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The Heroin Overdose Mystery

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Shepard Siegel
Department of Psychology, Neuroscience and Behaviour, McMaster University

Abstract
Heroin overdose deaths in the Unites States more than tripled from 2010 to 2014, reaching almost 11,000 per year. Despite the use of the term "overdose," many of these victims died after self-administering an amount of opiate that would not be expected to be fatal for these drug-experienced, and drug-tolerant, individuals. Various explanations of this overdose mystery have been proposed. I describe an explanation based on Pavlovian conditioning. Organisms associate cues present at the time of drug administration with the systemic effect of the drug. These drug-predictive cues come to elicit responses that attenuate the effect of a drug. Such anticipatory conditional responses mediate chronic tolerance. If the drug is administered in the presence of novel cues, tolerance fails to occur and the victim suffers an overdose. Overdose prevention strategies should incorporate information about the contribution of drug-associated cues to drug tolerance.

Keywords
addiction, overdose, drug tolerance, heroin, Pavlovian conditioning

Being a heroin addict is risky. In addition to other dangers inherent in being a criminal, death from overdose is a real possibility. Each year, 1% to 3% of heroin users die from overdose (Milloy, Kerr, Tyndall, Montaner, & Wood, 2008). In 2014, there were almost 11,000 heroin overdose deaths in the United States (National Institute on Drug Abuse, 2015).

Heroin, like other opiates, suppresses activity in the brain center that controls breathing. Sometimes this respiratory depressive effect is so profound that the addict dies. The illicitly supplied heroin is of unknown purity, and many addicts pursue ever-higher highs. Occasionally addicts simply take too much of the drug—at least, that's the usual narrative of heroin overdose.

This narrative is inadequate. Surprisingly, the initial impetus for reevaluation of the mechanism of heroin overdose came not from scientists but rather from a science journalist, Edward M. Brecher. In the era of drug hysteria surrounding President Nixon's 1971 call for a "war on drugs," Brecher (1972) authored (under the aegis of *Consumer Reports* magazine) a lucid and dispassionate analysis of drug use, *Licit and Illicit Drugs*. In that book, Brecher made the compelling case that "(1) The deaths *cannot* be due to overdose. (2) There *never has been any evidence* that they are due to overdose. (3) There has long been a plethora of evidence that they are *not* due to overdose" (p. 102). Brecher presented the evidence for these assertions in a chapter with the same title as this article. The bit of plagiarism is an homage to him.

Death of an Addict

Brecher summarized evidence concerning the misapplication of the term "overdose" that was available in 1972. The points he made are still valid. A case report of a heroin overdose, written 33 years later, illustrates many of the enigmatic features of heroin overdose that Brecher discussed.

In 2005, Gerevich and colleagues described the curious events surrounding the death of a heroin addict (identified as "K.J.") in Budapest on January 29, 1999 (Gerevich, Bácskai, Farkas, & Danics, 2005). The events were reconstructed from the medical report and from information given by drug-using friends who were with the addict on the day that he died. K.J., along with these friends, bought heroin from a dealer. Later that day, K.J. died. A syringe containing heroin solution and a spoon used for cooking the heroin mixture were beside the body. Metabolites of heroin were found in K.J.'s blood and urine. The authorities concluded that K.J. suffered a heroin overdose.

There were, however, several puzzling features of this overdose. Despite that fact that a number of people (in addition to K.J.) bought heroin from the same dealer at

Corresponding Author:
Shepard Siegel, Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, Ontario L8S 4K1, Canada
E-mail: siegel@mcmaster.ca

the same time, only K.J. died. The other purchasers did not find the drug especially potent. Moreover, post mortem examination revealed that the concentration of morphine in K.J.'s blood was a fraction of that required to kill an experienced heroin addict (heroin is metabolized to morphine). In fact, the amount of the drug that K.J. administered on the day he died was about the same as the amount he administered the previous day, when there was no toxic reaction. The post mortem examination provided no evidence that K.J. had administered other drugs in conjunction with heroin.

As noted by Gerevich et al., observations of puzzling circumstances like those surrounding K.J.'s death are not uncommon. It has been known for some time that addicts who die shortly after administering heroin often have blood morphine levels that are not higher than those seen in addicts who do not suffer an overdose (Darke, 2014). For example, in 1977 Joseph Monforte, a toxicologist in the Wayne County (which includes Detroit) Medical Examiner's Office, reported that about three-quarters of heroin overdose victims had blood levels of morphine no higher than those seen in a control group of heroin addicts who died as a result of homicide (rather than heroin overdose): "One must conclude that in the great majority of [overdose] cases, death was not the result of a toxic quantity of morphine in the blood" (Monforte, 1977, p. 720). A decade prior to Monforte's report, Milton Helpern, then the chief medical examiner of New York City, concluded that "there does not appear to be a quantitative correlation between the acute fulminating lethal effect and the amount of heroin taken" (Helpern & Rho, 1967, p. 72). Helpern and his deputy chief medical examiner, Michael Baden, noted that a fatal reaction to heroin may occur despite the fact that the individual self-administered a comparable dose the prior day with no ill effects, and that it is common for a number of users to take drugs from the same batch, but only rarely does more than one suffer a life-threatening reaction—an evocation of the circumstances of K.J.'s death as described by Gerevich and colleagues 38 years later. They further noted that examination of heroin packages found near dead addicts, syringes used by the victims, and tissue surrounding the sites of fatal injections all suggest that victims self-administered a normal, usually-nonfatal dose of heroin (see Brecher, 1972, pp. 107–108).

A more recent study compared blood morphine levels in overdose victims with those of automobile drivers who were arrested for suspicion of opiate intoxication but did not suffer an overdose (Meissner, Recker, Reiter, Friedrich, & Oehmichen, 2002). There was considerable overlap in the blood morphine levels of the two populations. As noted in a summary of this literature, "blood morphine concentrations in fatal cases are frequently below those of intoxicated heroin users, or users who died due to causes other than drug toxicity" (Darke, 2014, p. 111).

It would seem that K.J.'s death, and the deaths of many other heroin addicts, are not true "overdoses" as the term is usually understood. Despite the misuse of the word, it is convenient to use the generally accepted term "heroin overdose" when referring to these perplexing fatalities rather than more cumbersome alternatives such as "an idiosyncratic reaction to an intravenous injection of unspecific material(s) and probably not a true pharmacologic overdose of narcotics" (Cherubin, McCusker, Baden, Kavaler, & Amsel, 1972, p. 11). Various hypotheses have been advanced to explain these enigmatic deaths.

Usual interpretations of overdose

Heroin addicts sometimes take other central nervous system depressants, such as alcohol and benzodiazepines, and the fatal reaction may result from the combined effects of heroin and other concomitantly abused depressant drugs. Indeed, some cases of heroin overdose may be attributable to the interaction of heroin with other drugs (Hill et al., 2016), but there are many cases (like that of K.J.) of heroin overdose in the absence of other depressants.

Heroin often is bulked up with various adulterants, such as quinine, caffeine, or sucrose. Some have suggested that allergic or other reactions to such contaminants are responsible for apparent heroin overdoses, but there is little evidence to support this contention: "If we have learnt one thing over the past 25 years, it is that contaminants play little, if any, role in opioid overdose" (Darke, 2014, p. 111).

Many have suggested that the addict may inadvertently overdose following a period of abstinence, either self-initiated or as a result of incarceration. The tolerance that accumulated during a prolonged period of drug use, and that would be expected to protect the addict from the lethal effect of the drug, should have dissipated during this prolonged drug-free period (White & Irvine, 1999). This interpretation does not explain K.J.'s overdose, as he was not abstinent prior to his final drug injection. Moreover, there is evidence that tolerance typically does *not* substantially dissipate merely with the passage of time. There is considerable retention of tolerance, over a protracted drug-free period of many months (Fraser & Isbell, 1952) or even years (Andrews, 1943) in human addicts. Similar findings have been reported in experiments with rats (Cochin & Kornetsky, 1964).

Further evidence that abstinence-induced loss of tolerance cannot explain overdose comes from objective examination of overdose victims' premorbid drug-use history. A record of an addict's drug use is written in the hair. Many drugs, and drug metabolites, diffuse from the bloodstream into the growing hair shaft. Because this evidence remains in place as the hair grows, it is possible to reconstruct the addict's pharmacological record, including

periods of abstinence, using segmental hair analysis. Drug-positive bands in the hair can be evaluated, and drug-free segments indicate periods of no drug use. Hair of recently deceased addicts was analyzed to see if there was evidence for the abstinence hypothesis (Druid et al., 2007). There wasn't. The authors concluded, "abstinence is not a critical factor for heroin overdose death" (p. 223).

So why did K.J. die?

Gerevich and colleagues noted that a curious feature of K.J.'s final drug administration was the *location* of the event—a public toilet. Although this is not an unusual place to inject heroin for many addicts, it was unusual for K.J. K.J. had used heroin for about 4 years, but never in a public toilet. Rather, he and his wife (also a heroin addict) habitually shot up together at home, and they did so on January 28—the day before the overdose. On January 29, K.J. departed from his usual routine of returning home with his heroin purchase and sharing the drug with his wife. Earlier that day, K.J. and his wife had decided to begin a period of drug abstinence—a commitment that K.J. did not keep. To avoid confronting his wife with his continued drug use, K.J. clandestinely self-administered the drug alone, rather than in the company of his wife, and in a location where he had never injected. There was nothing unusual about the drug or the dose that K.J. administered on January 29. What was unusual was the novelty of the setting.

The possibility that K.J.'s death was attributable to the unusual (for him) physical location and circumstances of the fatal injection might seem unlikely. How can the drug-administration environment potentiate the effect of a drug? As Gerevich et al. pointed out, however, there are precedents for this observation.

Environmental Cues and Overdose

Not all overdose victims die. When administered an opiate-antagonist drug in a timely manner, the victim recovers. In independent studies, conducted both in Newark, New Jersey (Siegel, 1984), and Barcelona, Spain (Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, & Camí, 1994), heroin overdose survivors were interviewed to determine the circumstances of drug administration on the occasion of the overdose. The majority of overdoses occurred in novel drug-administration settings.

It is likely that drug-associated cues contribute to overdoses to medically prescribed opiates. Siegel and Ellsworth (1986) describe the case of a fatal overdose in a patient who regularly received medically prescribed morphine for pain relief. The overdose occurred when he was administered his usual dose of morphine in a novel environment. There also is a similar account of a near-fatal overdose in another patient (Johnson & Faull, 1997; Siegel & Kim, 2000).

Reports implicating the drug-administration environment in overdose are based on victims' recollections after they are revived or accounts of others following the victims' deaths. A conclusive demonstration of the importance of the environment in overdose would require an experiment: Some drug users would receive the drug in their usual administration environment, and others in an alternative environment. Obviously, the experiment cannot be done with people; however, it can be done, and has been done (several times), with animals (reviewed by Siegel, 2001). The results of these experiments demonstrate that altering the context of drug administration does indeed increase drug-induced mortality. In each experiment, two groups of animals (in different experiments, rats or mice) were administered a drug (in different experiments, heroin, pentobarbital, or alcohol) on a number of occasions. In a final test session, one group was administered the drug again in the same environment in which it had received the prior drug administrations (*same-tested*). Another group received the test administration of the drug in an environment not previously associated with drug administration (*different-tested*). The consistent finding was that mortality was significantly higher in different-tested than in same-tested animals. In an experiment with heroin, for example, mortality was twice as high in different-tested than in same-tested rats (Siegel, Hinson, Krank, & McCully, 1982). Thus, results of experiments with animals are consistent with case reports of human overdose victims.

Drug-Paired Cues and Tolerance

When a drug user takes drugs in locations other than those previously associated with drug use, the risk of overdose increases. Why? To answer this question, we first must understand why drug users typically do *not* suffer an overdose when they take the drug. Understanding the mechanism of survival will help us understand why this mechanism sometimes fails.

Why addicts usually don't overdose

Taking a drug disturbs the activity of many chemicals in the body—chemicals that are crucial for normal communication between nerve cells. These neurochemical changes have many effects. For example, opiate drugs induce a "rush" (euphoric effect), decrease pain sensitivity (analgesic effect), reduce gastrointestinal activity (constipating effect), suppress the cough reflex (antitussive effect), and decrease the frequency and depth of breathing (respiratory depressive effect). It is the respiratory depression that usually causes opiate-induced death—the victim stops breathing. But most heroin users (or patients receiving an opiate drug) do not die after taking the drug. People survive the pharmacologically induced chaos because potential threats

to survival are detected in their early stages and initiate homeostatic counter-responses that diminish the effect of the physiological alterations. Thus, even while an individual continues to have high levels of the drug in the body following drug administration, the effects of the drug decrease. Such a decrease in the effect of a drug over the course of a single administration is termed *acute tolerance*. Without acute tolerance, the individual would not survive the first drug administration.

The addict, of course, does not take a drug only once, and tolerance becomes enhanced with repeated drug use. The second time a drug is administered it has a smaller effect than it did the first time, the third time an even smaller effect, and so on. This is *chronic tolerance*. It happens, in part, because we learn to expect the drug. Addicts display homeostatic compensations when they anticipate a drug, rather than merely responding reflexively to pharmacological stimulation. The study of anticipatory responding is the study of Pavlovian conditioning.

Why addicts sometimes overdose

Pavlovian conditioning consists of pairing a neutral *conditional stimulus* with a biologically significant *unconditional stimulus*. At the start of conditioning, the unconditional stimulus (e.g., a drug effect) unconditionally elicits some response, termed the *unconditional response*. The unconditional response is the response of the central nervous system to the unconditional stimulus. As a result of conditional- and unconditional-stimulus pairings, the conditional stimulus becomes associated with the unconditional stimulus. The acquisition of this association is revealed by the emergence of a new response to the previously neutral conditional stimulus. Because this new response is conditional on pairings of the conditional with the unconditional stimulus, it is termed the *conditional response*.

Events occurring during drug administration correspond to a Pavlovian conditioning trial. When heroin is repeatedly administered, cues present at the time of drug administration serve as the conditional stimulus, and the homeostatic drug-compensatory responses serve as the unconditional response. These drug-compensatory responses come to be elicited by drug-predictive cues as conditional responses and, importantly, contribute to chronic tolerance (Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). These conditional responses attenuate the effect of a drug in anticipation of that drug; thus, the experienced addict typically can survive a high drug dose.

Sometimes, however, the usual drug-predictive cues are not present when the drug is administered, and chronic tolerance fails to be displayed. The cases of K.J. in Budapest and the patients who overdosed on medically prescribed morphine, the reports of overdose survivors in Newark and Barcelona, and the results of experiments with animals all indicate that the drug-experienced organism may suffer an overdose when the drug is administered in the absence of drug-associated stimuli. That is, addicts sometimes die because they do not display a life-saving conditional response.

Overdosing on Other Drugs

In 2014, more people in the United States died from drug overdoses than in any previous year on record: "There were approximately one and one half times more drug overdose deaths in the United States than deaths from motor vehicle crashes. . . . Opioids, primarily prescription pain relievers and heroin, are the main drugs associated with overdose deaths" (Rudd, Aleshire, Zibbell, & Gladden, 2016, p. 1379). Although this article is concerned primarily with illicit heroin overdoses, there is abundant evidence that pharmacological associations contribute to tolerance to many opiate and non-opiate drugs (Siegel et al., 2000). It is likely that some overdoses to drugs other than heroin are, like some heroin overdoses, attributable to drug administration in an environment other than that associated with the drug's effect.

Summary and Conclusion

There are several reasons why heroin addicts overdose. Some may simply take too much drug, especially when the heroin is enriched with even more potent opioids. Others may suffer from synergism between the opiate and other, concomitantly administered depressive drugs (e.g., alcohol). Another risk factor is the drug-administration environment. Addicts are in danger of overdose if they administer the drug in the context of stimuli that have not, in the past, reliably signaled the drug. On the occasion of the overdose, such victims do not make the preparatory conditional responses that mediate chronic tolerance, and thus are not sufficiently tolerant to the drug to survive.

The year that K.J. administered heroin in a novel environment and died, 1999, was also the year that Zador commented on potential mechanisms of heroin overdose. She noted that "ingesting heroin in an unusual or unfamiliar setting is not currently publicized as a risk" (Zador, 1999, p. 976). Unfortunately, that's still true. If heroin users (and likely other drug users, too) knew of this risk, lives would be saved.

Recommended Reading

Brecher, E. M. (1972). (See References). Contains a pioneering and influential discussion of the mystery of heroin overdose in its 12th chapter (pp. 101–114).

Darke, S. (2014). (See References). A recent review of some common misunderstandings concerning heroin overdose.

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the Pavlovian conditioning analysis of heroin overdose also is applicable to alcohol overdose.

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