Opiates In Litigation: Risk of Death and Addiction

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I. Introduction

Opiates are primarily used for treatment of pain. Opiates join with opiate receptors in the body and provide analgesia. Morphine is considered the primary opiate and the other opiates are compared to Morphine for potency and pharmacokinetics. Opiate receptors are throughout the body and a primary site of opiate induced action occurs in the brain. Hardman & Limbird, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 569-620 (10th ed 2001).

The primary opiates include morphine, methadone, hydrocodone and oxycodone. Opiates therapy may be administered in tablet form by mouth. This is usually the route of therapy for non- malignant pain. However, therapy can also be provided by patches, such as Duragesic patches which release the opiate fentanyl. Also, opiates can be administered intravenously in a hospital setting, usually for malignant pain. Additionally, opiates can be administered by an intrathecal pump directly into the spinal cord for outpatient treatment of spinal pain. Most of the cases that you will like encounter will involve prescribed opiate tablets. J. Loeser, Bonica's Management of Pain, 1682 - 1709 (3d ed. 2001).

Actionable injuries from overprescribing of opiates include death and addiction. Addiction became recognized as a serious problem during the heyday of Oxycontin prescriptions. Addiction is a recognized injury to the brain and will be discussed below. Death usually results from respiratory depression.

Most deaths occur while the patient is sleeping. The opiates depress the brain stem's actions to the point that the brain stem stops signaling the body to breath when carbon dioxide levels increase. Once breathing stops, the brain swells, the lungs can become congested and the person dies from lack of oxygen. Deaths from opiates, particularly methadone, have increased dramatically in recent years as methadone has been more often used for analgesia. U.S. Dept. of Health and Human Services, Methadone-Associated Mortality: Report of a National Assessment (2004) available at http://dpt.samhsa.gov/reports .

There are some basic characteristics of opiates that must be considered. These include tolerance, equianalgesia and elimination half-life. An understanding of these characteristics is important to liability and causation.

A. Tolerance

Patients treated with opiates may become tolerant to the effects of the opiate. This means that more and more opiate is needed to provide the same level of pain relief. Tolerance is the primary reason that greater and greater amounts of Oxycontin were prescribed for many patients. When a patient becomes tolerant to an opiate, he usually experiences less side effects.

Some doctors stop opiates when their patients become tolerant to increasing larger doses; this is known as a drug holiday. Other doctors switch their patients to different opiates; this is known as opiate rotation. Switching to a different opiate may create a problem because opiates are not completely cross- tolerant. In other words, a patient who has become tolerant to the

oxycodone in Oxycontin, is not likely completely tolerant to methadone.

Incomplete cross- tolerance is the result of the different chemical make up of the various opiates. Different opiates act on different opiate receptors and in different ways; their pharmacodynamics are different. Therefore, when someone is switched to a different opiate, he may experience serious side effects such as respiratory depression, that he did not experience on the prior opiate.

B. Equianalgesia

Just as not all opiates provide complete cross- tolerance to other opiates, not all opiates have the same potency. There are several published guidelines that address the potency of the various opiates. Some of them use morphine as the baseline for comparison. While the guidelines are not all identical, they are congruent. Methadone is always considered more potent than morphine. In other words, the tables show that less methadone needs to be administered to obtain the same pain relief provided by morphine. *See* Bonica's *supra*. at 1697;

The most well known equianalgesic chart is published by the American Pain Society. APA, Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain (5th ed. 2003) www.ampainsoc.org. Also, the Oregon Health Science University publishes a guideline that is available on line. OHSU, Guide to Prescribing Opioids for Chronic Non-Malignant Pain http://www.ohsu.edu/ahec/pain/painmanual.html. The U.S. Veterans Administration also publishes method for determining equianalgesic doses. http://www.oqp.med.va.gov/cpg/cot/G/OT_about.htm

C. Elimination Half-life

The elimination half-life is the length of time that occurs from point of administration to the point when a drug's plasma concentration is reduced by 50%. The elimination half-life should be distinguished from an analgesic half-life, which pertains to the amount of time that analgesia is provided by a drug. The difference in elimination half-lives of the various opiates is important because the side effects may be dependent on the elimination half-life rather than the analgesic half-life. The risk of an adverse event can remain even after the analgesic qualities have stopped.

Different opiates stay in the human body longer than others. Different opiates are metabolized differently; their pharmacokinetics are different. There are short half-life opiates and long half-life opiates. This difference is crucial for methadone, which has a very long half-life. When a patient is switched from a short half-life opiate, such as oxycodone, to a long half-life opiates, such as methadone, much care in the initial dosing must be exercised because of the likelihood of a serious adverse event, such as death from respiratory depression. This risk is well recognized and may account for the increased number of reported deaths from use of methadone as an analgesic. Dept. of Health and Human Services, Methadone-Associated Mortality: Report of a National Assessment (2004) available at http://dpt.samhsa.gov/reports. The various half-lives of the different opiates are readily available in guidelines and texts.

II. Liability

Liability for the over- prescribing of opiates usually presents as a professional malpractice action. A number of product liability cases were filed in the past against the manufacturer of Oxycontin, Purdue Pharma, but the litigation has not been a success story. One of the primary obstacles to proving product liability is that the risks of opiate therapy are well known. The learned intermediary defense is formidable.

To determine whether a doctor has over- prescribed opiates, you should obtain your clients medical records from the prescriber and the pharmacy records. If the prescriber has a reputation as a liberal prescriber of pain medications, then you may enjoy the benefit of a DEA investigation. Opiate prescriptions are subject to federal regulations. Usually, the prescriptions cannot be called into a pharmacy. The doctor must see the patient. This type of over-prescribing can lead to addiction.

One of the primary defenses in an addiction case is the behavior of the patient. If the patient is drug seeking and is getting multiple prescriptions from different doctors and filling the prescriptions at different pharmacies, then it is unlikely that any of the prescribers can be shown to be at fault.

Failure to determine the initial equianalgesic dose, with a consideration for the half-life of the new opiate, may creates liability in a death case. For instance, consider a patient who has been prescribed 80 mg of oxycodone daily [20 mg four times a day] for a year. He has become tolerant to the oxycodone, which has a short half-life of 4-6 hours, which is why the oxycodone has been prescribed four times daily. If the doctor switches the patient to 80 mg of methadone [20 mg four times a day], he has overdosed the patient and placed him at risk of death from respiratory depression.

The risk of death is the result of two differences between methadone and oxycodone. First, the methadone is more potent than oxycodone. They two are not equianalgesic. Most texts and guidelines show that methadone is at least 50% more potent that oxycodone. Second, methadone has a much longer half life than oxycodone. Oxycodone's half life is 4-6 hours. Methadone's half life is variable among individuals, but an accepted average half-life is 24 hours. Therefore, with each dose of methadone, the methadone in the blood plasma continues to increase in a stair step fashion until it reaches a steady state, which usually takes between 5 - 7 days because of its long half- life. Since oxycodone does not provide complete cross- tolerance to the methadone, the patient is seriously at risk during this first week of treatment.

According to the guidelines, the dose of methadone should have been about half to one third the dose of oxycodone because of the greater potency of methadone and to allow for a safe level of methadone accumulation during the first week. This safety factor is necessary because the patient's body is methadone naive, although not opiate naive, because the patient has not taken methadone before and so has not developed a tolerance to methadone.

III. Damages

A. Addiction

An addicted brain is a changed brain. The cells of an addict's brains are fundamentally changed. Drugs can change the brain to produce unconscious and uncontrollable compulsive behavior, which is the essence of addiction. Addiction has been compared to diseases such as diabetes and heart disease. However, as a disease of the brain, addiction disrupts a person's mechanisms responsible for generating, modulating and controlling

cognitive, emotional and social behavior. *See* A. Leschner, "What We Know: Drug Addiction is a Brain Disease," Principles of Addiction Medicine, (2d ed. 1998).

Another brain disease is Alzheimer's disease. Alzheimer's decreases a person's cognitive abilities because of deterioration of the brain. The behavioral consequences of Alzheimer's are readily observable. Alzhiemer's causes a change in the neurobiology of the brain. Addiction also changes the neurobiology of the brain. Addiction causes compulsive behavior.

Rats, mice and monkeys have been studied who could self-administer habit forming drugs. The animals became addicted and began to seek the drugs rather than sleeping or eating. When the drug was taken away for a period of time, the animals did not forget the experience. They labored for the drug as soon as it became available again months later.

Additionally, when a certain neurotransmitter receptors were removed from mice, they did not become addicted. This study emphasizes the biological basis of the dopamine system as a cause of addiction. A. Lingford-Hughes & D. Nutt, Neurobiology of Addiction and Implications for Treatment, Brit. J. Psychiatry (2003) 182, 97-100. Changes in the human brain have been shown with neuroimaging studies such as functional MRI's and PET scans. *Id.*

The molecular target of most addictive substances have been identified. *See* E. Nestler, "Historical Review: Molecular and Cellular Mechanisms of Opiate and Cocaine Addiction," Trends in Pharmacological Sciences, 25:4 at 210 - 218 (April 2004). Different areas of the brain are responsible for different activities and behavior. Behavior is the result of electrical and chemical activity in the brain. Dopamine is responsible for some of this activity. For instance, Parkinson disease is the result of chronically depressed dopamine levels. Addiction behavior is also the result of dopamine levels. See E. Nestler and R. Malenka, "The Addicted Brain", Scientific American, 79-85 (March 2004). Addiction is the result of permanently changed dopamine levels.

The mesolimbic dopamine system, also referred to as the reward system, of the brain is composed of several different areas of the brain that work together. The system triggers biochemical systems that reward people with feelings of pleasure when they engage in activities that promote basic life functions such as eating and sex. Components of this system include the prefrontal cortex[PFC]; the ventral tegmental area[VTA]; the nucleus accumens[NA] and the locus ceruleus[LC]. T. Kosten & T. George, "The Neurobiology of Opiod Dependence: Implications for Treatment", Research Reviews - the Neurobiology of Opioid Dependence, Science and Practice Perspectives 13- 21 (July 2002).

Not all people who take opiates become addicted. However, a large subset of the population is vulnerable to addiction. Opiates are particularly good at causing addiction. Treatment for opiate addiction may require that the patient be placed on a permanent methadone regimen.

B. Death

An autopsy with toxicology is necessary to prove death from an opiate overdose. The physical autopsy is expected to have non- specific findings such as would be found from any hypoxic event. The brain may be heavy from swelling, the lungs may be congested. Methadone of some level must be found in the blood. Hopefully, femoral blood is taken since it avoids any issue of postmortem redistribution. If tissue is sampled for toxicological testing, the liver is

usually the best organ to test. If high levels are found in the liver, then the blood levels may not be crucial. A commonly used forensic text discusses therapeutic and toxic levels of opiates and other drugs. Baselt, Disposition of Toxic Drugs and Chemicals in Man (7th ed. 2004).

Your investigation must first establish if the patient intentionally overdosed. This should be apparent from the blood levels. Although testing is unable to determine exactly how much drug a patient may have taken and when he took it, testing can show that the blood levels are not extraordinarily high. If the levels are extraordinarily high, then the patient may have intentionally overdosed himself.

Blood levels are a clue to what has happened and may not tell the whole story. For instance, the therapeutic levels of methadone overlap with the recognized lethal levels. Due to the individual variation in the metabolism of methadone as well as the difference in developed tolerance, a lethal level to one person may be a therapeutic level for another. In a methadone death case, the amount of time that the patient has been on the methadone may be the most important fact. Most methadone deaths occur within the first week of treatment initiation.

The pill bottle should be collected in an effort to determine how many tablets the patient has taken. Often, law enforcement will investigate the scene and collect the pill bottles, count the pills and make a report. Of course the pharmacy and medical records must be examined. Any testimony from witnesses who saw the patient fill and take his prescription will be helpful. Any testimony on the patient's behavior before his death, such as nausea and/or grogginess will be helpful to show that the patient was overmedicated.

Other medications that may have contributed to the death and must be investigated. For instance, benzodiazapines such as Xanax are contraindicated for use with most opiates because they use the same metabolic pathway and enhance the sedating effects of opiates. Anti-anxiety medications and antidepressants are often prescribed for chronic pain patients. You can expect an imaginative defense based on an adverse drug reaction with any other drugs that the patient was taking at the same time as his death.

Conclusion

The medical literature is growing in the area of opiate risks. Oxycontin, with its addictive properties at the high doses at which it was being prescribed, had the spotlight five years ago. Methadone, with its unpredictable long half-life is now under more scrutiny.

Methadone is being prescribed more often for analgesia because it is cheaper and can provide longer analgesia than the short half-life opiates. However, these benefits come at a risk. The unwary doctor who fails to consider the long half-life of methadone places his patient at great risk, particularly during the first week of treatment.