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Original Contribution

Characterizing Durations of Heroin Abstinence in the California Civil Addict Program: Results From a 33-Year Observational Cohort Study

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In accordance with the chronic disease model of opioid dependence, cessation is often observed as a longitudinal process rather than a discrete endpoint. We aimed to characterize and identify predictors of periods of heroin abstinence in the natural history of recovery from opioid dependence. Data were collected on participants from California who were enrolled in the Civil Addict Program from 1962 onward by use of a natural history interview. Multivariate regression using proportional hazards frailty models was applied to identify independent predictors and correlates of repeated abstinence episode durations. Among 471 heroin-dependent males, 387 (82.2%) reported 932 abstinence episodes, 60.3% of which lasted at least 1 year. Multivariate analysis revealed several important findings. First, demographic factors such as age and ethnicity did not explain variation in durations of abstinence episodes. However, employment and lower drug use severity predicted longer episodes. Second, abstinence durations were longer following sustained treatment versus incarceration. Third, individuals with multiple abstinence episodes remained abstinent for longer durations in successive episodes. Finally, abstinence episodes initiated >10 and ≤20 years after first use lasted longer than others. Public policy facilitating engagement of opioid-dependent individuals in maintenance-oriented drug treatment and employment is recommended to achieve and sustain opioid abstinence.

abstinence; Cox proportional hazards; frailty models; γ-frailty models; heroin use; illicit drug use; opioid dependence; substance abuse treatment

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HR, hazard ratio.

Drug dependence is acknowledged by the medical and scientific communities as a chronic, recurrent condition (1). Recent surveys indicate that the general public perceives addiction as difficult to overcome, requiring multiple attempts and successive treatment episodes (2). Relative to onset, maintenance, and relapse, deceleration and cessation of use are the least studied phenomena in drug abuse research (3–5). The process constituting cessation should be considered in the context of a drug use career, examined through a longitudinal conceptual and analytical approach (6).

To this end, several long-term cohort studies have provided some insight into the longitudinal patterns of drug use and cessation. Termorshuizen et al. (7) considered longitudinal patterns of opioid use cessation in the Amsterdam Cohort Study. Participants were recruited primarily from methadone treatment. At least 27% of the participants died within 20 years after starting regular drug use; among those alive, the estimated prevalence of opioid abstinence for at least the past 4 months was only 27% at 20 years after initiation. A subsequent analysis found that over 85% of all abstinence episodes were followed by relapse within 5 years (8).

Studying a cohort comprising cocaine-, alcohol-, opioid-, and marijuana-dependent individuals, Scott et al. (5) and Dennis et al. (9) used lifetime substance use and treatment histories, recorded at intake and annual follow-up interviews over a 5-year period, to estimate predictors of the time from first illicit drug use and first treatment until a reported 12 months of abstinence or death. The median time from first to last use was 27 years. During the 3 years after intake, 47% reached at least 12 months of abstinence. Years to recovery were significantly longer for males, those starting use under the age of 21 (particularly those starting under the age of 15), those who had participated in treatment 3 or more times, and those with high levels of mental distress. Subsequent research on this cohort found that higher percentages of time abstinent and longer durations of continuous abstinence were associated with a reduced risk of mortality (10).

Finally, prior studies on a cohort of male heroin-dependent individuals enrolled in the Civil Addict Program considered, among other endpoints, the predictors of long-term stable recovery, defined as 10-year abstinence. Results showed that, although both recovered and nonrecovered addicts tried formal treatment and self-directed recovery, stable recovery 10 years following an index assessment was predicted only by ethnicity, self-efficacy, and psychological distress (11).

Although these studies provide a unique perspective on the life course of drug addiction, each has considered drug use cessation as a discrete outcome rather than one part of a recurrent event process. In contrast, the acquired immunodeficiency syndrome (AIDS) Link to Intravenous Experience (ALIVE) Study found injection drug users (primarily heroin and cocaine injectors) followed multiple longitudinal patterns of drug injection over a 10-year time frame. Four primary patterns were noted: 29% remained persistent drug injectors, 20% ceased injection by the end of follow-up, 14% relapsed once, and 37% had multiple transitions between regular illicit drug use and treatment or abstinence (12). Evidence on patterns of methadone treatment suggests that, for most, recovery from drug abuse is a process with a cyclical pattern of sustained treatment and posttreatment relapse (13, 14).

The aforementioned study by Scott et al. (10) is among the few studies we found that considered the effects of drug abstinence on the risk of mortality. For opioid dependence, sustained drug treatment is known to reduce the risk of mortality (15), as well as to decrease acquisitive crime (16) and to improve health-related quality of life (17) among other positive benefits; these benefits are likely to be sustained or even improved during periods of abstinence, which should be considered key markers of the pathway toward recovery. Our objective was to characterize periods of heroin abstinence throughout the drug use career and to identify predictors of successive periods of heroin abstinence in the process of recovery from opioid dependence among participants of the Civil Addict Program, a 33-year follow-up of a set of male opioid-dependent individuals.

MATERIALS AND METHODS

Study population

The Civil Addict Program cohort consisted of 471 male heroin-dependent individuals successfully followed from 581 participants originally admitted to the Civil Addict Program from 1962 through 1964. The Civil Addict Program, established in 1961 by California legislation, was a compulsory drug treatment program for heroin-dependent criminal offenders committed under court order (18, 19).

The sample was selected from all admissions to the Civil Addict Program during 1964–1965 and first interviewed in 1974–1975 (20), then in 1985–1986 (18), and later in 1996–1997 (19). The 1996–1997 study had a 96% location rate (242 were interviewed, 31 refused or were too mentally dysfunctional to be interviewed, and 284 were confirmed to be deceased), with 24 participants lost to follow-up. Data on trajectories of drug use, abstinence, and other covariates were combined from the 3 interviews at 10-year intervals. Written, informed consent was obtained following a complete study description to the participants. The University of California, Los Angeles, Institutional Review Board approved and monitored the successive studies.

Data were collected using the Natural History Interview (20, 21). The Natural History Interview contains sections on personal and family background, physical and mental health, drug use and treatment (all instances, including medication-based and behavioral programs), criminal history, and risk behaviors. A timeline follow-back approach, anchored by data from official criminal justice- and Civil Addict Program-related treatment records, collected a continuous history describing drug use and other behaviors from first substance use until the interview. Using the anchor-based timeline, the interviewee noted major events for reference and then identified time periods associated with specific behaviors, with periods delineated by changes in behavior. These reported data were translated to monthly longitudinal data. The Natural History Interview has been shown to have generally high reliability; correlation coefficients of intervariable relationships, based on 46 variables measured at 2 interviews 10 years apart, ranged as high as 0.86 and 0.90 (22–24).

Study design

This study considers the durations of successive periods of heroin abstinence over a drug use career. These durations are formally defined as periods in which respondents indicated no heroin use (specific to heroin use) and were not enrolled in drug treatment or incarcerated, with no interruptions as a result of relapse to drug use, drug treatment, or incarceration. The latter criterion was applied as drug use (or drug abstinence) was not assessed during periods of incarceration. Our outcome measure can therefore be described more explicitly as community-based heroin abstinence.

An extensive set of covariates, collected throughout the Civil Addict Program study, was then organized into sets of 1) fixed covariates; 2) incident covariates, indicating status in the 30 days prior to initiation of an abstinence episode; 3) cumulative covariates, indicating status of a covariate over the duration of time from drug use initiation to abstinence episode initiation (either dichotomous, i.e., ever used stimulants, or continuous, i.e., percentage of time using drugs); or 4) concurrent covariates, indicating covariate status during the duration of abstinence under study. Summary statistics on the full set of covariates considered were presented in Table 1.

Table 1. Summary Statistics, Civil Addicts Program, California, 1962–1995

Covariate	No.	%	Mean (SD)
Race			
White	134	34.6	
Black	31	8.0	
Hispanic	222	57.4	
Age at heroin use initiation, years			18.6 (4.0)
Age at first arrest, years			15.2 (3.6)
Age at initial abstinence episode initiation			
<25 years	138	35.7	
26–35 years	137	35.4	
36–45 years	81	20.9	
>45 years	31	8.0	
Education			
Less than high school	186	52.5	
High school/GED	134	37.9	
College	34	9.6	
Missing	33	8.5	
Marital status, past 30 days[a]	68	19.1	
Single			
Divorced/separated	191	53.5	
Married	98	27.5	
Missing	30	7.8	
Drug treatment, past 30 days	8	2.1	
Treatment episode, <6 months			
Treatment episode, ≥6 months	55	14.2	
Employment			
Cumulative past employment, %[b]			38.5 (48.7)
Past 30 days	149	38.5	
Concurrent employment, %[c]			38.5 (48.7)
Crime			
Cumulative past criminal involvement, %			26.5 (24.5)
Past 30 days	42	10.9	
Concurrent criminal activity, %			7.0 (24.9)
Incarceration			
Cumulative past incarceration, %			35.8 (21.8)
Past 30 days	227	58.7	
Heroin use			
Cumulative past use, years used			61.6 (22.0)
Use in the past 30 days, days used			5.7 (11.2)
Stimulant use			
Cumulative past use, years used			5.4 (15.4)
Use in the past 30 days, days used			0.6 (3.8)
Concurrent use, days			0.0 (0.0)
Marijuana use			
Cumulative past use, years used			13.3 (22.5)
Use in the past 30 days, days used			1.5 (6.1)
Concurrent use, days			18.0 (37.6)
Alcohol use			
Cumulative past use, years used			24.5 (29.1)
Use in the past 30 days, days used			2.1 (5.0)
Concurrent use, days			49.1 (48.5)

Abbreviations: GED, high school general equivalency diploma; SD, standard deviation.

[a] Past 30 days: 30 days prior to first abstinence episode initiation.

[b] Percentage of past months prior to initial abstinence episode.

[c] Percentage of months during initial abstinence episode.

In some cases, continuous variables were either categorized (age, heroin use in past 30 days) or dichotomized. Categories were defined on the basis of the distributions of the individual covariates. Three additional covariates of interest were constructed: First, indicator variables for the first to the fifth or greater abstinence episode attempt were derived following construction of the repeated-measures data set. Second, the cumulative length of time to abstinence episode initiation was calculated for each successive episode to determine whether the time from abstinence episode initiation is a significant predictor of abstinence episode duration. Finally, we initially considered an indicator variable for drug treatment (primarily methadone maintenance or detoxification but also including residential forms of treatment) in the 30 days prior to abstinence episode initiation in preliminary analyses and then expanded our approach to consider the duration of treatment prior to abstinence episode initiation in order to compare the effectiveness of shorter-duration treatment (<6 months) versus longer, presumably maintenance-oriented treatment (≥6 months).

Statistical analysis

Cox proportional hazards γ-frailty models can be fitted to account for the dependence in the length of homogeneous repeated episodes (25–33). A prior application considered the duration of repeated exposure to methadone maintenance treatment (14). Like standard Cox proportional hazards applications, the outcome is the bivariate pair (duration, censorship). In instances where there are multiple repeated durations of interest, the Cox proportional hazards γ-frailty model provides a means of explicitly modeling these repeated measures within a standardized longitudinal framework. Like other mixed-effects modeling applications with longitudinal data, the Cox proportional hazards frailty model captures the correlation in episode lengths within an individual; conditional on the frailty terms, the episode lengths are independent (27). The unobserved random effect, or frailty, for the ith individual (v_j) can be assumed to follow a γ distribution ($v_j \sim \gamma(1/(\theta), 1/(\theta))$). Frailties are unobservable random variables corresponding to each individual's underlying modification of the baseline hazard function. Conceptually, they represent covariates capturing time-invariant unmeasured confounding (34). The maximum likelihood function is optimized by using the expectation-maximization algorithm; however, other techniques have been applied (31).

It should be noted that, although times between acute events, or "gap times," have been assessed in other frailty model applications, here we incorporated only durations in which individuals were continuously abstinent from heroin. Although the choice of time scale differs, the Cox proportional hazards γ-frailty model can be useful in either application (25).

The initial set of covariates were selected in part on the basis of prior studies on factors associated with abstinence and success in treatment (7, 8); however, given the paucity of such evidence, we considered this an exploratory analysis and endeavored to use the data set to its greatest extent, particularly in regard to creating fixed, incident, cumulative, and concurrent covariates, as specified above. Variable selection for the final multivariate regression model was conducted iteratively, first fitting models by variable classes 1–4 and then combining reduced sets of covariates from each class into a final regression model incorporating covariates from each class. Variables were otherwise excluded if a high degree of collinearity was identified. For instance, incident employment and cumulative employment were found to be highly collinear; that is, employment in the past 30 days was highly correlated with cumulative employment or ever having been employed during the individuals' drug use career, and thus the covariate with the greater strength of association was included into the final model.

The proportional hazards assumption was tested for each covariate by using the weighted residuals score test (32) and by inspecting Schoenfeld residual plots (33). As noted elsewhere (14, 35), hazard ratios obtained from classical Cox proportional hazards models are time-averaged effects, weighted by the duration of the time-to-event intervals under study. Schoenfeld residual plots provide a visual representation of each parameter over the range of time-to-event intervals under study—$\beta(t)$. We inspected each covariate with the diagnostic tests above, not accounting for intraindividual correlation between repeated abstinence episodes. Hazard ratios >1 indicated faster time to discontinuation or shorter abstinence episodes compared with the referent group. Analyses were conducted by using SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) and R, version 2.5.1, language (Lucent Technologies, Murray Hill, New Jersey).

RESULTS

A total of 471 heroin-dependent individuals were recruited into the Civil Addict Program, with 387 (82.2%) reporting an episode of opioid abstinence lasting at least 1 month during study follow-up; this subset of individuals comprised our analytical sample. The mean duration of follow-up for the sample was 33.1 years.

Patient characteristics at the time of first abstinence episode initiation are presented in Table 1. The cohort comprised only males—57% Hispanic, 35% white, and 8% black. Exactly 38.5% were employed in the month prior to their first abstinence episode, while 58.7% had been incarcerated. Another 16.3% had spent time in some form of drug treatment, with 14.2% spending at least the past 6 months in a treatment program. Heroin use was pervasive in the cumulative months leading up to abstinence, as were uses of marijuana and alcohol; however, stimulant use was uncommon. We note that drug use frequency was not ascertained during periods of incarceration; therefore, estimates of cumulative drug use and use in the 30 days prior to abstinence were likely underestimated.

Table 2 summarizes the primary study outcome: the durations of successive abstinence episodes. Overall, 932 heroin abstinence episodes were observed. Their median duration was 15 months (interquartile range: 6–46), with 60.3% lasting at least 1 year, 21.4% lasting at least 5 years, and 20.1% ongoing at the end of follow-up. Individuals had a maximum of 13 heroin abstinence episodes; however, only 86 (22.2%) had 4 or more episodes. Patterns of abstinence episodes among individuals with 1, 2, 3, and 4 or more episodes are illustrated in Web Figure 1 available at http://aje.oxfordjournals.org/. Individuals with only 1 heroin observed-abstinence episode initiated abstinence 14.6 years (median = 176 months, interquartile range: 107–265) after heroin use initiation, and their abstinence episode lasted 2 years (median = 24 months, interquartile range: 7–141). Those with 2, 3, and 4 or more heroin abstinence episodes generally initiated abstinence sooner than those with 1 abstinence episode, and their abstinence episodes tended to last progressively longer in subsequent attempts.

Results of the multivariate Cox proportional hazards frailty model are presented in Table 3. First, using a random intercept (frailty) model was advantageous, as witnessed by a greatly increased pseudo-R^2 value for the frailty model compared with a pooled Cox proportional hazards model (R^2 (frailty model) = 0.27 compared with R^2 (pooled model) = 0.11) and joint statistical significance of the vector of individual frailty terms ($P < 0.01$). Weighted residuals score tests indicated that the null hypothesis of proportionality was not rejected for each of the covariates listed in Table 1.

Covariates described in Table 1 but excluded in the final multivariate model were not statistically significantly associated with abstinence episode durations in univariate analyses. With control for other covariates, neither race nor age

Table 2. Description of Abstinence Episode Counts and Durations, Civil Addicts Program, California, 1962–1995

Abstinence Episode Count	No.	Abstinence Episode Duration, months		12 Months[a]		60 Months[b]		Censored[c]	
		Mean (SD)	Median (IQR)	No.	%	No.	%	No.	%
1	387	51.2 (88.0)	13 (6–40)	220	56.9	78	20.2	57	14.7
2	235	42.6 (62.1)	16 (7–46)	153	65.1	50	21.3	53	22.6
3	135	36.8 (44.5)	18 (7–49)	85	63.0	31	23.0	22	16.3
4	86	43.2 (56.8)	19 (7–58)	56	65.1	21	24.4	28	32.6
5	42	43.5 (45.2)	26 (8–77)	26	61.9	13	31.0	17	40.5
6	21	21.4 (31.4)	12 (4–21)	12	57.4	2	9.5	5	23.8
7	11	17.8 (25.8)	9 (3–18)	5	45.5	1	9.1	1	9.1
8	7	31.9 (29.8)	29 (5–67)	4	57.1	2	28.6	3	42.9
9	2	10.0 (1.4)	10 (9–11)	0	0	0	0	0	0
10	2	7.5 (2.1)	7.5 (6–9)	0	0	0	0	0	0
11	2	7.0 (2.8)	7 (5–9)	0	0	0	0	0	0
12	1	9.0	9	0	0	0	0	0	0
13	1	156.0	156	1	100	1	100	1	100
Overall	932	44.4 (70.4)	15 (6–46)	562	60.3	199	21.4	187	20.1

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a] Abstinence episode lasted at least 12 months.
[b] Abstinence episode lasted at least 60 months.
[c] Abstinence episode ongoing at the end of study follow-up.

at abstinence episode initiation was a statistically significant predictor of the duration of abstinence.

High levels of heroin use in the 30 days prior to heroin abstinence episode initiation led to shorter periods of abstinence: over 1.70 times shorter among those using at least 28 of the 30 days versus users for <7 days (hazard ratio (HR) = 1.77, 95% confidence interval (CI): 1.33, 2.33).

Heroin abstinence episodes initiated immediately following incarceration (HR = 1.70, 95% CI: 1.37, 2.13) were shorter on average than episodes initiated at other time points. In contrast, episodes initiated following drug treatment tended to be longer than those initiated in the absence of treatment. This effect was statistically significant when the prior treatment episode lasted at least 6 months (HR = 0.50, 95% CI: 0.33, 0.74).

Employment in the month prior to heroin abstinence episode initiation was predictive of longer durations of abstinence (HR = 0.65, 95% CI: 0.53, 0.79). Evidence of cumulative past use of stimulants (either cocaine or methamphetamine) had a large and statistically significant negative impact on durations of opioid abstinence (HR = 1.34, 95% CI: 1.09, 1.66). Both alcohol intake and marijuana use during the episode of opioid abstinence were associated with longer durations of opioid abstinence.

The duration of successive episodes of heroin abstinence among those with repeated attempts tended to increase in subsequent episodes. Second attempts were 21% longer than initial attempts, on average (HR = 0.78, 95% CI: 0.63, 0.97), and fifth or greater attempts were 46% longer than initial attempts (HR = 0.64, 95% CI: 0.45, 0.92).

Finally, heroin abstinence episodes initiated 10–20 years after heroin use initiation were longer than those initiated within the first 5 years of use. However, episodes initiated 5–10 or >20 years after initiation were not statistically significantly different in duration from those commencing within the first 5 years after initiation.

DISCUSSION

The primary result of our analysis was that durations of heroin abstinence among individuals with multiple episodes were successively longer in subsequent attempts. Further, heroin abstinence episodes commencing within 5 years of use initiation were substantially shorter than those initiated 10–20 years after the onset of use. These results affirm the chronicity of heroin dependence and underline the difficulty individuals have in remaining abstinent. Drug relapse does not preclude later sustained abstinence; rather, it is a commonly observed step toward a drug-free state, often occurring multiple times before sustained abstinence can be achieved. These results are corroborated in other substances of abuse, particularly smoking cessation (36, 37), as well as durations of successive periods of methadone maintenance treatment (14).

Factors indicative of drug use severity and social stability such as heroin use intensity, cumulative past use of stimulants, drug treatment, and employment were key predictors of the durations of periods of abstinence. Our results on the effect of employment suggest that it is an important factor in the social rehabilitation of drug-addicted individuals. Despite the strong hypothetical relationship between employment and either sustained treatment or successful recovery, evidence on associations or, more importantly, temporal relationships between these factors is scarce. Subjects in the

Table 3. Results of Multivariate Analysis on the Duration of Successive Episodes of Opioid Abstinence, Civil Addicts Program, California, 1962–1995

Covariates	Adjusted HR	95% CI
Age		
<25 years	1.00	Referent
26–35 years	1.14	0.82, 1.58
36–45 years	0.94	0.61, 1.45
>45 years	0.82	0.50, 1.35
Race		
White	1.00	Referent
Black	1.29	0.90, 1.87
Hispanic	1.22	0.99, 1.51
Heroin use in past 30 days		
<7 days	1.00	Referent
7–28 days	1.45	0.98, 2.16
>28 days	1.72	1.30, 2.28
Incarcerated in past 30 days	1.70	1.37, 2.13
Employed in past 30 days	0.65	0.53, 0.79
Prior treatment		
None in past month	1.00	Referent
Treatment lasting <6 months	0.36	0.12, 1.09
Treatment lasting ≥6 months	0.50	0.33, 0.74
Abstinence episode attempts		
1	1.00	Referent
2	0.78	0.63, 0.97
3	0.80	0.62, 1.04
4	0.64	0.45, 0.90
≥5	0.64	0.45, 0.92
Concurrent alcohol use	0.75	0.63, 0.90
Concurrent marijuana use	0.74	0.60, 0.92
Cumulative past stimulant use	1.34	1.09, 1.66
Time since drug use initiation, years		
<5	1.00	Referent
5–10	0.87	0.64, 1.19
11–15	0.65	0.44, 0.97
16–20	0.61	0.39, 0.94
>20	0.78	0.48, 1.28

Abbreviations: CI, confidence interval; HR, hazard ratio.

Drug Abuse Treatment Outcome Study who were in recovery in follow-up reported that they had relied primarily upon personal motivation, treatment experiences, religion/spirituality, family, and their job for their own long-term recovery (38). Drug treatment should include employment interventions as a means to encourage social rehabilitation; evaluations of such programs need to be conducted longitudinally to better understand and characterize the intermediate and causal pathways to recovery from illicit drug abuse.

Interestingly, both alcohol intake and marijuana use during the episode of opioid abstinence were associated with longer durations of opioid abstinence. As these indicators were captured during the course of abstinence episode, we cannot affirm any temporal and therefore causal relationship between the exposure and outcome. However, the results are suggestive of some degree of substitution between heroin and alcohol and marijuana. Within the specified context, use of other drugs during opioid cessation has been observed in other studies (7, 8).

Many episodes of abstinence were preceded by durations of incarceration and treatment. Even if drug use can be effectively discontinued during incarceration, we find that subsequent abstinence following release tends to be shorter lived than that observed as a result of drug treatment. Policy responses in accordance with this point (39) have been implemented in many settings worldwide. However, evidence of the continued use of detoxification treatment (still offered in 60.1% of all US facilities offering substitution treatment surveyed by the Substance Abuse and Mental Health Services Administration in 2009) (40) and a lack of capacity for drug treatment during incarceration in the United States in particular (41) significantly hamper efforts to promote cessation from drug abuse.

Some questions have been raised recently regarding the interpretation of hazard ratios obtained from standard (single interval) Cox proportional hazards models (35). Briefly, this critique has highlighted the fact that hazard ratios are average effects weighted by the time-to-event durations and, thus, highly sensitive to the duration of follow-up and the rate of censorship. Analyses of repeated time-to-event durations over long timeframes are less susceptible to these effects because 1) only the last time-to-event duration for each individual can necessarily be censored, and 2) rates of censorship tend to be lower in studies with longer durations of follow-up required for repeated time-to-event durations. Further, we assert that inferences drawn from these forms of analysis are, and should be, based on the mean. Mean estimates of hazard ratios provide the most representative and, therefore, generalizable results from a given data set. As for the attribution of causality, we believe that these results should be regarded no differently from other well-designed analyses based on observational data (42, 43). Such an assertion requires acceptance of a number of criteria that may not be able to be drawn from a single study.

Our study had several limitations that require consideration. First, as noted, data came from self-reported interviews at 10-year intervals from which monthly records of the outcome and measures of exposure were constructed. The temporal ordering of events within the recurrent event process may have been influenced by rounding error and recall bias given the long duration between follow-up interviews, and the level of error likely increased as a function of time from the interview date. As noted, recall bias was minimized by using records-based anchors. We have no reason to believe the resulting bias in either case was differential, resulting in attenuation of hazard ratios toward the null hypothesis. Second, although a substantial number of participants died during the study follow-up period, we did not model mortality explicitly. Given the 10-year follow-up intervals, data on drug use and other factors between the date of last interview and death were unobserved. This precludes any direct inference on the potential protective effects of abstinence or the duration of abstinence against mortality. Nonetheless, the Civil Addict Program is among the longest and most comprehensive follow-up studies of heroin users available. Third, data on drug use were not measured during periods of incarceration, thus making us infer the effects of covariates on periods of community-based heroin abstinence. Fourth, as with any nonexperimental study, ours may be subject to residual and/or unmeasured time variant confounding (43). Data on other predictors of durations of abstinence, such as motivational status and social support, were unavailable for the duration of follow-up. Although we cannot ascertain the individual effects of the unobserved factors, we can confidently state that their omission did not bias the coefficients on the existing fixed effects included in the analysis.

Finally, the cessation process may not be generalizable to opioid-dependent individuals not mandated into drug treatment. Although we have considered individual-level factors associated with opioid cessation, the process of cessation may also be influenced by external factors, such as the state legislation on drug-related crime and repeated offenders, and changes in these factors over time. Further study is required to define the no-doubt heterogeneous opioid use cessation process over time and across settings with disparate social and legislative conditions.

Our results further affirm the chronicity of heroin dependence and illustrate the point that the road to recovery is aided by prolonged drug treatment, often marked by multiple periods of relapse. Further emphasis is needed to facilitate long-term engagement of opioid-dependent individuals with drug treatment and other social supports to maintain stable recovery.

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REFERENCES

1. McLellan AT, Lewis DC, O'Brien CP, et al. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284(13):1689–1695.
2. Harvard School of Public Health, Robert Wood Johnson Foundation. Illegal drugs and end of life survey. Health poll search. Mansfield, CT: The Roper Center for Public Opinion Research, University of Connecticut; 2000. (http://roperweb.ropercenter.uconn.edu/cgi-bin/hsrun.exe/Roperweb/HPOLL/StateId/RBIcbup10rBU0bv0td6EWDJVZF2Nm-4p5V/HAHTpage/Summary_Link?qstn_id=440182). (Accessed: January, 2011).
3. Schomerus G, Matschinger H, Angermeyer MC. Alcoholism: illness beliefs and resource allocation preferences of the public. *Drug Alcohol Depend*. 2006;82(3):204–210.
4. Laudet AB. What does recovery mean to you? Lessons from the recovery experience for research and practice. *J Subst Abuse Treat*. 2007;33(3):243–256.
5. Scott CK, Foss MA, Dennis ML. Pathways in the relapse–treatment–recovery cycle over 3 years. *J Subst Abuse Treat*. 2005;28(suppl 1):S63–S72.
6. Hser Y-I, Anglin MD, Grella C, et al. Drug treatment careers: a conceptual framework and existing research findings. *J Subst Abuse Treat*. 1997;14(6):543–558.
7. Termorshuizen F, Krol A, Prins M, et al. Prediction of relapse to frequent heroin use and the role of methadone prescription: an analysis of the Amsterdam Cohort Study among drug users. *Drug Alcohol Depend*. 2005;79(2):231–240.
8. Termorshuizen F, Krol A, Prins M, et al. Long-term outcome of chronic drug use: the Amsterdam Cohort Study among drug users. *Am J Epidemiol*. 2005;161(3):271–279.
9. Dennis ML, Scott CK, Funk R, et al. The duration and correlates of addiction and treatment careers. *J Subst Abuse Treat*. 2005;28(suppl 1):S51–S62.
10. Scott CK, Dennis ML, Laudet A, et al. Surviving drug addiction: the effect of treatment and abstinence on mortality. *Am J Public Health*. 2011;101(4):737–744.
11. Hser YI. Predicting long-term stable recovery from heroin addiction: findings from a 33-year follow-up study. *J Addict Dis*. 2007;26(1):51–60.
12. Galai N, Safaeian M, Vlahov D, et al. Longitudinal patterns of drug injection behavior in the ALIVE Study cohort, 1988–2000: description and determinants. *Am J Epidemiol*. 2003;158(7):695–704.
13. Bell J, Burrell T, Indig D, et al. Cycling in and out of treatment; participation in methadone treatment in NSW, 1990–2002. *Drug Alcohol Depend*. 2006;81(1):55–61.
14. Nosyk B, MacNab YC, Sun H, et al. Proportional hazards frailty models for recurrent methadone maintenance treatment. *Am J Epidemiol*. 2009;170(6):783–792.
15. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*. 2011;106(1):32–51.

16. Zarkin GA, Dunlap LJ, Hicks KA, et al. Benefits and costs of methadone treatment: results from a lifetime simulation model. *Health Econ*. 2005;14(11):1133–1150.
17. Nosyk B, Guh D, Sun H, et al. Health related quality of life trajectories of patients in opioid substitution treatment. *Drug Alcohol Depend*. 2011;118(2-3):259–264.
18. Hser YI, Hoffman V, Grella CE, et al. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001;58(5):503–508.
19. Hser YI, Huang D, Chou CP, et al. Trajectories of heroin addiction: growth mixture modeling results based on a 33-year follow-up study. *Eval Rev*. 2007;31(6):548–563.
20. McGlothlin WH, Anglin MD, Wilson BD. *An evaluation of the California Civil Addict Program*. Washington, DC: Government Printing Office; 1977. (NIDA services R monograph series). (DHEW publication no. ADM78-558).
21. Nurco DN, Bonito AJ, Lerner M, et al. Studying addicts over time: methodology and preliminary findings. *Am J Drug Alcohol Abuse*. 1975;2(2):183–196.
22. Anglin MD, Hser YI, Chou C. Reliability and validity of retrospective behavioral self-report by narcotics addicts. *Eval Rev*. 1993;17(1):91–108.
23. Chou CP, Hser Y-I, Anglin MD. Pattern reliability of narcotics addicts' self-reported data: a confirmatory assessment of construct validity and consistency. *Subst Use Misuse*. 1996;31(9):1189–1216.
24. Hser YI, Anglin MD, Chou C. Reliability of retrospective self-report by narcotics addicts. *Psychol Assessment*. 1992; 4(2):207–213.
25. Cook RJ, Lawless JF. *The Statistical Analysis of Recurrent Events*. New York, NY: Springer-Verlag Publishers; 2008.
26. Sargent DJ. A general framework for random effects survival analysis in the Cox proportional hazards setting. *Biometrics*. 1998;54(4):1486–1497.
27. Vaida F, Xu R. Proportional hazards model with random effects. *Stat Med*. 2000;19(24):3309–3324.
28. Huang X, Wolfe RA. A frailty model for informative censoring. *Biometrics*. 2002;58(3):510–520.
29. Liu L, Wolfe RA, Huang X. Shared frailty models for recurrent events and a terminal event. *Biometrics*. 2004; 60(3):747–756.
30. Huang X, Liu L. A joint frailty model for survival and gap times between recurrent events. *Biometrics*. 2007;63(2): 389–397.
31. Liu L, Huang X. The use of Gaussian quadrature for estimation in frailty proportional hazards models. *Stat Med*. 2008;27(14):2665–2683.
32. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81(3):515–526.
33. Therneau TM, Grambsch PT. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer-Verlag Publishers; 2000.
34. Raudenbush SW, Bryk AS. *Hierarchical Linear Models: Applications and Data Analysis Methods*. 2nd ed. Newbury Park, CA: Sage; 2002.
35. Hernan MA. The hazard of hazard ratios. *Epidemiology*. 2010;21(1):13–15.
36. Gourlay SG, Forbes A, Marriner T, et al. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ*. 1995;311(7001):363–366.
37. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. *Clin Pharmacol Ther*. 2001;69(6):438–444.
38. Flynn PM, Joe GW, Broome KM, et al. Recovery from opioid addiction in DATOS. *J Subst Abuse Treat*. 2003; 25(3):177–186.
39. Evans E, Longshore D. Evaluation of the Substance Abuse and Crime Prevention Act: treatment clients and program types during the first year of implementation. *J Psychoactive Drugs*. 2004;(suppl 2):165–174.
40. Substance Abuse and Mental Health Services Administration. Opioid treatment program directory. Rockville, MD: Division of Pharmacologic Therapies, Center for Substance Abuse Treatment, Substance Abuse, and Mental Health Services Administration, Department of Health and Human Services; 2012. (http://dpt2.samhsa.gov/treatment/directory.aspx). (Accessed October 2011).
41. Nunn A, Zaller N, Dickman S, et al. Methadone and buprenorphine prescribing and referral practices in US prison systems: results from a nationwide survey. *Drug Alcohol Depend*. 2009;105(1-2):83–88.
42. Hill AB. The environment and disease association or causation. *Proc R Soc Med*. 1965;58:295–300.
43. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet*. 2002;359(9302):248–252.