J Forensic Sci, Jul. 1974, Vol. 19, No. 3

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Opiate Overdose Deaths in the District of Columbia. Part II—Methadone-Related Fatalities*

With widespread clinical utilization of methadone as a treatment modality for heroin addiction, public attention has been drawn increasingly of late to its potential for diversion to nontherapeutic situations. Deaths directly related to the abuse of black-market methadone have received considerable notoriety in the District of Columbia and elsewhere. Much can and has been learned relating to the complex epidemiological dynamics of the situation, where careful examination of a cohort of methadone-related fatalities has afforded promulgation of reasoned public policy decisions relative to community methadone utilization. Countermeasures taken to control the problem here have proven remarkably effective.

This paper presents a detailed discussion of methadone-related deaths among abusers of narcotic drugs. Considerations addressed here include the following: (1) the specific demographic, pathological, and toxicological characteristics of those victims whose deaths were found to have been directly related to methadone abuse; (2) additional circumstantial, pathological, and toxicological factors which may have contributed to a fatal result following utilization of illicit methadone; (3) the pharmacophysiological mechanism of methadone-related deaths, relative to the syndrome of sudden death among heroin addicts; and (4) those community countermeasures that have been taken to control the methadone-related death rate in the District of Columbia.

Context of the Methadone Problem in the District of Columbia

In February 1970, the District of Columbia's Narcotics Treatment Administration (NTA) was established as a coordinated, multimodality addiction treatment program, in response to a rapidly growing local epidemic of heroin abuse. Since its inception, the program has treated nearly 15,000 heroin-addicted persons (roughly 10,000 during the study period) relying heavily, but by no means exclusively, on methadone therapy. During the first two program-years an average of 1.25 methadone deaths per month were recorded in the District of Columbia.

Received for publication 20 June 1973; revised manuscript received 16 Nov. 1973; accepted for publication 10 Dec. 1973.

* Part I of this paper, entitled "Opiate Overdose Deaths in the District of Columbia. Part I—Heroin Related Fatalities," appeared in the April 1974 issue of *Medical Annals of the District of Columbia*.

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In late 1971, a number of private physicians in the metropolitan Washington area began prescribing for profit large amounts of methadone in unsupervised fashion. Pilferage of methadone supplies further increased its general black-market availability. Approximately 3800 addicted persons were enrolled at that time in the NTA's maintenance (60 percent), detoxification (27 percent), and abstinence (13 percent) programs. All of these factors, coupled with an extreme heroin shortage born of the nationwide dock strike, served to produce a significant upsurge in the demand for and availability of illicit methadone in the District of Columbia.

Not unexpectedly, January and February of 1972 produced a peak clustering of fatalities directly related to methadone abuse (see Fig. 1). In addition, toxicological urine screening analyses of arrestees entering the criminal justice system, and of patients admitted to Narcotics Treatment Administration programs in early 1972, revealed 11 and 35 percent rates of methadone positivity, respectively, an all-time maximum level. A strongly positive correlation was demonstrated between the monthly methadone death rate and the number of urines positive for illicit methadone in the District of Columbia Superior Court urine screening facility ($r = 0.59$, $p < 0.05$).

The following steps were initiated here in February and March of 1972 to reduce the availability of illicit methadone.

1. Complete removal of methadone dispensation from the private sector.
2. Conversion by the Narcotics Treatment Administration to a noninjectable liquid methadone preparation dispensed in unit dosage, tamper-proof bottles.
3. Rigorous enforcement and restriction of methadone take-home privileges among Narcotics Treatment Administration patients, with reduction of maximum allowable therapeutic dosage for all patients from 160 to 80 mg per day.
4. Institution of a computerized accounting system to monitor methadone distribution in Narcotics Treatment Administration clinics.

In the aggregate, the above countermeasures have achieved noteworthy (if still only partial) success, in that availability of street methadone has been sharply curtailed, with a corresponding reduction in the methadone death rate. Superior Court and Narcotics Treatment Administration methadone urine screening positivity rates declined synchronously to 3 and 21 percent of those individuals tested, respectively, while the per-bottle price of street methadone increased by 50 percent.

Obviously, much remains to be done to deliver comprehensive, effective therapy to those addicted persons in need, while at the same time reducing even further the availability of illicit methadone. Enhanced understanding of the various considerations addressed in this paper will be afforded if they are viewed within the context of the dynamics of the complex epidemiological problem which faced the community during the study period.

There were 118 deaths that were directly related to heroin and/or methadone abuse investigated by the Office of the Chief Medical Examiner of the District of Columbia during the eighteen-month study period from July 1971 through December 1972. Thirty-nine of these fatalities were attributed to methadone alone and 21 to the combination of heroin and methadone. These 60 cases form the basis of this report.

Materials and Methods

In July 1971, Washington, D.C. converted to a medical examiner system for medicolegal death investigation. Since that time there has been uniform, systematic investigation of sudden, unexpected, and/or medically unattended deaths in the District of Columbia,

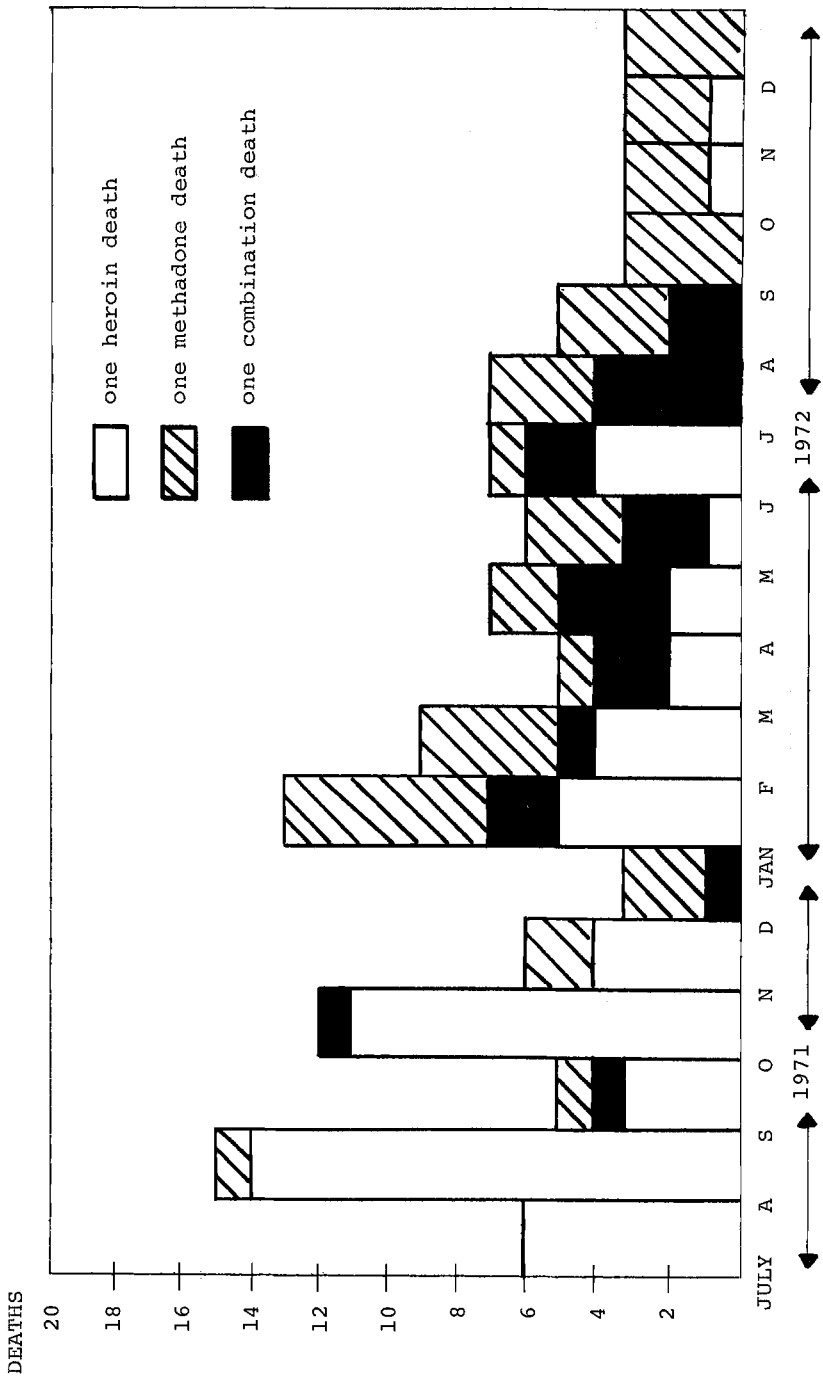

FIG. 1—*Opiate overdose deaths in the District of Columbia, July 1971–December 1972.*

including all known or suspected narcotic-related fatalities. Investigation of drug-related deaths is supported by a modern, comprehensive, on-site toxicology capability.

All deaths directly related to opiate abuse identified from July 1971 through December 1972 form the basis of this report. There were 118 heroin and/or methadone "overdose" deaths investigated during the study period. All such cases were subjected to complete postmortem and toxicological examination. Marked pulmonary edema and hyperplasia of the lymph nodes of the porta hepatis constituted the only significant pathologic abnormalities.

Excluded from the study group were deaths resulting from the various recognized medical complications of narcotism (sepsis, bacterial endocarditis, tetanus, viral hepatitis, etc) and unnatural deaths among users of narcotic drugs. Also excluded were those addicted persons who were found to have died from natural causes. Generically, the study group was found to be comprised primarily of young, black, inner-city males with a history of acute and/or chronic opiate abuse, and with the cutaneous stigmata of acute and/or chronic narcotism. Positive morphine/quinine and/or methadone toxicology was obtained in 98 percent of cases.

The case records of the study group were examined retrospectively and data were analyzed summarizing specific demographic variables, death scene investigative findings, the circumstances surrounding death, postmortem pathology, and toxicological results.

A control group consisting of 75 homicidal fatalities among opiate users during the same study period was analyzed in similar fashion.

In an effort to characterize the various components of the addict study and control group populations in terms of longevity of opiate usage, current tolerance status, route of opiate administration, etc, certain assumptions were necessarily made. While these considerations are admittedly somewhat arbitrary, they were applied equally to both the study and control groups in random fashion and without knowledge of the particular circumstances of death prior to tabulation.

A decedent was considered to have been opiate addicted in the past if the cutaneous stigmata of chronic intravenous narcotism were present, or if a positive history of regular opiate use were elicited during the death investigation. A decedent was considered to have been addicted at the time of death if there were a clear history of regular heroin use immediately prior to death in conjunction with a fresh venipuncture site(s) and if there were no historical evidence suggesting a recent period of opiate abstinence (incarceration, hospitalization, etc) in the two months prior to death. Those classified as active addicts at the time of death were characterized as having opiate tolerance; those who were not known to have been using heroin regularly at the time of death were considered to lack opiate tolerance.

If fresh venipuncture sites were found at autopsy, and toxicological analysis of stomach contents were negative, the route of opiate administration was considered to be intravenous. If no fresh venipunctures were found, and stomach content toxicology were positive, the route was considered oral. If both a fresh venipuncture site and positive stomach toxicology were present, the route was considered both intravenous and oral. If neither were present, the route was characterized as indeterminate.

Since tissue drug levels are a function of dose, route of administration, time elapsed between drug administration and death, and many other factors, we decided to concentrate simply on the presence or absence of a particular drug(s) in analyzing toxicological results. Blood ethanol levels of less than 20 mg percent were not considered positive.

If methadone alone were recovered toxicologically, the death was classified as a methadone death. A heroin death was defined as a case toxicologically positive for morphine or quinine or both. (Unpublished laboratory data here indicate that cases found to be positive for quinine alone connote heroin administration in which blood and/or urine morphine levels are too low for detection by standard photofluorimetric and other analytical techniques.) Cases in which both heroin and methadone were detected were classified as combination deaths.

All methadone and combination deaths were classified according to the relative length of time that had elapsed between administration of the opiate drug and the time of death. Those in whom the history clearly supported a brief interval between drug administration and death (less than 15 min) were classified as sudden deaths. Those cases where there was circumstantial documentation of a more prolonged period between drug administration and death (that is, over 30 min) were classified as not sudden deaths. Those cases where such a temporal determination could not be made were classified as indeterminate deaths.

Results were analyzed for statistical significance using the Student "t" test, Chi square, and Pearson correlation coefficient (r). Results were considered statistically significant if the p value were less than 0.05.

Results

General

During the study period, there were 118 acute opiate "overdose" deaths of all types. For purposes of comparison, during the same interval there were 15 deaths from medical complications of narcotism, 100 violent deaths among addicts (including the control group of 75 homicidal deaths among addicted persons), and 12 natural deaths among opiate abusers. To recapitulate, among acute overdose victims, the distribution by toxicology was heroin alone, 58 cases; methadone alone, 39 cases; and combination deaths, 21 cases.

Analysis of demographic variables among the various study subgroups revealed only two significant differences (see Table 1). Victims of heroin overdose (mean = 27.1 years) were significantly older than methadone fatalities (mean = 21.9 years) ($t = 2.94, p < 0.01$). There was a marked shift in toxicology positivity relative to drugs of abuse from heroin predominant during the first six months of the study period, to methadone predominant in the last six months (see Fig. 1).

The control group was entirely similar to the methadone study group in all variables examined except lung weight.

Route of Administration

Methadone was administered orally in nearly 60 percent of the cases studied. It is of interest that six of the seven deaths following intravenous methadone administration occurred prior to February of 1972, when a noninjectable liquid methadone preparation was instituted by the District of Columbia's Narcotics Treatment Administration addiction treatment program.

Addiction/Tolerance Status

Only 25.6 percent of all methadone fatalities occurred among decedents who had not been addicts at some point in their lives. However, a larger percentage (46.2 percent)

TABLE 1—*Data comparing opiate fatalities with methadone victims and control population.*

Category	Sub-category	Opiate Deaths		Methadone Deaths		Control Group	
		No. of Cases	Percent of Total	No. of Cases	Percent of Total	No. of Cases	Percent of Total
Number of Cases		118		39		75	
Mean Age, years		24.7		21.9		26.3	
Sex	male	99	83.9	34	87.2	70	93.3
	female	19	16.1	5	12.8	5	6.7
Race	black	114	96.6	36	92.3	72	96.0
	white	4	3.4	3	7.7	3	4.0
Marital Status	single	75	63.3	26	66.7	53	70.7
	married	33	28.0	10	25.6	17	22.7
	other	10	8.4	3	7.7	5	6.6
Employed	yes	63	53.4	22	56.4	41	54.7
	no	53	44.9	17	43.6	32	42.7
	unknown	2	1.7	0	0	2	2.6
Fatty Liver		23	19.5	10	25.6	11	14.7
Hyperplastic Portal Lymph Nodes		48	40.8	19	48.7	28	37.3
Chronic Needle Tracks		73	61.9	22	56.4	64	85.3
Ethanol Positive		44	37.3	7	17.9	24	32.0
Mean Lung Weights, g		1293.1		1306.4		914.4	

were not known to have been addicted at the time of their death. The latter were decedents in whom lack of opiate tolerance may well have contributed to death. Roughly half of those lacking tolerance had never been addicts, and half were addicts who had recently become abstinent. It should be noted that this is almost certainly an underestimation of the number of decedents who lacked opiate tolerance. In addition, the group which appeared to have tolerance certainly included individuals for whom the required history of abstinence could not be elicited, but who were in fact abstinent. It also may include those persons using heroin intermittently who were considered regular users by history.

Pulmonary Edema

Severe pulmonary edema is said to be a characteristic postmortem finding in methadone overdose victims [*1,2*]. Comparison of lung weights between the study group (mean = 1306.4 g) and the control group (mean = 914.4 g) verifies this observation ($t = 7.12$, $p < 0.001$).

Time Elapsed Between Drug Administration and Death

No cases of sudden death were identified among the methadone group. The majority (77 percent) of methadone fatalities was clearly identified as not sudden deaths. Of the remainder, no temporal determination could be made. In all cases where the postadministration/premortem interval could be determined, survival between drug administration and death was prolonged.

Presence of a Second (Nonopiate) Drug

Thirteen (33.3 percent) of the methadone decedents and 36 (48.0 percent) of the control group demonstrated the presence of a nonopiate drug by toxicological analysis (see Table 2). All amphetamine positive cases were identified during the last six study months, a time during which there was an epidemic of amphetamine abuse in the District of

TABLE 2—*Nonopiate drugs detected by toxicological analysis in the tissues of methadone victims and addict homicide control population.*

Drug(s) Identified	Methadone Deaths	Control Group
Ethanol Only	6	19
Ethanol + Another Drug	1[a]	5[b]
Other Depressant Drug Only	0	0
CNS Stimulant Only	6[c]	12[d]
Total	13	36

CNS = central nervous system.

[a] One amphetamine.

[b] Five amphetamine.

[c] Five amphetamine, one phenmetrazine.

[d] Ten amphetamine, one phenmetrazine, one cocaine.

Columbia [*3*]. Fifteen of the controls (20 percent) were positive for amphetamines during this same period. It is unlikely that the presence of these central nervous system stimulatory agents contributed to any of the methadone deaths reviewed in this paper.

Seven (17.9 percent) of the methadone decedents were positive for a depressant drug, which was found to be ethanol in each instance. Ethanol was much less likely to be noted in association with cases classified as methadone fatalities than it was in either heroin or combination deaths ($\chi^2 = 11.6590$, $p < 0.01$, $df = 2$).

Coexisting Hepatic and Renal Disease

Both the liver and the kidney play important roles in opiate metabolism and excretion [*4*]. Functional impairment of either organ system might potentiate the pharmacological effects of opiates, thereby enhancing drug morbidity and mortality. However, similar rates of hepatic and/or renal pathology were found in the study and control groups.

Childhood Poisoning

One of the epidemiological differences between heroin and methadone is that methadone has been associated with a syndrome of accidental poisoning among children [*5–13*]. Only one such fatality, which occurred prior to the study period, has been identified in the District of Columbia.

Discussion

Victims of fatal methadone abuse were significantly younger than their heroin overdose counterparts. Methadone deaths became proportionately more frequent in the latter part of the study period.[3] A significant percentage of methadone decedents synchronously abused amphetamines, but only a minority were positive for ethanol. Death usually followed the oral administration of methadone and occurred over a relatively prolonged interval in the majority of cases.

[3] Fourteen methadone deaths have been documented in the District of Columbia during 1973. All but 3 occurred during the first four months of the year. During this interval there were no combination deaths and only five heroin fatalities. May of 1973 represents the first month of the preceding 48 consecutive months where no opiate overdose fatalities were recorded here. There were no deaths recorded in June, July, November, and December of 1973 as well.

There were no examples of the sudden death syndrome in this group of cases. A search of the literature failed to reveal a single case of sudden death following methadone use. The clinical histories were quite characteristic: the decedent was commonly described as having come home in the evening acting either "high" or drowsy, and upon going to bed, was then found dead the following morning. With respect to all other demographic, pathological, and toxicological variables examined, methadone victims were indistinguishable from the heroin fatalities in this series, as well as in those described by others [*1,2*].

Combination deaths were grouped separately because of the inability to determine if it were the heroin or the methadone administered that was responsible for a particular death. However, given the fact that combination deaths tended to resemble methadone deaths in terms of age of victim, to follow a prolonged terminal course, to have a relatively low ethanol positivity rate, and to participate in the amphetamine abuse pattern, it is tempting to speculate that methadone is the primary factor in such fatalities. In further support of this possibility is the finding of trace to negative blood morphine levels in all combination decedents tested. In contrast, almost all heroin overdose cases analyzed in this series had positive blood morphine levels. Given the rapidity with which morphine is cleared from the blood [*14*], this finding suggests that combination decedents survived sufficiently long enough following drug administration to have cleared their blood of morphine, and that it was the methadone-induced coma which ultimately proved fatal.

Death from "morphine poisoning" is said to be a gradual process [*15*], but it has been suggested that a substantial proportion of heroin deaths occurs too rapidly to invoke gradual central nervous system depression as a reasonable mechanism of death [*1,2,16–18*]. In addition, the protective effect of methadone in blocking the pharmacological effects of large doses of opiates has been well demonstrated [*19,20*]. These experimental observations were corroborated in this series, in that none of the victims were enrolled in a methadone treatment program at the time of their death. These observations make it difficult to conceptualize how persons using methadone on a regular basis can die from an opiate overdose. We therefore examined other factors that could possibly have contributed to a fatal outcome.

Although most of the 39 methadone dececents in this study were known to have been heroin addicts at some time in the recent past, a surprisingly large percentage (46.2 percent) clearly lacked opiate tolerance at the time of death. An unknown number of intolerant individuals were classified as being tolerant because the required abstinence history could not be elicited. It should be noted that tolerance is a relative phenomenon. Patients on methadone maintenance have high tolerance relative to street level heroin, whereas the street heroin addict has been shown to demonstrate relatively low tolerance. This may partially explain why methadone patients can shoot heroin and survive, while street heroin addicts risk death from the same activity.

The route of opiate administration varies with the opiate utilized. Heroin was administered intravenously in almost all cases in this study, where most of the methadone (particularly in the latter months of the study) was taken by mouth. These procedural differences may account for some of the discrepancies observed between these two toxicological subgroups. Gradual absorption of an oral dose of a long acting agent like methadone might well be expected to produce death in a gradual fashion. The sudden, physiologic impact of an intravenous bolus of heroin might, on the other hand, be expected to produce more rapid physiological effects. The infrequent administration of methadone by the intravenous route may contribute to the lack of sudden death following its illicit use.

Conclusions

The following conclusions seem justified from the above data.

1. The incremental appearance of methadone as a street drug of abuse in the District of Columbia followed its widespread use in legitimate treatment programs and its uncontrolled dispensing by private physicians, who failed to provide the necessary ancillary support services characteristic of well-run addiction treatment programs. The role played by the latter individuals in potentiating this and other drug abuse problems in the District of Columbia has been significant [*3*]. A sharp decline in the methadone death rate followed directly upon the removal of methadone from the private sector in March 1972. A detailed discussion of the control of methadone abuse in Washington has been presented elsewhere [*21*].

2. Fatal accidental childhood poisoning with methadone has not been a significant problem in Washington since the introduction of appropriate control measures.

3. The following differences between victims of fatal methadone and heroin abuse are noteworthy:

(a) Methadone victims are significantly younger than their heroin counterparts.

(b) Methadone deaths increased proportionately as heroin deaths declined during the study period for the reasons enumerated. However, the absolute methadone death rate rose to a peak in early 1972 and has declined steadily ever since.

(c) Ethanol was identified significantly less frequently in the tissues of methadone decedents than either in the control group or among heroin victims. Ethanol could not be statistically associated with a fatal outcome in conjunction with methadone abuse.

(d) Methadone deaths appear to represent opiate overdose deaths in the classic sense of the term, with gradual central nervous system depression and coma eventuating in cardiopulmonary arrest and death. There is no evidence to support the existence of a sudden death syndrome similar to that purported to occur with heroin.

4. Abnormal opiate metabolism is probably not a meaningful consideration in methadone-related fatalities.

5. Lack of opiate tolerance almost certainly contributed to the deaths of nearly one half of the methadone fatalities.

6. Methadone is probably instrumental in producing a fatal outcome in those cases in which both heroin and methadone are identified by toxicological analysis.

The implications of the above findings relative to the prevention of opiate fatalities are clear. Reduction of the opiate supply available to the community at large should minimize the risk of a large dose of heroin or illicit methadone or both being readily available. Second, addiction treatment programs must give their patients meaningful understanding of the concept of opiate tolerance and of the very real dangers that exist when an addict returns to opiate abuse following a prolonged period of abstinence. The risks inherent in the synchronous abuse of other depressant drugs such as ethanol and barbiturates in conjunction with opiates require repeated emphasis, in spite of lack of statistical proof of an association with methadone deaths. Finally, most methadone deaths could be prevented, since they occur over a sufficiently prolonged period of time to permit an enlightened friend or relative to obtain lifesaving medical assistance.

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