The Impact of Harm-Reduction-Based Methadone Treatment on Mortality Among Heroin Users

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A B S T R A C T

Objectives. The purpose of this study was to investigate the impact of harm-reduction-based methadone programs on mortality among heroin users.

Methods. A prospective cohort investigation was conducted among 827 participants in the Amsterdam Cohort Study. Poisson regression was used to identify methadone maintenance treatment characteristics (dosage, frequency of program attendance, and type of program) that are significantly and independently associated with mortality due to natural causes and overdose.

Results. From 1985 to 1996, 89 participants died of natural causes, and 31 died as a result of an overdose. After adjustment for HIV and underweight status, there was an increase in natural-cause mortality among subjects who left methadone treatment (relative risk [RR] = 2.38, 95% confidence interval [CI] = 1.28, 4.55). Leaving treatment was also related to higher overdose mortality, but only among injection drug users (RR = 4.55, 95% CI = 1.89, 10.00).

Conclusions. Harm-reduction-based methadone treatment, in which the use of illicit drugs is tolerated, is strongly related to decreased mortality from natural causes and from overdoses. Provision of methadone in itself, together with social–medical care, appears more important than the actual methadone dosage. (*Am J Public Health.* 2001;91:774–780)

Users of illicit drugs are at increased risk of premature mortality.[1–3] The most important natural causes of death among such individuals are infections (e.g., AIDS, hepatitis, endocarditis), which are acquired mainly through nonsterile injection practices and needle sharing. Common nonnatural causes of death are overdose, suicide, violence, and accidents.[4–6] The HIV epidemic has contributed greatly to increased mortality in this population,[7–10] but in most countries, overdose is the leading cause of death among drug users.[11]

Methadone is widely used for detoxification, but it is also used as maintenance treatment to prevent withdrawal symptoms. When administered in adequate dosages, it can relieve the "narcotic hunger" or craving for heroin. Randomized controlled trials and observational studies have shown that methadone maintenance can reduce heroin use, crime, and injection-related risk behaviors.[12] Opiate-dependent drug users who receive methadone maintenance treatment appear to have a reduced risk of dying in comparison with drug users who have never been treated with methadone and drug users who have left methadone treatment.[13–16]

The literature on the association between mortality and treatment is based largely on detoxification clinic programs or maintenance programs with waiting lists and strict entry criteria. In these strict programs, use of illicit drugs during methadone treatment is not allowed. In contrast, the Netherlands and some other countries, such as the United Kingdom and Australia, take a harm-reduction approach in which illicit drug use is tolerated. To stop drug users from using drugs remains the ultimate goal; when this is not possible, however, the policy is to minimize the damage they do to themselves, other persons, and society at large.[17]

The Amsterdam methadone maintenance system aims to keep in contact with as many drug users as possible through different types of programs (low, medium, and high threshold) that provide methadone in combination with social–medical care and needle-exchange facilities.[18,19] These programs involve no waiting lists, and it is relatively easy to enter and reenter the programs. Ongoing drug use during treatment is tolerated in low- and medium-threshold programs. The low-threshold programs are operated by the Municipal Health Service via a mobile bus and local outposts, including one outpatient clinic for addicted prostitutes and individuals of foreign nationality. Among clients who have regulated their drug use, methadone can be prescribed in a medium-threshold program by a general practitioner. Clients who are willing to undergo detoxification can receive methadone in a high-threshold program (outpatient addiction clinic).

Circulation between the different programs is possible, and "promotion" to higher-threshold programs is encouraged. All services are free of charge, but one must be registered as a resident of Amsterdam. The Amsterdam methadone programs, with their harm-reduction approach, reach an estimated 60% to 70% of the city's 5000 opiate-dependent drug users.[20]

To our knowledge, there are no published reports of longitudinal studies using detailed registered methadone data to investigate the independent effects of harm-reduction-based

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methadone treatment on mortality. The aim of the present study was therefore to evaluate methadone maintenance treatment characteristics (dosage, frequency of program attendance, and type of program) in Amsterdam in relation to mortality due to natural causes and overdose. To ensure valid and detailed assessment of methadone treatment, we linked data from a large cohort of drug users with data from the Amsterdam Central Methadone Register. The present study was part of a project evaluating harm-reduction-based methadone treatment in relation to HIV infection[18,21,22] and mortality.

Methods

Participants

Our study group was selected from drug-using participants in the Amsterdam Cohort Study. This open and ongoing study, initiated in December 1985, assesses the prevalence, incidence, and natural history of HIV infection and evaluates AIDS prevention measures.[23–25] Participants are mainly recruited from local methadone outposts, and until 1997 they were recruited as well from a sexually transmitted disease clinic for drug-addicted prostitutes.

At study enrollment, a blood sample is taken and participants are interviewed via a standard questionnaire; follow-up visits are scheduled every 4 months. At each visit, questions about current behavior refer to the period between the preceding visit and the present visit. Sera are tested for the presence of HIV-1 antibodies via enzyme-linked immunosorbent assay (ELISA) and confirmed through immunoblotting.[23] Absolute numbers of CD4+ lymphocytes are determined through cytofluorometry.

If study participants do not appear for a follow-up visit within 5 months after their previous visit, they are sent a reminder letter. If there is no response, a repeat letter follows. If there is still no response after the second reminder letter, the register of population in the participant's town of residency (usually Amsterdam) is approached for information on possible change of address and on vital status. Participants who refuse to return for follow-up visits or cannot return (e.g., because of leaving the area) are not contacted again; however, if they remain in the country, their vital status is determined at regular intervals through inquiry at the register of population. Causes of death are ascertained by locating and examining hospital records or on the basis of information provided by the coroner's office. Autopsies are infrequently performed.

Assessment of Methadone Treatment

As mentioned above, to ensure detailed and valid assessment of methadone treatment, we linked data from the Central Methadone Register in Amsterdam with Amsterdam Cohort Study data.[18] The central register records methadone dosage and form (liquid, tablet, or intravenous) and dispensing location of all methadone prescriptions in Amsterdam. From 1985 to 1988, methadone data were available on a weekly basis (i.e., the final prescription of the week); after 1988, they were available on a daily basis. Methadone data collection for the present study ended in December 1996.

Between December 1985 and December 1996, the number of Amsterdam Cohort Study participants was 1218. Among these individuals, the names of 1099 (90%) were available for linkage to the Central Methadone Register; 41 (4%) were not registered and were therefore excluded from the analysis. Among the remaining 1058 participants, all methadone prescriptions dated from 6 months before entry into the Amsterdam Cohort Study until December 1996 were selected. The prescriptions were ascribed to the intervals between the follow-up visits. Only visits at which the participant was reportedly living in Amsterdam were included, resulting in the exclusion of 0.9% of all visits.

Study Group

Of all drug users who entered the Amsterdam Cohort Study, 21% participated only once. Many of these individuals were of foreign nationality (46%), and no attempt was made to trace participants across the national border. Therefore, it was decided to include in the present study only participants with at least 1 follow-up visit, resulting in 827 of 1058 cohort participants with methadone data for analysis. There were no significant differences between subjects with and without follow-up visits in terms of sex, mean age at intake into the cohort, recent drug injection experience, and drug injection history. Participants without follow-up visits were more often of foreign nationality.

The vital status of 774 of 827 (94%) drug users could be ascertained at the end of the present study (December 1996). The 83 drug users with incomplete follow-up data (among whom 87% were of non-Dutch nationality) were censored at the last date for which information on their vital status could be obtained. The median time between 2 cohort visits was 4.1 months (interquartile range: 3.8–4.8 months); the median time between the last cohort visit and censoring or death was 3.2 months (interquartile range: 1.6–7.3 months), and for 158 participants this time interval was more than 12 months.

Definition of Variables

Methadone treatment was defined by most recent methadone dosage, mean methadone dosage, frequency of program attendance (i.e., percentage of weeks with methadone prescriptions out of the total weeks since the previous visit), most recent type of program, and main type of program. Most recent dosage and most recent type of program were defined as the dosage and type of program experienced by the participant in the week before a cohort visit or censoring. Methadone dosage was coded "no methadone" or 1 to 20, 21 to 40, 41 to 60, 61 to 80, or more than 80 mg/day; frequency of program attendance was coded "no methadone," 1% to 24%, 25% to 75%, 76% to 99%, or 100%. Type of program was coded "no methadone," low threshold (methadone via the Municipal Health Service), medium threshold (methadone through a general practitioner), high threshold (methadone via an outpatient addiction clinic), or "other" (methadone through a police station or prison; no main type of program).

Variability in population characteristics or behavior may confound the association between methadone treatment characteristics and mortality. Three sets of variables describing sociodemographic characteristics (set 1), physical and mental health (set 2), and drug use (set 3) were used to adjust for possible confounding. Set 1 included sex (male, female), calendar years (1985–1989, 1990–1992, 1993–1994, 1995–1996), nationality (Dutch, German, other), ethnic background (Western Europe, Surinam/Antilles, other), homelessness, age (<31, 31–34, 35–39, >39 years), and history of prostitution (no history, past but not current, current).

Set 2 included HIV status (HIV negative, HIV positive with CD4+ lymphocyte count $\geq 500\times10^6$/L, HIV positive with CD4+ lymphocyte count $<500\times10^6$/L), body mass index (<18, ≥18), and psychopathology (General Health Questionnaire score <5, ≥5). A CD4+ count below 500×10^6/L indicates immunosuppression. Body mass index was calculated in the conventional manner (weight in kg/height in m^2).

Because of economic constraints, psychopathology was assessed for a limited sample of the Amsterdam Cohort Study: a cross section taken in 1989 and 1996 based on scores on the 30-item version of the General Health Questionnaire.[26,27] We defined the presence of psychopathology as a General Health Questionnaire score of 5 or higher.[28] In our study group, 517 (63%) participants had received at least 1 General Health Questionnaire assessment, and 79 had assessments in both 1989 and 1996. After the 1989 assessment, psychopathology status was considered stable until the second assessment of 1996.

Set 3 included years since first drug injection (0, <9, 9–13, 14–18, >18); years since initiation of regular heroin use (<3, 3–6, 7–12, >12); current frequency of injection, current use of heroin, current use of cocaine, current use of barbiturates, and current use of tranquilizers (all coded as none, less than daily, or daily); total number of illicit drugs currently used (heroin, cocaine, amphetamine; coded none, 1, 2, or 3); and (standardized) drinks of alcohol per day (0, 1–5, >5).

Statistical Analysis

Among the 827 study participants, the total number of cohort visits was 11 039, and the total amount of follow-up was 4961 person-years. Person-time methods were used to investigate the relationship between methadone treatment characteristics and mortality. Mortality rates were expressed as deaths per 1000 person-years. Variables that could vary within an individual over time (methadone treatment variables, behavioral variables, HIV status, age) were treated as time-dependent variables.

Methadone data were available from the Central Methadone Register for the time interval between the last cohort visit and the end of follow-up. Age, number of years since first injection, and number of years since initiation of regular heroin use could be calculated after the last cohort visit. For the other time-dependent variables, the value at the last cohort visit was extrapolated.

Poisson regression analysis was used to construct univariate and multivariate models predicting death due to natural causes or overdose and to calculate 95% confidence intervals (CIs). Multivariate models were constructed via forward stepwise techniques; variables with a P value of less than .10 in univariate analyses were considered as potential independent determinants. A P value below .05 (2-sided) was considered statistically significant. Interactions between important variables (methadone, current injection, HIV status, and calendar year) were assessed.

Mortality due to natural causes is often preceded by a period of hospitalization. In this case, the fact that an individual is not currently in methadone treatment (and has interrupted the methadone program) is due to the underlying illness. Therefore, the most recent methadone dosage, most recent type of methadone program, and frequency of program attendance variables were not considered as potential determinants of mortality due to natural causes.

Subanalyses were performed to examine the stability of the associations between methadone treatment and mortality. First, to assess the effect of long intervals between last cohort visit and censoring, we reanalyzed the data for (1) Dutch participants—for whom complete information on vital status was available—and (2) participants censored 1 year after their last cohort visit. We compared these results with our original results. Second, we added length of time between 2 visits to the multivariate models to assess the potential confounding of this variable. None of the subanalyses changed the results of the multivariate models substantially (data not shown).

TABLE 1—Cause-Specific Death Rates per 1000 Person-Years, by HIV Serostatus, in a Cohort of Drug Users: Amsterdam, the Netherlands, 1985–1996

	HIV Positive		HIV Negative		Total	
Cause of Death	No.	Rate	No.	Rate	No.	Rate
AIDS	55	33.7	. . .	. . .	55	11.1
Overdose	14	8.6	17	5.1	31	6.3
Suicide	4	2.4	7	2.1	11	2.2
Accident/violence	4	2.4	7	2.1	11	2.2
Pneumonia/sepsis	4	2.4	4	1.2	8	1.6
Liver failure	6	3.7	0	0.0	6	1.2
Cerebral/neural	4	2.4	2	0.6	6	1.2
Endocarditis	3	1.8	0	0.0	3	0.6
Other[a]	8	4.9	3	0.9	11	3.4
Unknown	4	2.4	4	1.2	8	1.6
All causes	106	64.9	44	13.2	150	30.2

[a]Carcinoma (n = 3), lung embolism, thrombosis, hypothermia, exhaustion, drowning (n = 2), chronic obstructive pulmonary disease, unknown natural cause.

Results

Of the 827 drug users included in the analyses, 60% were male, and 27% were of foreign nationality. At Amsterdam Cohort Study enrollment, participants' mean age was 31.0 years (SD = 6.3, range = 16–57), and 27% were HIV positive. The majority of the group (77%) had a history of drug injection, and the mean duration of injection drug use was 10.0 years (SD = 6.2, range = 1–28). Sixty-seven percent used more than one type of hard drug, most often a combination of heroin and cocaine.

The total follow-up time was 4961 person-years. Methadone was received mainly via low-threshold programs for 65% of these person-years, mainly via medium-threshold programs for 16%, mainly via high-threshold programs for 3%, and mainly via other means (no main type of program, police, prison) for 4%. For 13% of all person-years, no methadone was received.

One hundred fifty deaths were recorded, and the overall death rate was 30.2 per 1000 person-years. Table 1 presents cause-specific death rates in groups defined by HIV serostatus. The death rate among HIV-positive drug users was about 5 times the rate among HIV-negative drug users. Overdose was the major cause of death among the latter group, whereas most HIV-positive subjects died of AIDS (i.e., after AIDS diagnosis).[29]

Mortality Due to Natural Causes

Of the 150 deaths, 89 were due to a natural cause (AIDS, pneumonia/sepsis, liver failure, cerebral/neural, or "other"); the overall death rate was 17.9 per 1000 person-years. The mortality rate increased markedly after 1992 (Table 2), mainly because of the evolving AIDS epidemic.

Table 2 presents the significant univariate determinants of mortality due to natural causes. The only significant variable among those related to methadone treatment was mean methadone dosage. The death rates for persons receiving no methadone or methadone dosages above 60 mg/day were higher than the rates for those receiving 40 to 60 mg/day, but only the relative risk (RR) for dosages above 80 mg/day was significantly elevated (RR = 3.66, 95% CI = 2.00, 6.71).

Among variables related to sociodemographics, health, and drug use, those significantly related to higher death rates were older age, calendar year post-1991, positive HIV status, underweight status, longer duration of injection drug use, longer duration of heroin use, no illicit drug use, and a history of prostitution. Current heroin use was associated with lower mortality.

Table 3 shows the results of the multivariate analysis. Among variables related to sociodemographics, health, and drug use, positive HIV status and underweight status were independent determinants of mortality. To investigate whether the association between methadone dosage and mortality was confounded by these 2 variables, we added them to the model with mean methadone dosage. The "no methadone" relative risk increased and became statistically significant, and there was no longer

TABLE 2—Determinants of Mortality Due to Natural Causes: Univariate Results, Amsterdam, the Netherlands, 1985–1996

	No. of Deaths	Person-Years	Rate[a]	RR	95% CI	*P*
Mean methadone dosage, mg/d						<.001
0	13	614	21.2	1.62	0.79, 3.30	
1–20	5	431	11.6	0.89	0.33, 2.39	
21–40	12	1272	9.4	0.72	0.35, 1.50	
41–60	18	1375	13.1	1.00		
61–80	16	696	23.0	1.76	0.90, 3.44	
>80	25	521	47.9	3.66	2.00, 6.71	
Age, y						<.001
<30	9	1365	6.6	1.00		
30–34	24	1237	19.4	2.94	1.37, 6.33	
36–39	30	1325	22.6	3.43	1.63, 7.23	
>39	26	1035	25.1	3.81	1.79, 8.14	
Calendar years						<.001
1985–1989	5	1107	4.5	1.00		
1990–1991	11	976	11.3	2.49	0.87, 7.18	
1992–1994	44	1673	26.3	5.82	2.31, 14.68	
1995–1996	29	1206	24.1	5.32	2.06, 13.75	
HIV serostatus						<.001
Negative	9	3328	2.7	1.00		
Positive, CD4≥500	8	478	16.8	6.19	2.39, 16.05	
Positive, CD4<500	69	967	71.4	26.40	13.18, 52.87	
Underweight (body mass index<18)						<.001
No	50	3786	13.2	1.00		
Yes	24	401	59.9	4.54	2.79, 7.38	
Years since initiation of injecting						<.001
Never injected	3	683	4.4	0.59	0.16, 2.20	
≤8	9	1219	7.4	1.00		
9–13	20	1099	18.2	2.47	1.12, 5.42	
14–18	30	994	30.2	4.09	1.94, 8.60	
>18	20	615	32.5	4.40	2.01, 9.67	
Years since initiation of heroin use						<.001
≤3	10	1579	6.3	1.00		
4–6	25	1079	23.2	3.66	1.76, 7.61	
7–11	30	1101	27.3	4.30	2.10, 8.80	
>11	22	1180	18.6	2.94	1.39, 6.21	
Current heroin use (injection and noninjection)						.002
None	26	848	30.6	1.00		
Less than daily	54	3032	17.8	0.58	0.36, 0.93	
Daily	8	1013	7.9	0.26	0.12, 0.57	
Current number of illicit drugs used[b]						.034
0	19	615	30.9	2.04	1.20, 3.47	
1	14	813	17.2	1.14	0.63, 2.06	
2	48	3167	15.2	1.00		
3	7	229	30.6	2.02	0.91, 4.46	
Prostitution						.009
Never	40	2615	15.3	1.00		
Formerly, not currently	35	1345	26.0	1.70	1.08, 2.68	
Currently	8	866	9.2	0.61	0.28, 1.29	

Note. RR = relative risk; CI = confidence interval.
[a]Death rate per 1000 person-years.
[b]Cocaine, heroin, amphetamines, or any combination.

an effect of methadone dosages above 80 mg/day. In this model, the overall *P* value for methadone dosage was significant at the borderline level (*P*=.055).

When, instead of methadone dosage, the dichotomous "in methadone treatment" variable was included in the model, the results suggested that having left the methadone program (because all participants had a history of methadone treatment) was an independent predictor of mortality due to natural causes (RR=2.38, 95% CI=1.28, 4.55, *P*=.006). There were no indications of effect modification; adjustment for nonsignificant variables did not change the results substantially.

Mortality Due to Overdose

Thirty-one overdose deaths were recorded, resulting in an overdose mortality rate of 6.3 per 1000 person-years. No statistically significant time trend was observed (data not shown). None of the methadone variables were significantly related to overdose death in univariate analyses; however, no recent use of methadone (i.e., most recent methadone dosage, coded as a dichotomous variable) was significant at the borderline level (RR=1.89, 95% CI=0.93, 3.85). It should be noted that, although there were about 500 person-years (see Table 2) among subjects with a mean or most recent methadone dosage of more than 80 mg/day, there were no deaths in this category for either variable.

Among the sociodemographic, health, and drug use characteristics, homelessness was the only variable significantly related to death from overdose (RR=2.58, 95% CI=1.04, 6.43). Current injectors were at increased risk of over-

TABLE 3—Determinants of Mortality Due to Natural Causes: Multivariate Results, Amsterdam, the Netherlands, 1985–1996

	Univariate		Multivariate Model 1		Multivariate Model 2	
	RR	95% CI	RR	95% CI	RR	95% CI
Mean methadone dosage, mg/d						
0	1.62	0.79, 3.30	. . .		2.40	1.13, 5.10
1–20	0.89	0.33, 2.39	. . .		0.42	0.10, 1.81
21–40	0.72	0.35, 1.50	. . .		0.80	0.36, 1.77
41–60	1.00	1.00				
61–80	1.76	0.90, 3.44	. . .		1.05	0.50, 2.18
>80	3.66	2.00, 6.71	. . .		1.40	0.73, 2.71
HIV serostatus						
Negative	1.00	1.00	1.00			
Positive, CD4≥500	6.19	2.39, 16.05	5.13	1.78, 14.79	5.36	1.84, 15.36
Positive, CD4<500	26.40	13.18, 52.87	22.22	10.62, 46.49	22.04	10.37, 46.83
Underweight (body mass index>18)						
No	1.00	1.00	1.00			
Yes	4.54	2.79, 7.38	3.77	2.32, 6.14	3.65	2.24, 3.84

Note. RR=relative risk; CI=confidence interval.

TABLE 4—Determinants of Mortality Due to Overdose: Amsterdam, the Netherlands, 1985–1996

	Injectors		Noninjectors	
	RR	95% CI	RR	95% CI
In methadone treatment and currently receiving methadone	1.00		1.00	
In methadone treatment but not currently receiving methadone	2.93	1.14, 7.56	0.48	0.06, 4.24
Not in methadone treatment	5.66	1.97, 16.28	0.51	0.06, 4.02

Note. RR=relative risk; CI=confidence interval.

dose death, but the *P* value was of borderline significance (RR=2.14, 95% CI=0.96, 4.79). To assess confounding and effect modification, we constructed a multivariate model including no current use of methadone, current injection, and homelessness. Homelessness was not an independent predictor in this model, but the relative risk was fairly high (RR=2.1, 95% CI=0.8, 5.2). There was effect modification between current injection and not currently receiving methadone in that the interaction between these variables contributed significantly to the model (*P*=.02).

Further inspection of the data revealed that not currently receiving methadone was a predictor of overdose mortality only among injectors (RR=4.55, 95% CI=1.89, 10.00). The dichotomous "in methadone treatment" variable (which was significantly related to death due to natural causes) was not a significant predictor of overdose mortality in the univariate analysis but appeared to be statistically significant in the subanalysis among injectors.

A new variable combining "in methadone treatment since previous visit" and "currently receiving methadone" was constructed (Table 4). In comparison with currently receiving methadone, the relative risk for not currently receiving methadone was 2.93 (95% CI=1.14, 7.56); the relative risk for not being in treatment during the entire period since the previous visit was 5.66 (95% CI=1.97, 16.28). Adjustment for the other nonsignificant variables did not change the results substantially.

Discussion

This study shows significantly lower rates of natural-cause and overdose mortality among drug users attending a harm-reduction-based methadone program than among drug users leaving such programs. The methadone dosage itself was not significantly related to mortality.

It is known that high methadone dosages (more than 80 mg/day) reduce injection-related risk behavior,[30] which is associated with mortality from infectious diseases and overdose. In this study, a high methadone dosage was related to increased mortality due to natural causes in univariate analyses, but this association could be explained by the different dosing policies used for HIV-positive and HIV-negative subjects. HIV-positive individuals receive higher methadone dosages because (among other reasons) they are more often drug injectors; they are more likely to receive such dosages as part of their medical care or at their own request.[18] There were no overdose deaths among those with methadone dosages above 80 mg/day; however, the overall *P* value was not statistically significant.

The absence of an effect of methadone dosage on mortality in our study group can probably be explained by self-selection. Results of a previous study among Amsterdam drug users suggest that high dosages of methadone were most common among the severely addicted drug users,[18] who might have been at higher risk of mortality. Concurrent use of illicit drugs is tolerated in the harm-reduction approach to methadone treatment, so our study group was very heterogeneous in terms of risk behavior. The large overall difference in mortality rates between drug users attending the methadone programs and those who had left the programs, however, suggests that "being in care" is important in itself, independent of the pharmacologic effect of methadone dosage.

Clients of the Amsterdam methadone programs are seen by a physician at regular intervals for a social, medical, and psychologic checkup and health counseling. Although causality can never be proven in an observational study, the strong protective effect of attending the methadone programs suggests that methadone provision, together with social support and medical care, has a beneficial effect on the health of drug users, resulting in higher survival rates. Stenbacka et al. found that incidence of inpatient hospitalizations decreased with number of years in methadone treatment.[31]

In regard to the lower overdose mortality rates among methadone recipients who were injection drug users, attending methadone programs could reduce injection drug use, stabilize opiate tolerance levels, regulate concurrent use of alcohol and other drugs, and

improve drug users' general health status, reducing several important risk factors for overdose mortality.[32] Drug users who were not injecting at their last cohort visit and who were no longer in methadone treatment may have ceased all illicit drug use; this could explain why overdose mortality was lower (albeit not significantly lower).

The increased mortality risk of drug users who left the methadone programs could reflect selection bias; that is, drug users who leave the methadone programs are a select group in terms of psychopathology or health status. For our study group, this issue remains unclear, because determinants of methadone treatment dropout have not yet been investigated. However, adjustment was made for some factors, such as HIV status and injecting, and we believe that selection bias is of limited importance in regard to this study. Because drug users who drop out of treatment are at increased risk of mortality, they should be targeted for prevention measures. We found indications that homeless drug users are at increased risk of overdose death; thus, this vulnerable group also should be specifically targeted for public health interventions.

The finding that drug users outside of methadone treatment are at increased risk of dying is supported by a number of other studies.[11,13–16,33] Results of 2 previous studies in our cohort indicated that among injection drug users, high methadone dosages could be protective in terms of overdose mortality[34] and daily methadone use had no effect on overall mortality.[10] These findings contrast with those of the present study but could possibly be explained by methodological differences. In the previous studies, methadone treatment was self-reported instead of registered, and, more important, the methadone treatment variables had to be extrapolated from the last cohort visit onward.

Before we formulate an overall conclusion, several limitations of our study should be noted. First, follow-up was not complete for 6% of the study participants (mainly individuals of foreign nationality moving out of the Netherlands), and for 20% of the participants, the interval between the last cohort visit and censoring was more than 12 months. Bias may occur when completeness of follow-up and length of the interval between last cohort visit and censoring are related to both mortality risk and methadone treatment. Quality of follow-up was good, however, and the subanalyses restricted to Dutch participants and participants with intervals of less than 12 months showed the same results as the analysis of the larger study group. These potential biases are probably of limited importance within this study.

Second, current drug use behavior and HIV status variables had to be extrapolated from the last cohort visit onward, whereas methadone treatment data were available from the last cohort visit until censoring. The association between mortality and methadone program attendance could be adjusted for drug use characteristics (e.g., frequency of injection, multidrug use) to provide insight into the mechanism(s) by which methadone treatment prevents mortality. However, adjustment was limited because of the extrapolation. Behavioral variables are subject to a certain degree of nonrandom misclassification; for example, noninjectors can switch to injecting and die as a result of overdose.

Third, misclassification of causes of death could have occurred, particularly for overdose deaths. In an unknown percentage of cases, fatal overdose could have been intentional. Whereas unintentional overdose is potentially preventable[35] by such means as methadone treatment, prevention of suicide requires other strategies. Misclassification of overdose deaths would result in an underestimation of the true effect.

Our results support the hypothesis that harm-reduction-based methadone maintenance treatment decreases the risk of natural-cause and overdose mortality. Furthermore, our data suggest that in harm-reduction-based methadone programs, being in methadone treatment is important in itself, independent of the pharmacologic effect of methadone dosage. To decrease mortality among drug users, prevention measures should be expanded for those who dropout of treatment. □

Contributors

M. W. Langendam designed the study, analyzed the data, and wrote the paper. All coauthors contributed to the writing of the paper. In addition, R. A. Coutinho and E. J. C. van Ameijden assisted with the study design and supervised the study.

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