

News & Views in ...

Opioid therapy



NEWS



A series of recent articles and editorials have closely examined chemical dependency and recovery in patients and physicians. The articles offer a crucial overview of the challenges of this timely subject, including the potential tragedies of prescription chemical addiction and abuse.

INTERVIEW



Reviewing addiction to prescription painkillers among patients and physicians

RESEARCH HIGHLIGHTS



According to Steven Passik (Department of Psychiatry and Behavioral Sciences at the Memorial Sloan-Kettering Cancer Center, New York, USA) in the article '*Issues in long-term opioid therapy: unmet needs, risks, and solutions*', addiction to and abuse of prescribed opioids is indeed prevalent, and exacts an immense toll on patients, doctors and society.

Opioids work by binding to receptors in the nervous system and gastrointestinal tract, and decrease the perception of and reaction to pain. However, there are various side effects, including sedation, constipation and respiratory depression. Physical dependence will also develop whilst opium consumption is ongoing, leading to uncomfortable withdrawal symptoms when the medication is taken away abruptly. The reason for abuse of opioids is due to the feeling of euphoria that they can induce and the terrible symptoms of discontinuation.

William Lanier, editor-in-chief of *Mayo Clinic Proceedings*, believes that the recent expanding interest in opioids comes from five different sources: expansion and innovation in methods of drug delivery; advances in the design of these drugs; pain relief as a fundamental human right and increased public awareness of pain management options and the appropriateness of aggressively treating pain as the 'fifth vital sign'; growing recognition of the serious consequences of opioid misuse, misadventure and addiction; and medicolegal aspects of practitioners' prescribing practices and legal consequences for under- or overprescribing.

As well as patients with chronic pain, anesthesiologists have the highest risk of opioid abuse and dependence among healthcare providers. Sedation nurses and nurse anesthetists are also in the high-risk group for healthcare providers. Michael Oreskovich from Washington Physicians Health Program in Seattle (WA, USA) and Ryan Caldeiro from the Department of Psychiatry and Behavioral Sciences at the University of Washington (WA, USA) discuss these groups in an article entitled, '*Anesthesiologists recovering from chemical dependency: can they safely return to the operating room?*'

According to Dr Passik, healthcare professionals who are helping patients with chronic pain must balance aggressive treatment with the requirement to minimize risks of abuse and misuse. Charles Argoff and Daniel Silvershein from the Department of Neurology at Albany Medical College (NY, USA) note that the management of chronic noncancer pain, for example, requires comprehensive assessment of each patient; the establishment of a structured treatment regimen or program; ongoing reassessment of the pain condition and the response to therapy; and a continual appraisal of the patient's adherence to the treatment. The importance of understanding the metabolism of opioids in individual patients is also stressed.

It has been pointed out that keen awareness by families and friends of potential addiction is vital for those who might be at risk. This includes doctors, other healthcare providers and the general public. It



is important that families, friends and colleagues confront any suspected addiction or abuse, as there is potential harm to patients as well as themselves. Keith Berge and his colleagues from the Mayo Clinic suggest that healthcare facilities should have

written policies and procedures in place that will assist when these emotionally charged situations surface.

It is hoped that novel opioid formulas that are in late-stage development will minimize abuse. They are designed to diminish euphoric effects and possibly reduce misuse. All the authors concur that responsibility, expertise, insight, diligence and compassion are among the elements that can meet the challenges of opioid use for pain management.

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Sources: Passik SD: *Issues in long-term opioid therapy: unmet needs, risks, and solutions.* Mayo Clin. Proc. 84(7), 593 (2009);

Oreskovich MR, Caldeiro RM: *Anesthesiologists recovering from chemical dependency: can they safely return to the operating room?* Mayo Clin. Proc. 84(7), 576 (2009);

Argoff CE, Silvershein DI: *A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs.* Mayo Clin. Proc. 84(7), 602 (2009);

Berge KH, Seppala MD, Schipper AM: *Chemical dependency and the physician.* Mayo Clin. Proc. 84(7), 625–631 (2009).

Possible safety risks for methadone maintenance treatment patients

Researchers from Boston Medical Center (MA, USA) have discovered that there are possible safety risks among methadone maintenance treatment (MMT) patients owing to the quantity and accuracy of medical record documentation. It is thought that better communication and coordination among substance use treatment and medical providers could mitigate the adverse effects of methadone and interacting medications.

Typically provided separately from medical care, MMT is a chronic therapy for opioid dependence, a chronic relapsing disease that often requires lifelong treatment. The ideal situation is that when a patient in MMT begins outpatient or inpatient care, the doctors are aware of MMT and note down both methadone on the medication list and opioid dependence on the medical problem list. If this is not done then there is a chance that medication–methadone interactions can take place, which may contribute to adverse events such

as decreased cognitive function, cardiac arrhythmias and overdoses.

The aim of the study was to identify safety risks in MMT patients who were in medical care by assessing the frequency that opioid dependence and MMT documents were missing in medical records and characterizing potential adverse drug interactions.

Opioid-dependence documentation was absent from the medical record in 30% of subjects; MMT documentation was missing from either the last discharge summary or last primary care note in 11% of subjects; among subjects seen by a primary care doctor, MMT documentation was lacking in 7%; and in those discharged from the inpatient hospital, MMT documentation was missing in 10%. A total of 69% of study participants were taking at least one medication that could possibly interact with methadone, and 19% were taking three or more potentially interacting medications.

“Among patients receiving MMT and medical care at different sites, documentation of opioid dependence and MMT in the medical record occurs for the majority, but is missing in a substantial number of patients,” explains lead author Alexander Walley, general internist in the Clinical Addiction Research and Education Unit at Boston Medical Center and assistant professor of medicine at Boston University School of Medicine. “Most of these patients are taking prescribed medications that potentially interact with methadone. This study demonstrates opportunities to improve communication, care coordination and patient safety among patients receiving medical and substance use treatment.”

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Source: Walley AY, Farrar D, Cheng DM, Alford DP, Samet JH: *Are opioid dependence and methadone maintenance treatment (MMT) documented in the medical record? A patient safety issue.* J. Gen. Intern. Med. 24(9), 1007–1011 (2009).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine. If you have newsworthy information, please contact:

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Onsolis™ approved for breakthrough pain

Onsolis™ (fentanyl buccal soluble film) has recently been approved by the US FDA for the treatment of breakthrough cancer pain. Onsolis delivers an opioid drug termed fentanyl via an absorbable film that adheres to the inside of a patient's cheek.

Pain can be caused by cancer or can present as a side effect of the disease. If this pain is not managed correctly, it can have a significant effect on an individual's quality of life. Opioids are selected to treat chronic pain in many cancer sufferers, but they continue to experience flares of pain referred to as breakthrough pain. This can become intensely painful within just a few minutes, and opioids can take up to an hour to take effect.

The new drug is designed to act more rapidly and is presently indicated for treatment of patients over the age of 18 years, who have developed tolerance to the more classic opioid therapy.

Like other opioids, Onsolis can be abused and was approved with a Risk Evaluation and Mitigation strategy, which is needed for managing risks associated with a drug. A warning label is attached to the medication indicating that it is not suitable for other pains including migraines, dental pain or post-operative pain.

The drug will only be available via a restricted distribution program called the FOCUS program. Only pharmacies and prescribers who are registered will be able to prescribe the drug to patients. A counseling call to educate patients will be required before they can receive the drug and it will be sent directly to their home.

Source: FDA News Release. July 16, 2009. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm172366.htm.

"The new drug is designed to act more rapidly and is presently indicated for treatment of patients over the age of 18 years, who have developed tolerance to the more classic opioid therapy."

Stop selling illegal narcotics: the US FDA sends a warning to drug companies

The US FDA has warned nine companies to end the production of 14 narcotic painkillers that have not received regulatory approval. An estimated 2% of prescription drugs reach the market without approval, and most of these are generic variations of other drugs already being marketed.

Each of the targeted drugs highlighted in the recent warning letters are morphine relatives. They are either immediate-release, fast-acting morphine, hydromorphone or oxycodone pills, or highly concentrated liquid forms of morphine. The drugs under scrutiny either did not go through the approval process or were introduced before the US FDA had ruled on the applications to approve them.

The US FDA has cautioned that because of the euphoric feelings that opioids produce and because tolerance and dependence is easily developed, the abuse potential is very high. Side effects can include impairment of motor or cognitive

skills, and overdose or other improper use can cause serious injury or illness. In severe cases, death can occur from heart attack or cessation of breathing.

None of the drugs were recalled, but the warning stated that the companies in question have 60 days to stop manufacture of the products and 90 days to cease shipments. Not complying with this may result in fines or seizure of the drugs.

"We estimate there are several hundred unapproved drugs out there," states Deborah Autor, director of the office of compliance within the US FDA's Center for Drug Evaluation and Research.

"We will continue to take aggressive action against those firms that do not have the required FDA approval for their drugs ... warning letters are another demonstration of our commitment to remove illegal, unproved drugs from the market."

Source: FDA www.fda.gov

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Abrupt opioid withdrawal increases pain sensitivity

Experiments from a recent study have now demonstrated that the abrupt withdrawal of opioids may increase pain sensitivity. This is thought to be caused by a memory-like process, the long-term potentiation (LTP) of synaptic strength in the spinal cord. The study also discovered ways to avoid this effect.

A research project, carried out by the Department of Neurophysiology at the Center for Brain Research at the Medical University of Vienna, Austria, has attempted to explain the excessive increase in pain sensitivity experienced by patients who stop receiving treatment.

The abrupt withdrawal of opioids results in LTP of synaptic strength in the pain pathways of the spinal cord. LTP is a physical mechanism in the brain for memory and learning. Activity-dependent increases

in transmission between synapses can be long-lasting. Pain stimuli, for example, may trigger LTP, creating a long-lasting 'pain memory'. The researchers at the Medical University of Vienna have now proven that opioids are able to leave this kind of 'memory' in the pain system when they are taken away abruptly.

The team deciphered the molecular mechanisms of the process, and was able to demonstrate that abrupt withdrawal can increase the concentration of calcium in the nerve cells of the spinal cord, much like a pain stimuli.

Calcium ions are known to be important messengers that can cause LTP. They move into the nerve cells of the brain through NMDA receptor channels. The theory was that if the channels were blocked, then LTP would be prevented.

"To test our theory, we used selective blockers that only close off NMDA receptor-type calcium channels," explained the project manager, Prof. Sandkühler. The results demonstrated that the blockers (also available as drugs) reliably prevented LTP on the withdrawal of opioids. "However, the blocker has to be administered in good time before the start of the withdrawal," noted Sandkühler.

Another significant finding was that if opioids are reduced gradually and in a controlled way, instead of being taken away abruptly, LTP can be prevented and so can the withdrawal symptoms.

Source: Drdla R, Gassner M, Gingl E, Sandkühler J: Induction of synaptic long-term potentiation after opioid withdrawal. *Science* 325(5937), 207-210 (2009).