Straight Tox

Methadone: Old Drug, New Challenges

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Introduction

The late Professor Randy Pausch began his *Last Lecture* with the statement, "My father always told me, 'If there is an elephant in the room, introduce them.'" With that in mind, I would like to introduce you to the toxicological elephant in the room, the fact that there has been a huge increase in methadone-related deaths over the past ten to fifteen years. No introduction is really necessary, is it? Forensic toxicologists are quite aware of this trend, but for the most part, we haven't discussed it much, at least publicly. The media has reported on these deaths at length, but as they often do, fail to actually understand them, and more often than not, they simply cloud the issue. I read an article recently with the following quote: "(Methadone) is killing people at therapeutic doses!" I want to ask, "Therapeutic for whom? Obviously not the patient who died." Or perhaps the question, "What exactly is the therapeutic range versus toxic or even lethal range for any opioid?" As forensic toxicologists we know we must consider many issues when interpreting opioid concentrations surrounding a death: What was the goal of the opioid therapy; analgesia, narcotic replacement? What was the likely tolerance of the patient? Did the patient have any co-morbidities? Was the patient taking other medications? To name but a few. These issues notwithstanding, the fact remains, the number of methadone-related deaths has skyrocketed.

Those of us who have investigated or studied many of these deaths can probably recite the circumstances surrounding the death even before reading the report: The decedent usually has begun using methadone within the last 5 to 7 days, was observed to be sleeping and "snoring loudly" prior to being found dead with, often profuse, pulmonary edema. There is also a good chance that a benzodiazepine was involved as well.

To be quite candid, I am afraid toxicologists may be somewhat reticent to speak publicly about this trend for fear that our words will be taken out of context by some attorney the next time we testify about a methadone death. This fear is not unfounded. I too have been called upon to testify in disputes involving both sides of the civil litigation arising from these deaths. It is for this reason that I feel it prudent at this point to issue this disclaimer:

> ***Every case is different, with differing: dose, patient tolerance, co-morbidities, drug interactions, physical circumstances, etc. No attempt has been made by***

the author of this article to provide an exhaustive treatise on the complex subject of methadone, pharmacology, use, abuse, toxicity, or death.

History

Methadone was first synthesized by German scientists during World War II after the United States and their allies cut off the opium supply to Germany. The synthetic opioids meperidine and propoxyphene were also developed during this time. Methadone was given the trade name, "Dolophine". A common misconception, or urban legend, about Dolophine, was that it was named in tribute to Adolf Hitler, evolving from the original name, "Adolphine". This is untrue. The name Dolophine was derived from the Latin root "dolor," meaning pain, and was actually named by the American branch of Eli Lilly, after the war.

Methadone was brought into the United States in 1947, and for the most part, until recently, has been used primarily as a treatment for narcotic addictions, mostly involving heroin.

Pharmacology

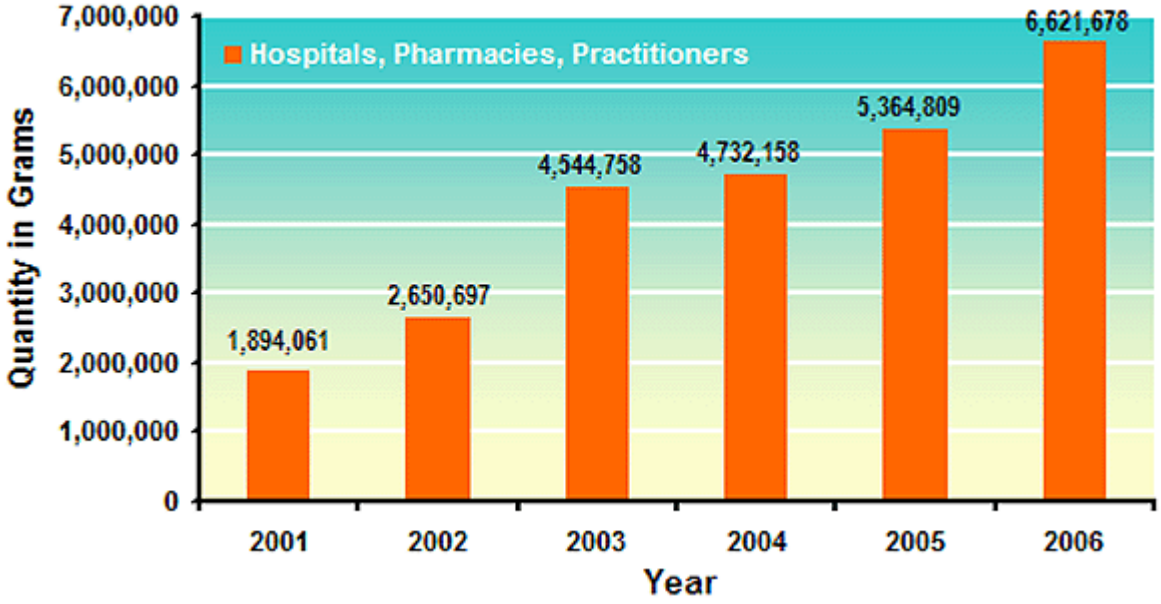
Methadone has much the same effects as morphine but differs in some very important ways which we will discuss in more detail later. Although in most countries the drug is administered as the racemic mixture of (R)- and (S)- isomers, (R)-methadone accounts for most, if not all, the opioid effects. Methadone primarily acts at the μ opioid receptor.

According to one source, methadone has a bioavailability ranging from 36 – 100% and a Tmax of 2.5 – 5 hours. Its volume of distribution ranges from 2 – 13 L/kg and its half-life ranges from 4 – 130 hours, with the half-life of the (R)-enantiomer being somewhat longer. *(I have purposely avoided the use of mean values in this citation. The subjects and conditions of the studies from which these data were drawn are so diverse, that any attempt to distill them to mean values would be misleading at best.)*

Methadone is metabolized by the cytochrome P450 system with CYP3A4, and to a lesser extent, CYP2D6 being the main isoforms involved.

Availability

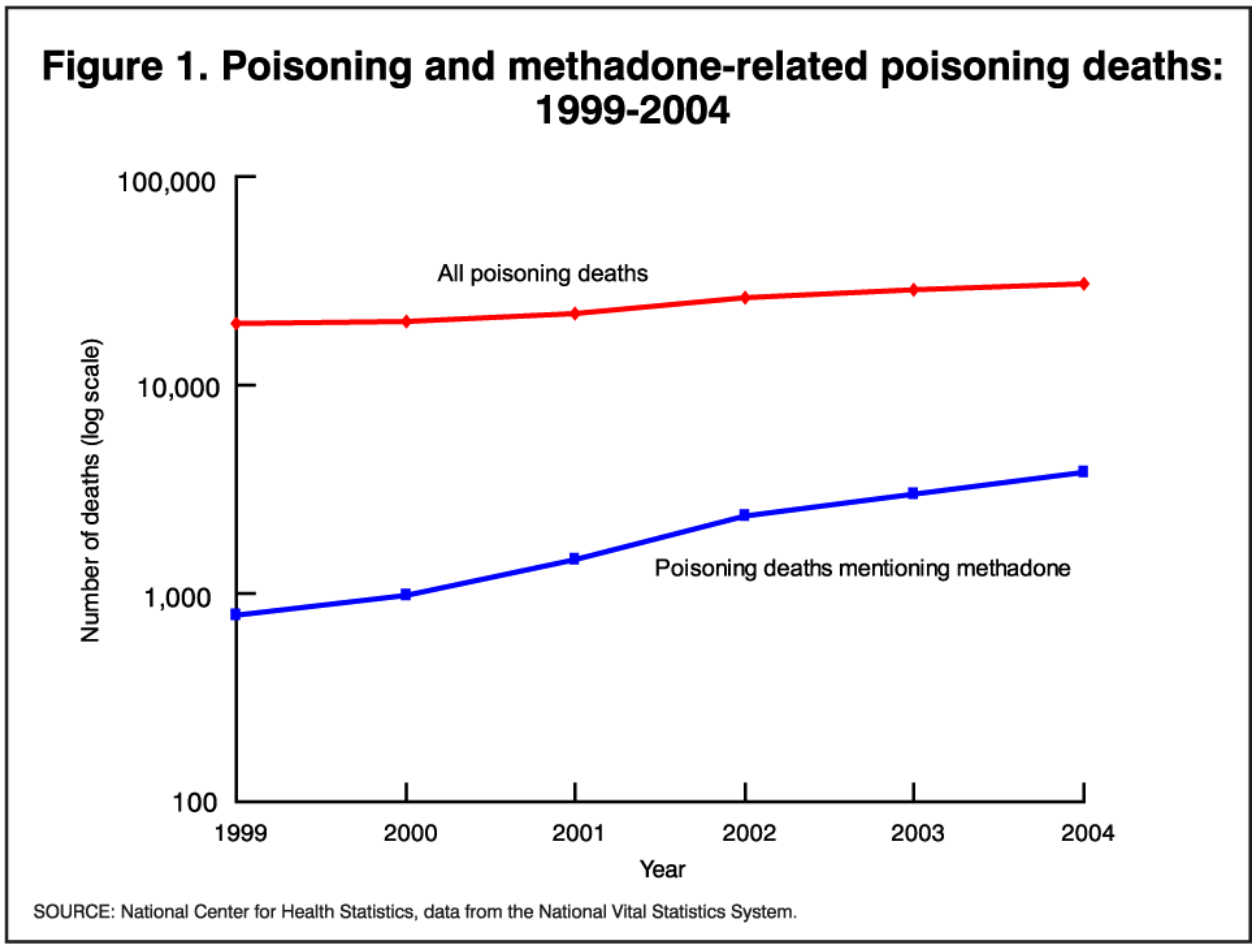
Since the late 90's there has been a marked increase in methadone related fatalities as practitioners seeking alternatives to oxycodone and hydrocodone began to prescribe methadone for pain management. Contributing to the rise in the popularity of methadone as an analgesic is its low price and long half-life. The quantity of methadone being supplied to hospitals, pharmacies and practitioners has increased 350% between 2001 and 2006.



Deaths

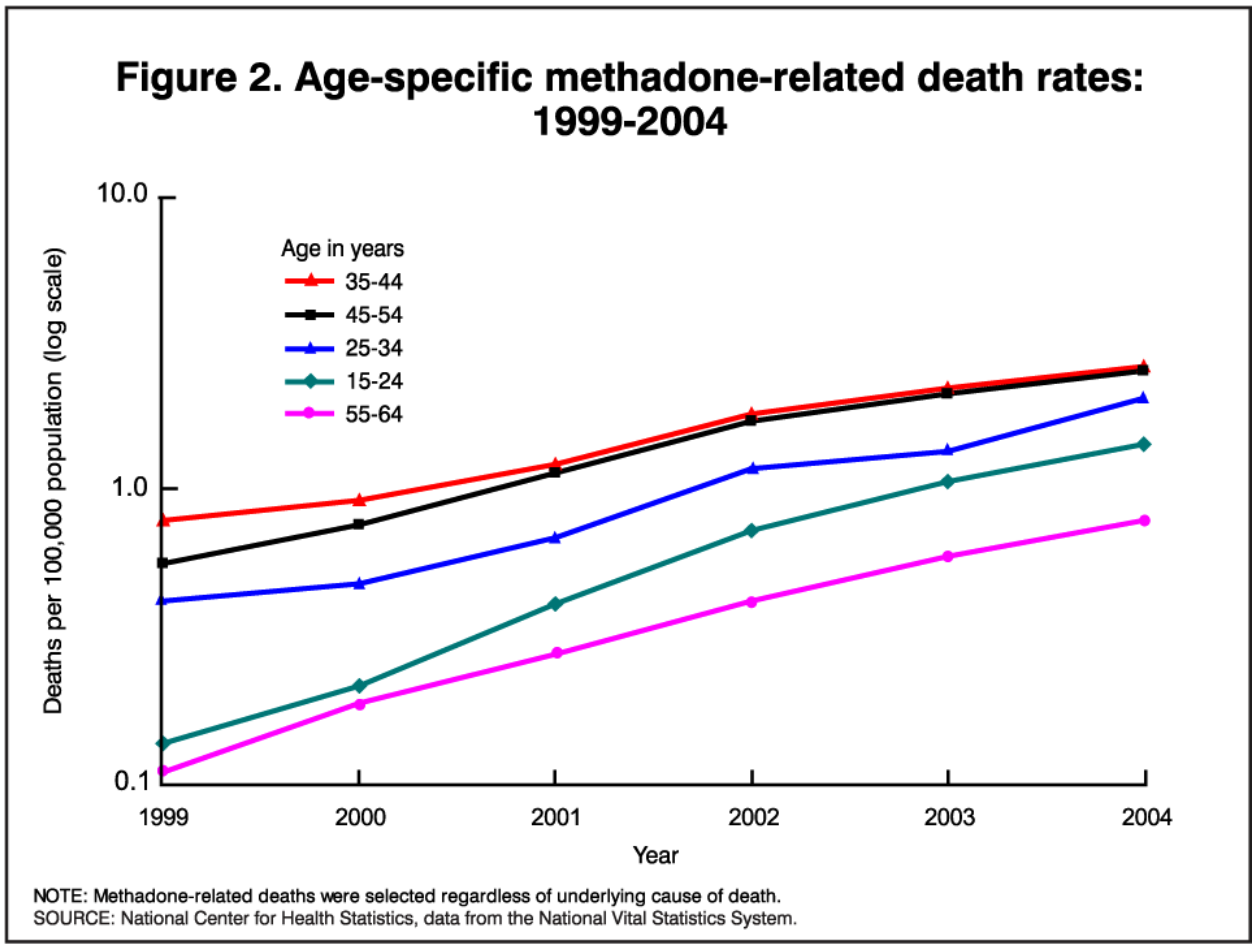
In a study by the U.S. Department of Health and Human Services, National Center for Health Statistics that studied the increase of poisoning deaths, including methadone, between 1999 and 2004, the number of all poisoning deaths increased 54% to 30,308 over the 1999-2004 period, while the number of poisoning deaths mentioning methadone increased 390% to 3,849 (**Figure 1**). Poisoning deaths mentioning methadone increased from 4% of all poisoning deaths to 13% of all poisoning deaths. Most recently, all poisoning deaths increased 6% from 2003-04, while those mentioning methadone increased 29%.

Of all narcotics mentioned in poisoning deaths, methadone had the largest relative increases. The relative increase in methadone-related poisoning deaths from 1999 to 2004 was greater than for any individual substance.



Age

Age specific rates of methadone death are higher for persons age 35-44 and 45-54 years than for those younger or older. This pattern has been true for most of the 1999-2004 period (**Figure 2**). Among those age 55-64 years, the rate in 2004 was seven times the rate in 1999; for those in each of the 10-year age groups covering the span 25-54 years, the rates in 2004 were 3-5 times the rates in 1999. The largest increase, however, is noted for young persons 15-24 years; the rate in 2004 was 11 times that in 1999.



Regionality

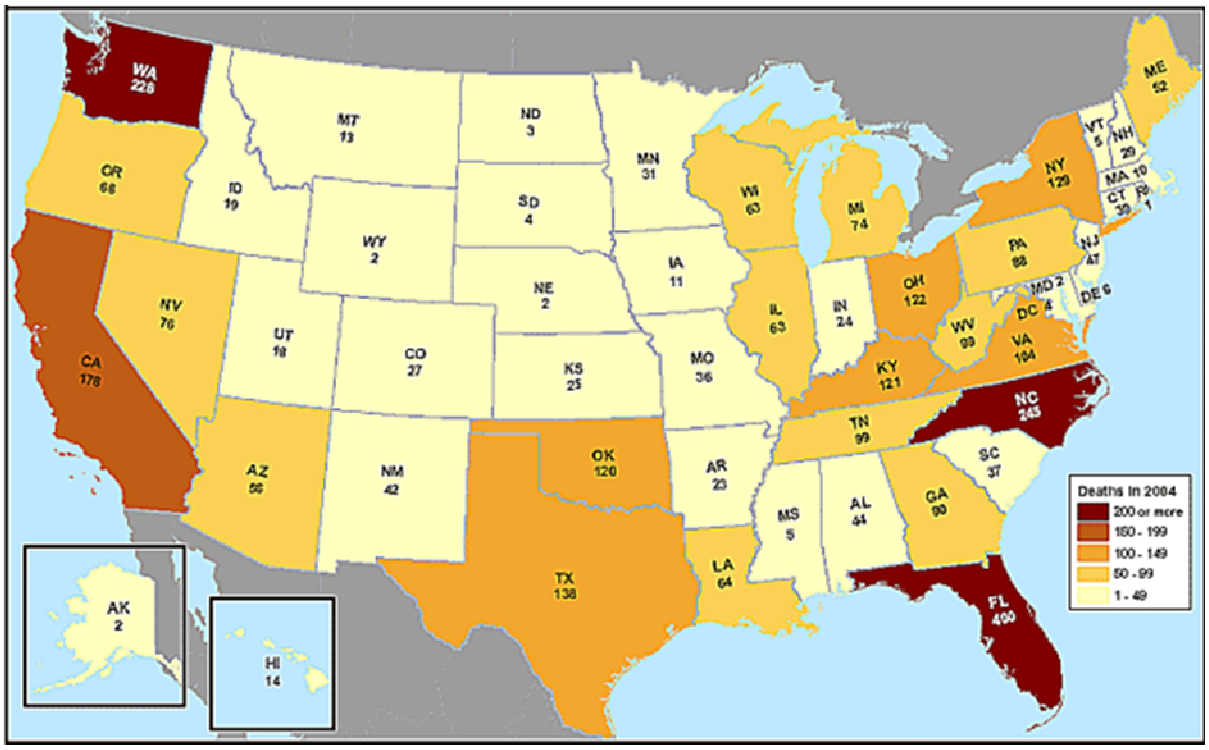
Methadone-related deaths appear to be highly regional in character. The following two graphics are illustrative of this fact:

Top 10 States with the Highest Percent of Increase in Methadone Poisoning Deaths, 1999-2004

State	1999	2000	2001	2002	2003	2004	Approximate Percent of Increase
West Virginia	4	3	25	52	67	99	2,400
Ohio	7	14	30	48	62	122	1,650
Louisiana	4	4	19	34	47	64	1,500
Kentucky	8	28	46	72	122	121	1,400

State	1999	2000	2001	2002	2003	2004	Approximate Percent of Increase
New Hampshire	2	7	11	26	32	29	1,350
Florida	29	47	117	195	255	400	1,300
Oregon	5	18	24	60	66	68	1,250
Pennsylvania	7	17	14	36	67	88	1,150
Tennessee	8	10	14	37	58	99	1,150
Wisconsin	6	16	18	34	35	63	950

Source: Centers for Disease Control and Prevention.



Methadone Related Deaths in 2004

Source: National Center for Health Statistics

Potential Causes of Death

There are several factors that contribute to the increase in methadone related deaths. Perhaps the first and most obvious, as mentioned previously, is the increased availability of methadone. Practitioners are at an increasing rate prescribing methadone for pain management, as they look for replacement drugs for, the much-maligned and often abused, oxycodone and hydrocodone. Furthermore, practitioners often wish to exploit the long half-life of methadone for their chronic pain patients, allowing them less frequent dosing, and to help them avoid chronic exposure to high doses of acetaminophen, often compounded with more traditional pain medications. Also weighing heavily in prescribing decisions is the fact that methadone is inexpensive as compared to many of the other pain medications available today.

A second factor in the increasing death rate is that the pharmacology of methadone can be quite unpredictable. A detailed discussion of the pharmacokinetic variability of methadone was authored by Eap, Buclin, and Baumann in 2002. Among some of the more important factors contributing to this variability are a long Tmax, a long and highly variable half-life, and the effect of co-ingested medications.

Due to the long Tmax of methadone, the respiratory depressing effects of methadone may develop several hours after the last dose, often after the patient has gone to bed, making the loss of respiratory drive even more dangerous.

The half-life of methadone is quite long as compared to most other opioids and its respiratory depressant effects often last much longer than its analgesic effects. Adding to its unpredictability is the fact that studies have indicated that methadone induces CYP3A4 and therefore enhances its own metabolism after a period of use.

Co-ingested medications may also play a role in methadone toxicity. There appears to be a strong correlation between the concomitant use of benzodiazepines and methadone fatality. Caplehorn and Drummer, 2002, postulated that this may be primarily due to the benzodiazepine-induced relaxation of the upper airway, causing airway obstruction which in turn exacerbates the loss of respiratory drive, as previously mentioned.

Beyond the additive effects of co-ingested CNS depressants, many medications have been shown either to induce or inhibit CYP3A4. Inhibition of CYP2D6 has also been indicated by some of the SSRI medications, in particular. This unpredictable induction and/or inhibition of methadone's metabolizing enzymes contributes to its unpredictable half-life.

Yet a third factor is patient compliance, or rather, a lack thereof. Methadone has been found effective as a narcotic replacement medication for opioid addicts primarily for two reasons: Its long half-life allows for infrequent and clinic-controlled dosing and its long Tmax minimizes or eliminates the euphoric effects sought by opioid abusers. However, it is often this "delayed onset" of analgesia and lack of psychotropic effects that lead patients to overmedicate themselves. Patients who are switched to

methadone from oxycodone, hydrocodone, or the like, may feel that their medication is not working, since they may not achieve the analgesia they seek in the time period they have come to expect, therefore they take additional doses. Similarly, those patients seeking or expecting euphoric effects from methadone, may also take additional doses in an attempt to achieve those effects. Additionally, as discussed previously, patients may use other potentially interfering medications, even against medical advice.

Lastly, one cannot ignore the role of "therapeutic misadventure". As one can readily discern from the forgoing discussion, methadone therapy can be quite unpredictable. Many doctors who are not routinely involved in addiction medicine or pain management practices may not adequately understand the difference in the pharmacology of methadone as compared to the more traditional opioid analgesics. This may lead to over prescribing, too rapid an escalation in dosage, or a lack of patient education and proper warnings, especially for new methadone patients.

Summary

The incidence of methadone-related deaths has grown rapidly over the past 10 to 15 years. High variability in volume of distribution, bioavailability, half-life, and a long Tmax contribute to the difficulties in the management of methadone therapy. Furthermore, drug interactions, causing additive CNS depression or unpredictable effects on methadone metabolism, as well as poor patient compliance, further obfuscate methadone therapy. Methadone is a powerful tool in the physician's arsenal for use in combating pain or fighting addiction, however, like everything powerful, it must be understood and it must be respected.

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