

## Prescription Drug Dependence and Evolving Beliefs About Chronic Pain Management

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This is the case of a woman whose addiction to prescription drugs lasted for more than 3 decades, causing deterioration of functioning and ultimately death. The course of her illness included over 20 inpatient hospitalizations for physical and emotional complications related to her substance abuse. The case reveals a great deal about the doctor-patient interactions involved because of the availability of virtually lifetime medical records, including two detailed independent psychiatric evaluations associated with insurance claims.

It also reveals how medical attitudes toward pain management shifted, making it possible for the patient to become dependent on high-dose prescription opioids, with lethal consequences.

### Case Presentation and Historical Perspective

Dr. Johansen: Ms. A was born the fourth of six children of Puerto Rican and Italian heritage. She described her mother as being very loving but overwhelmed by raising six children. She was a good child who never got into trouble. She received good grades and had a small circle of friends but was involved in minimal extracurricular activities in high school. She was not acquainted with her father until she was in the 10th grade as he had been in prison for 11 years for forging checks. He was emotionally abusive toward her after his return from prison.

After his return, she began to develop headaches that led to visits to emergency rooms, where she received injections of meperidine. This began her problems with addictive medications, which were to continue the rest of her life. She specifically recalled when she had a minor accident and received a pain shot that "put me to sleep for 2 days." She felt wonderful and had no worries or problems. Another incident she distinctly remembered was when she was newly married and her husband gave her an oxycodone-aspirin tablet for her toothache that had been prescribed for him. She found that the pill worked just as wonderfully as the injection. Thereafter, she persistently wanted to obtain medications to recapture the feeling she'd had while taking the medication.

Ms. A married at 18 to get away from her father. The marriage survived, but she described it as not happy, claiming that her husband never provided her with emotional support. Medical records reveal that he complained to her doctors on multiple occasions about her

prescription abuse, beginning early in the marriage. They had three children, but one died shortly after birth from a congenital heart defect. She felt guilty about this because she believed that it had happened because of the drugs she took during pregnancy.

She was a shy, attractive woman, and she later stated that medications were very easy for her to obtain from physicians. She worked off and on as a nurses' aide. By her early 20s, she was using amphetamines and benzodiazepines extensively. The amphetamines were prescribed for diet purposes, although she was never significantly overweight. Initially, Ms. A was careful not to use the medications at work, but she would carry a glass of water with her after work so that she could take her pill in the parking lot. She was arrested on at least two occasions for forging and altering prescriptions.

Medical records from the 1970s revealed that Ms. A received frequent prescriptions for opioids, diazepam, and sedatives from several doctors at the same time for complaints of headaches and back pain. At least one physician recognized this situation and refused to prescribe for her.

During a hospitalization for back pain, she was found to have smuggled in her own supply of a sedative drug (ethchlorvynol).

Dr. Streltzer: In the 1960s, the prevalence of drug abuse grew more than 10-fold by some estimates.

It infected the middle classes and the suburbs, and polysubstance abuse became widespread. Fear of drug addiction led to changes in physicians' prescribing habits for pain, minimizing the dose and frequency of narcotic medications, even for acute, severe pain. By the 1970s, studies showed that acute pain was commonly undertreated (1, 2).

With regard to chronic pain, it had long been known that some patients complained far out of proportion to objective findings. In the 1970s, multidisciplinary pain clinics were formed to address this problem, and they reported great success (3). They invariably detoxified patients who were opioid dependent, and it was these patients who were likely to be the successful cases (4, 5). In those days, patients who demanded several opioid pain pills daily raised a red flag for many physicians. This apparently occurred with Ms. A, but she maintained her addiction by seeing several doctors at once.

Dr. Johansen: During the 1980s, Ms. A obtained prescriptions for neck, hip, knee, and abdominal pain, in addition to her back pain and headaches. She had five medical hospitalizations, for medical and surgical complications of medication use, and two psychiatric admissions, during which she was detoxified, only to relapse shortly thereafter. She found physicians who did not

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know of her detoxifications and convinced them to prescribe narcotics for her various complaints.

From the records of the hospitalizations, I chose one illustrative of Ms. A's morbidity related to opioid dependence. She came to the emergency room of a community hospital complaining of severe pain of 5 hours' duration that radiated to her upper gastric and substernal areas, and she had additional complaints of chest pain and vomiting. During the examination, she was noted to be writhing, hyperventilating, and moaning. Her abdominal examination revealed upper gastric tenderness but no guarding or rebound. Of note, her current medications at the time of this emergency room visit included oxycodone-acetaminophen, one dose every 2–4 hours as needed for pain. She had been given a prescription for this 2 days earlier upon discharge from another hospital, following a lumbar sympathectomy for possible reflex sympathetic dystrophy. At that hospital, she had been receiving high doses of narcotic pain medication continuously until discharge. On the morning of discharge from that hospital, she had received three injections of meperidine, 100 mg; one of morphine, 10 mg; and two oral narcotic pills. She had also been receiving diazepam, 15 mg/day. She then used up her 10-day supply of pain medicine on the first day after discharge.

At the second hospital, the emergency room physician did an extensive workup for this abdominal pain. It included X-rays, laboratory studies, and an abdominal sonogram; the results were all normal. The impression was "nonspecific abdominal and chest pain," and the etiologies considered by this physician included a withdrawal syndrome and malingering. She was admitted for further evaluation, and the admitting physician's differential diagnosis included pancreatitis, bowel obstruction, acute spasm of the upper gastrointestinal tract, bowel perforation, and peptic ulcer disease. He noted a benign past history and did not mention the emergency physician's impressions. Both her doctor and the nursing staff noted Ms. A's frequent requests for opioid pain medication and also how her pain quickly resolved temporarily when she was given such medication.

The results of the workups for pancreatitis, obstruction, and other conditions were negative, but Ms. A's pain complaints and pain medication continued. A percutaneous cholangiogram produced negative results, but it perforated the gall bladder, causing bile peritonitis, which led to surgery and removal of Ms. A's gall bladder. Postoperatively, she had constant pain complaints, for which she received parenteral morphine, 10 mg, every 3 hours around the clock. After 1 week, she was switched to oral medication with a rapid decrease in opioid dose. She then complained of severe abdominal pain similar to the pain she had had at admission, with vomiting. An internist specializing in pain and addiction then consulted on the case. He started intravenous morphine with patient-controlled analgesia at 2–3 mg/hour, a new technique at that time, and it made her comfortable. She was discharged on a high dose of oxycodone. She later described this hospitalization as due to "toxic hepatitis" caused by the wrong prescription drugs. She was angry at the former prescribing doctor and was pleased with the new internist.

Over the next 6 months, despite the internist's notes promising to taper the narcotics, the dose reached 10 narcotic pills per day with clonidine, carisoprodol, and

lorazepam (to 6 mg/day) plus emergency visits for opioid injections. Her complaints of pain from her hip to her foot remained constant at a rating of 7–9 out of 10. The records document intermittent disorientation during this period.

Dr. Streltzer: During this period of time, the medical literature began suggesting the use of opioids chronically for persistent pain (6, 7). "Pseudoaddiction" emerged as a concept suggesting that addictive behaviors can result from undertreated pain, although this is based on a single case report (8). The use of opioids as maintenance treatment for pain remains a minority opinion, however.

In this case, the patient's physician had trouble saying no to her even though he initially planned not to maintain her on narcotics. Adverse complications of her narcotic use occurred. Some of her physicians did not know her true history, which she withheld and distorted, and she even received unnecessary and preventable surgery. Some physicians clearly recognized her problem with prescription drugs, resulting in two hospitalizations for detoxification, but each time she quickly relapsed by convincing other physicians that she was in acute pain and by continuously demanding and receiving narcotics.

Dr. Johansen: In the 1990s, the problems became more severe. She was referred to a methadone maintenance program by a pain specialist who refused to prescribe narcotics. She seemed to stabilize while taking 95 mg of methadone per day, but soon she was getting prescriptions from doctors again. She told one doctor that she was only using acetaminophen for pain when she was actually getting prescriptions for high doses of propoxyphene and oxycodone, in addition to methadone.

Dr. Streltzer: The physician who referred Ms. A to the methadone program told her that she was addicted to opioids and should be treated with methadone maintenance. She reluctantly accepted this because it was becoming very difficult for her to get physicians to prescribe the amount of opioids that she wanted. She was not the usual methadone patient in that she did not use heroin or illicit drugs, only prescription drugs. She liked taking methadone, and she no longer suffered withdrawal symptoms when she ran out of her pain medications, but it did not stop her from continuing to seek and obtain prescriptions. Her level of opioid dependence was now much higher because she took methadone plus her prescribed analgesics.

Dr. Johansen: For years, Ms. A had chronic difficulties with constipation and urinary retention due to her drug use. During a medical admission for pain complaints, an orthopedic surgeon unaware of her history performed emergency back surgery for cauda equina syndrome. She was discharged with prescriptions to take even higher doses of opioids than she had been taking before admission.

For the last few years of her life, Ms. A was treated by a senior psychiatrist who had an excellent reputation as a psychotherapist but who had not been known to treat patients with addiction problems or chronic pain. He prescribed freely for her and was apparently not aware that she would obtain prescriptions from other physi-

cians. She was arrested for impersonating a physician and writing narcotic prescriptions, and he wrote a letter for her in which he gave the diagnosis “pseudoaddiction” and stated that it was “inhumane” not to treat her chronic pain. Her husband reported that she often passed out because of her drugs. He had no faith in her current doctors, and he had only minimal contact with his wife.

**Dr. Streltzer:** Since the 1990s, the popular press has featured articles that call for the liberal use of opioids for chronic pain (9, 10). The scientific literature suggested that maintenance opioids might be helpful for some, but these were short-term studies using low doses (11, 12). Nevertheless, increasing numbers of clinicians became comfortable prescribing opioids chronically in large doses. Ms. A's life had become very constricted since she had become alienated from her husband and children and was unable to work. Despite this situation, it became easier for her to obtain prescriptions than in previous decades.

**Dr. Johansen:** One year prior to Ms. A's death, she was hospitalized for removal of a lump in her armpit that turned out to be a benign enlargement of a lymph node. Postoperatively, she was unusually lethargic. Prescription bottles of oxycodone, propoxyphene, diazepam, and methadone were found in a bedside drawer.

Eight months before her death she had an independent psychiatric consultation related to an old insurance claim for a work-related back injury. She acknowledged that she was an addict and that she often did not remember whether she had taken her pills and would take more. She reported often passing out. All her time was taken up in obtaining and using pain pills. She stated that she had no difficulty getting doctors to give her prescriptions, but she tried to control her addiction by not filling all the prescriptions. She said she knew that she really needed to be treated firmly, but her doctors would comfort her and make excuses for her. She insisted she was ready to cut down.

Her psychiatrist was contacted, but he insisted that he was treating her with the minimum dose of medications necessary for her intractable pain and was monitoring her for “signs of addiction.”

Eight months later, she was found dead. An autopsy revealed that she had died from the toxic effects of methadone, propoxyphene, oxycodone, and benzodiazepines, all of which she had been taking by prescription in large doses.

## Discussion by Dr. Streltzer

Despite the lack of long-term studies, promotion of opioid treatment for chronic pain seems to have become a medical subculture by this time (13). The following belief system develops: opioids do not cause tolerance if pain is present, and they remain effective; only opioids can treat significant pain; central sensitization explains pain in the absence of objective findings; the patient who complains of pain and wants opioid therapy will benefit from such; if the patient becomes dependent on the opioids but is not an “addict,” then this dependence is not a problem; some patients require ultrahigh doses to control pain. These be-

liefs allowed well-meaning physicians to be convinced by Ms. A to prescribe continuous high-dose narcotics.

None of these beliefs is supported by solid evidence. In fact, findings increasingly refute the safety and efficacy of opioids when taken regularly for sustained periods of time, especially in high doses, and furthermore, enhanced pain sensitivity is likely to develop (14). We are familiar with the dangers to patients of maintenance treatment with high-dose steroids. The effect on an individual changes over time as the body makes adaptations. A similar situation occurs with long-term opioid use.

Tolerance and desensitized opioid receptors develop in response to chronic opioid administration, and this has been termed “the cascade of cellular adaptation” (15). Sophisticated animal studies reliably demonstrate that chronic morphine administration causes both tolerance to its analgesic effects and also increased pain sensitivity (16, 17). The mechanisms are multiple and overlapping (18–20) and include a diverse array of structures and peptides: substance P (21), glial cells (22), *N*-methyl-D-aspartic acid (NMDA) (23), cAMP (24), alpha calcitonin gene-related peptide (CGRP) (25), orphanin FQ/nociceptin (26), serotonin (27), cholecystokinin (28), and several others. Chronic morphine administration increases the level of dynorphin, a kappa opioid agonist, in the dorsal horn of the spinal cord (29). Dynorphin is associated with increased pain (30). The presence of an ongoing painful condition does not prevent the rapid and profound development of opioid tolerance (31, 32), as has sometimes been claimed. It has become clear that enhanced pain sensitivity is a response to chronic morphine administration and is not just due to brief withdrawal effects when blood levels fall (33).

Viewed from another perspective, chronic morphine administration produces changes in the nervous system that lead to hyperalgesia, and these are the same changes that occur when nerve injury leads to hyperalgesia (34)! In recent years, the evidence that chronic opioid administration causes changes leading to hyperalgesia in animals has been consistent and convincing at the molecular, cellular, physiological, and behavioral levels. This is likely also true for humans, with individual variation. Indeed, we know that patients receiving maintenance treatment with high-dose methadone for heroin addiction are not protected from pain but demonstrate enhanced pain sensitivity, both experimentally (35, 36) and clinically.

Chronic nonmalignant pain often appears to be a condition in and of itself, with no clear reason why some people suffer greatly from it and others with similar objective medical findings do not. Many nonspecific treatments are available, including physical therapy, massage therapy, biofeedback, transcutaneous electrical nerve stimulation, nerve blocks, steroid injections, psychotherapy, and numerous medications. All of these treatments work for some people, but none is likely to work for the opioid-dependent patient.

Cancer pain is often treated with opioids, and they are effective and rarely a problem. This is because most can-

cer pain is time limited because of either beneficial treatment or a terminal course. Persistent, or long-term, cancer-related pain can be a problem if managed with opioids in high doses owing to tolerance and hyperalgesia, similar to that with chronic nonmalignant pain. When the cancer is stable or in remission, persistent pain is best managed by eliminating opioids and using nonopioid analgesics, often with psychotherapeutic support.

A treatment model for the opioid-dependent pain patient has been proposed (37) and shown to be successful (38). It involves education as to why chronic opioids are likely to maintain pain, detoxification, treatment of pain with nonopioid analgesics, psychological support, coordination of care, and promotion of healthful behaviors. As seen in this case, detoxification alone is rarely sufficient. The psychology of drug dependence is powerful and must be taken into account.

In addition to being ineffective, chronic opioid treatment of pain is associated with substantial risks, including unnecessary invasive procedures and tests, accident proneness, adverse health consequences, impaired judgment and cognitive function (39), a decline in occupational and social functioning, and strained family relationships.

Prescription of opioids and prescription drug abuse have risen exponentially in the last several years (40, 41). Unfortunately, deaths from prescription opioids are also rapidly increasing (42). We hope that learning about this tragic case will help prevent these problems in the future.

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