorder. Although the U.S. Preventive Services Task Force has found insufficient evidence to support universal screening for substance use disorder,[9] screening was warranted in this patient on the basis of her history, which included multiple risk factors for substance use disorder, such as tobacco use disorder, underlying mood disorder, fatigue and daytime drowsiness, and motor vehicle accidents. Although overdose has replaced motor vehicle crashes as the leading cause of injury-related death in the United States, this case reminds us that a substantial proportion of motor vehicle crashes involve the use of substances — most commonly alcohol but increasingly other substances, such as marijuana and opioids.[10]

Effective screening can be accomplished with one question: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?"[11] In this patient, the answer to this question, followed by further exploration of the frequency of her substance use and the quantity that she used each time as well as exploration of the consequences of her use, could have allowed her providers to address her substance use disorder at an earlier stage. When the patient requested medication for opioid use disorder, she most likely had already met criteria for this diagnosis. However, it is useful to review the diagnostic

criteria with the patient to confirm the diagnosis and its severity (Table 1). The criteria will continue to be useful for monitoring this patient. As her condition improves, the number of criteria she meets will decrease, indicating reduced severity.

NEXT STEPS

This patient has at least two promising prognostic characteristics. First, she is seeking treatment and has sought treatment in the past. It is normal for patients with substance use disorder to have multiple episodes of attempted treatment and relapse, but over time, the relapse periods should shorten and the remission periods should lengthen. Second, she abstained from drug use for years after the birth of her daughter, which is a sign that she may be able to abstain in the future.

The patient is receiving care from primary care and mental health care providers. Who would best treat her opioid use disorder? Does she need specialty treatment? If she and her providers decide that methadone is the best option, then she will need to enroll in an opioid treatment program, which is typically separate from primary care and mental health care. If they choose naltrexone or buprenorphine, either treatment can be delivered effectively in the primary care or community mental health care setting. The patient should receive care in the setting in which she is least likely to discontinue treatment, thus minimizing her risk of relapse and overdose.

DR. ALEXANDER Y. WALLEY'S DIAGNOSIS

Severe opioid use disorder.

PATHOLOGICAL DISCUSSION

Dr. George Eng: In this patient, liquid chromatography–mass spectrometry of oral fluid was positive for oxycodone, buprenorphine, benzoylecgonine, and cocaine. Urine is a more commonly tested specimen type than oral fluid, since it can easily be obtained noninvasively, with the additional benefit that drugs of interest or their metabolites are often concentrated in it. However, urine testing for drugs of abuse is potentially complicated by deliberate manipulation of the specimen; adulteration, substitution, and dilution can all affect drug detection. Although an abnormal creatinine level, pH, or osmolality can suggest specimen manipulation, these measures are not entirely sensitive or specific.[12]

In addition, enzyme immunoassays of urine specimens are associated with substantial rates of false positive results. The nonspecificity of enzyme immunoassays can lead to interpretive difficulties when there is a need to distinguish between an opiate-containing treatment regimen and illicit opioid use. Thus, many laboratories use a two-step testing algorithm that consists of initial screening with enzyme immunoassays followed by confirmation with liquid chromatography–mass spectrometry.[13]

The use of oral fluid for drug testing is also a noninvasive technique and may mitigate the potential for specimen manipulation, since collection of the specimen is observed directly. Testing of oral fluid may be particularly useful in clinical practices in which the prevalence of specimen adulteration is high.[14] Such testing requires a higher degree of technical sophistication, may result in a longer turnaround time, and may not be widely available in local practice settings, but it is offered at reference laboratories.

In this patient, the results of oral-fluid testing confirmed her report of oxycodone use and further revealed evidence of nonprescribed buprenorphine use. In addition, there was evidence of recent cocaine use, including detection of the parent molecule cocaine and the metabolite benzoylecgonine. There was no detection of 6-monoacetylmorphine, a unique metabolite of heroin, or fentanyl, a common heroin adulterant; together, these findings suggest that she was not using heroin.

FOLLOW-UP

Dr. Sarah E. Wakeman: When the patient presented to her primary care clinic for a follow-up visit, she described her history of opioid use and again requested injectable intramuscular naltrexone. In further discussion, it became clear that she preferred naltrexone because of the stigma re-

lated to buprenorphine, which she had heard from friends in recovery and observed in meetings of mutual-help organizations.[15] Despite her initial preference for naltrexone, after she considered her unsuccessful previous attempts to use naltrexone and her successful experience with nonprescribed buprenorphine, she agreed to initiate buprenorphine treatment.

This patient's history of nonprescribed buprenorphine use is consistent with studies that have shown that the three most commonly reported reasons for use of diverted (nonprescribed) buprenorphine are to prevent withdrawal, to maintain abstinence, and to wean off opioids.[16] In addition, the outcomes associated with prescribed buprenorphine treatment are better among those who report a history of nonprescribed buprenorphine use than among those who have never taken buprenorphine.[17]

This patient was given instructions to start buprenorphine treatment at home, and close follow-up was arranged. Unobserved initiation of buprenorphine treatment, also called home induction, has been shown to be noninferior to in-office induction and offers more flexibility for patients and providers.[18] At the patient's next visit, she was connected to a recovery coach, who offered ongoing peer support. Although there is limited research regarding the effectiveness of recovery coaches in primary care, a qualitative study showed that patients with substance use disorder perceive the coach to play an important role.[19]

Because the patient had ongoing concerns about her ability to continue treatment with buprenorphine, she was initially hesitant to take doses of buprenorphine and naloxone of more than 8 mg and 2 mg, respectively. After initiation of treatment, her toxicology screenings were consistently negative for opioids but she continued to use cocaine intermittently. Eight months after initiation of treatment, she agreed to try increasing her doses of buprenorphine and naloxone to 12 mg and 3 mg, respectively, and her subsequent toxicology screens were negative for cocaine and all opioids. She is now in full, sustained remission. She is working full-time and parenting, and she continues to engage regularly with her medical team and recovery coach.

A Physician: Would you comment on how you determine when to involve child protective services in situations in which a parent has substance use disorder?

Dr. Wakeman: In Massachusetts, the criterion for mandatory reporting by a health care provider is having reasonable cause to believe that a child younger than 18 years of age is suffering from abuse or neglect. I apply this standard to my patients regardless of whether they have a substance use disorder. The parent's use of substances does not necessarily mean that the child is suffering from abuse or neglect. If I become aware of a circumstance in which a child is suffering from abuse or neglect, then I will report my concern. If I think that it is necessary to report, I disclose to my patients that I am reporting and why, so that they are aware, although this is not required in Massachusetts.

A Physician: At what point do you consider tapering treatment for opioid use disorder?

Dr. Wakeman: The decision to taper treatment should be initiated by the patient and should be based on the clinical scenario. Tapering therapy at less than 1 year typically results in recurrence of active opioid use. One of the longest observational studies of buprenorphine for the treatment of prescription-opioid use disorder, in which patients were followed for up to 42 months, showed that, although many patients elected to taper off buprenorphine during the follow-up period, the strongest predictor of abstinence at 42 months was continued buprenorphine treatment. Long-term treatment with buprenorphine has powerful benefits.[20] However, if a patient feels strongly about trying to taper treatment and has had a stable condition for years, I suggest beginning a slow taper. If cravings develop, the dose should be increased again. I emphasize to patients that the goal is not to be off the medication but to have what they need to stay alive and healthy.

FINAL DIAGNOSIS

Oxycodone and cocaine use.

This case was presented at the Harvard Medical School postgraduate course, "Primary Care Internal Medicine 2018," directed by John D. Goodson, M.D.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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