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Gender differences in mortality among treated opioid dependent patients

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Abstract

Aims—To assess gender differences in characteristics, mortality rates, and the causes and predictors of death among treated opioid-dependent individuals.

Methods—Linked vital statistics data were obtained for all individuals first enrolled in publicly-funded pharmacological treatment for opioid dependence in California from 2006–2010. Standardized mortality ratios (SMR) were calculated by gender. Cox proportional hazards models with time-varying covariates were fitted to determine the effect of gender on the hazard of all-cause mortality, controlling for covariates.

Results—Over a median 2.6 years (interquartile range: 1.4 – 3.7), 1,031 deaths were observed, including 2.2% (259/11,564) of women and 3.7% (772/20,758) of men. Women had a greater increased risk of mortality compared to the general population (SMR 5.1 95% CI: 4.5, 5.7) than men (SMR 4.3 95% CI: 4.0, 4.6). The relative risk of death for women compared with men was 1.18 (95% CI: 1.02, 1.36). Women had a lower instantaneous hazard of all-cause mortality than men (HR 0.58, 95% CI 0.50, 0.68), controlling for other factors. Significant interaction effects indicated that among men, mortality risk was decreased by full-time employment and increased by non-daily heroin use (relative to daily use) and medical problems. Concurrent opioid and methamphetamine/cocaine use increased mortality risk among women and decreased it among men.

Conclusions—Treatment for opioid dependence is likely to reduce mortality risk among men by addressing employment and medical problems, and via interventions to reduce overdose risk after heroin abstinence, and among women by attending to the concurrent use of methamphetamine/cocaine and opioids.

Keywords

Opioid dependence; Mortality; Gender differences; Detoxification treatment; Methadone treatment; Longitudinal

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1.0 Introduction

National prevalence data indicate that from 2009–2011, women in the USA were less likely than men to use heroin (SAMHSA, 2013). At the same time, however, rates of prescribed opioid abuse have escalated dramatically, particularly among women (Mack, 2013; SAMHSA, 2014). These increases are alarming because opioid-dependent individuals face mortality risks that are 6 to 20 times higher than the general population (Darke et al., 2011; Degenhardt et al., 2011). This context helps to explain why since 2007, more adult women of all ages have died each year from drug overdoses than from motor vehicle–related injuries, and in 2010, 4 times as many women died from drug overdose as were homicide victims (CDC, 2013a b). Opioid overdose deaths among women have increased fivefold in the past decade and this problem is now recognized to be a national epidemic among both women and men (CDC, 2013a b). Despite the rapid growth of this epidemic, women are typically outnumbered by men in opioid treatment settings by approximately 3 to 1 (Brady & Ashley, 2005; Nosyk et al., 2014). This phenomenon highlights the need to consider if and how opioid mortality outcomes are impacted by gender. Understanding factors that influence mortality risk differentially by gender has important implications for addressing gender-specific treatment needs, thereby aiding efforts to eliminate gender disparities in opioid-related mortality.

There are substantial differences by gender in the course of opioid use disorders, engagement in treatment for these disorders, and related health outcomes. A key finding is that more women than men rapidly decrease their heroin use over time (Grella & Lovinger, 2011), women remain engaged in maintenance treatment for a longer period of time (Nosyk et al., 2014), and women and men encounter different risk and protective factors that alter the course of the disorder (Hser et al., 2015). Few studies have examined gender differences in mortality among treated opioid-dependent populations. These studies have mostly focused on documenting mortality rates by gender, and have typically reported lower crude mortality rates for women compared with men, but higher standardized mortality ratios (SMRs) (Degenhardt et al., 2009, 2010). This pattern likely reflects, in part, less risk-taking behavior among women in the general population than men that, in turn, results in fewer accidents and traumatic deaths for women and therefore a longer life expectancy for women.

Less is known regarding the potential for gender-specificity in the way that demographic characteristics, substance use, and treatment may affect mortality risk among individuals with opioid use disorders (Bawor et al., 2014). In studies of opioid-dependent populations that have not specifically examined gender differences, it is clear that older age is a key risk factor for mortality (Peles et al., 2010; Stoove et al., 2009), as is injection drug use (Brugal et al., 2005), alcohol use (Degenhardt et al., 2014; Larney et al., 2013; Shah et al., 2008), benzodiazepine use (Cousins et al., 2011; McCowan et al., 2009; Peles et al., 2010), chronic illness (e.g., positive for HIV or hepatitis B or C) (Brugal et al., 2005; Muga et al., 2014; Peles et al., 2010), mental illness (Cousins et al., 2011; McCowan et al., 2009), and inadequate exposure to methadone maintenance treatment (Amato et al., 2005; Degenhardt et al., 2011, 2014; Evans et al., 2015). The few studies of opioid-dependent populations that have focused on gender and mortality have revealed significant gender differences. For example, an examination of gender differences in opioid/cocaine fatal overdoses in

Luxembourg between 1985 and 2011 found that the time between the onset of drug use and death was shorter for women than for men (Origer et al., 2014). A study of injection drug users in Norway reported that the risk of death was heightened among women by sex work and among men by experiences of being incarcerated in prison (Gjersing & Bretteville-Jensen, 2014). Findings are consistent with those generated by other studies that have attributed gender differences in the course of addiction to both socio-cultural (Cloud & Granfield, 2008; Roberts et al., 2010) and biological (Lynch et al., 2002) factors. In other health-related research, gender differences in health are thought to reflect intertwined social and biological factors that vary over the life course (Short et al., 2013).

Despite these advances in knowledge, little empirical evidence has been generated regarding whether gender modifies the effects of factors known to influence mortality among populations with opioid use disorders. Lacking information on gender-specific effects, incorrect conclusions may be drawn about the underlying causes of mortality and the optimal methods to treat opioid use disorders. Knowing about gender differences in the causes and predictors of mortality can contribute to discussions regarding whether gender-focused treatment is desirable and how it may be performed. In the present paper, we aim to build on our prior research (Evans et al., 2015; Nosyk et al., 2014) to assess gender differences in characteristics at treatment entry, mortality rates, causes of death, and predictors of death. A broader goal is to better understand the factors and experiences that elevate mortality risks among treated opioid-dependent individuals in ways that may be unique to each gender.

2.0 Methods

2.1 Sample

We examined all 11,564 women and 20,758 men first admitted to publicly-funded agonist treatment for opioid dependence in California during the 5-year period covering January 1, 2006, to December 31, 2010. The median observation time for follow-up was 2.6 years (interquartile range: 1.4 – 3.7). Treatment data was provided by the California Outcomes Monitoring System (CalOMS), a statewide information management system. Each state- or federally-funded opioid treatment program licensed to dispense methadone is required to submit CalOMS data monthly (California Alcohol and Drug Programs, 2005). To focus on first-time treatment entrants, we omitted from analysis those who had been admitted to treatment in the 20 years prior to January 1, 2006 as indicated by records available in CalOMS and its predecessor, CADDS. Patient data recorded in CalOMS by treatment staff at admission include demographics, alcohol and drug use, educational attainment and employment, and physical and psychological health. Discharge records are filed when appointments are missed without notification for ≥3 consecutive days for detoxification and for ≥14 days for MMT. Most individuals in our sample (86%) received treatment from only one treatment program during the study time-period.

Mortality data was obtained from the Centers for Disease Control and Prevention (CDC) National Death Index (NDI). NDI data linkage was performed by CDC staff using probabilistic record linkage methods that utilized patient Social Security Number (SSN), full name, birth date, and sex. Approximately 5% of CalOMS individuals had an invalid SSN

and therefore were omitted from NDI linkage. NDI shared date and cause of death (International Classification of Diseases [ICD-10th revision]) in November 2012 for deaths that occurred as of December 31, 2010. The Institutional Review Boards at UCLA and the State of California approved the protocols.

2.2 Measures

The *dependent variable* is mortality, indicated by time to death, crude mortality rates (CMR) and standardized mortality ratios (SMR). Drawing on previously-defined classifications (Evans et al., 2015; Nosyk et al., 2014), we coded cause of death into five categories: (1) drug-related (drug or alcohol poisoning, other drug-related); (2) disease (e.g., cardiovascular disease, cancer, liver disease, infectious disease, diabetes, other); (3) trauma (accidental injury, traffic accidents); (4) suicide; and (5) homicide (intentional self-harm or self-poisoning).

The key *independent variable* is gender, categorized as female or male according to information provided by individuals at the first treatment admission.

We also considered several fixed and time-varying covariates. Fixed covariates (e.g., gender, age, race/ethnicity, educational attainment) were provided by the first treatment admission. Time-varying measures were provided by repeated assessment at each treatment admission. These reflect patient demographics, drug-use severity, and co-morbidity (Table 4 shows a complete list). Also, following previous analyses (Evans et al., 2015; Nosyk et al., 2014), treatment was constructed as episodes of time in which an individual received detoxification, methadone maintenance treatment (MMT), or no-treatment. We used the earliest admission and latest discharge to consolidate records into treatment episodes. If records were not available for episode t, but a subsequent episode t+1 was initiated, discharge dates were imputed using a discharge date of (episode start date(t+1)–14) for episode t for MMT or (episode start date(t+1)–3 for detoxification. About 11% (5,749 of 52,769) of treatment episode discharge dates were imputed. We merged successive episodes when discharge and subsequent admission dates were within the 3-day (detoxification) and 14-day (MMT) discontinuation thresholds. Time periods in which an individual was not receiving either detoxification or MMT were coded as out-of-treatment periods.

2.3 Data analysis

Follow-up duration was determined using first treatment admission to death or last observation (ending on December 31, 2010). Crude mortality rates (CMRs) by gender were calculated by summing person years and numbers of deaths by age and sex and calculating a rate per 1,000 person-years. Indirect standardized mortality ratios (SMR) by gender were calculated by dividing observed deaths in the cohort by expected deaths based on US population mortality rates (as provided by the Centers for Disease Control and Prevention, National Vital Statistics System) by year, sex, and age group.

Cox proportional hazards models with time-varying covariates were fitted to investigate the effect of gender on all-cause mortality, controlling for covariates. To address issues of small sample size and to enhance model parsimony, secondary drug problem type was categorized

to group together substances with similar physiological effects (e.g., heroin/prescription opioids; methamphetamine/cocaine) or similar social stigma and adverse social consequences (alcohol/marijuana). Next, models stratified by gender were fitted to characterize differences in the predictors of mortality by gender. Finally, whether there were gender differences in the association between predictors and risk for mortality was tested with the inclusion of interaction terms. Interaction terms that were statistically significant were tested simultaneously. For parsimony, only those terms that remained significant when tested simultaneously were retained in a final model. All hypotheses were tested using a significance level of α=0.05. Analyses were conducted using SAS 9.3 (SAS Institute) and R (R Core Team).

3.0 Results

Differences were evident in the characteristics of women and men at treatment admission (Table 1). Most notably, fewer women than men worked full- or part-time (23.7% vs. 34.0%) or were involved with the criminal justice system (11.2% vs. 16.5%). Differences by gender were also apparent in drug use behaviors. Specifically, more women than men report first use of their primary drug at an older age, fewer women reported heroin to be the primary drug problem type (55.9% vs. 67.5%), more women reported their secondary drug problem type to be prescribed opioids (16.3% vs. 13.9%) or methamphetamine/cocaine (17.2% vs. 14.2%), fewer women had injected drugs (49.0% vs. 58.6%), and women reported fewer years between first use of their primary drug and first entry into drug treatment. More women than men reported comorbid mental and physical health problems as indicated by mental illness (32.1% vs. 18.0%), recent medical problems (24.1% vs. 16.2%), and physical disability (18.6% vs. 14.2%). Finally, more women than men had been tested for HIV (70.4% vs. 62.6%) and more had received Medi-Cal benefits (37.7% vs. 21.1%).

Over the 5 years of follow up, women spent more time in treatment for opioid dependence than men, (48% vs. 40% of the follow-up time) (Table 2). By treatment type, women had fewer detoxification episodes (a mean of 0.68 vs. 0.80 episodes) and days of detoxification (32 vs. 39 days) than men; in contrast, women had more maintenance episodes (a mean of 0.92 vs. 0.84 episodes), and subsequently spent more time (42% vs. 33%) in maintenance treatment. Over this same time period, women spent less time out-of-treatment than men, as indicated by the number of out-of-treatment episodes (1.08 vs. 1.22 episodes) and proportion of time out-of-treatment (52% vs. 60% of the follow-up time).

Over a median 2.6 years (interquartile range: 1.4 – 3.7) of follow-up, 1,031 deaths were observed, including 2.2% (259/11,564) of all women and 3.7% (772/20,758) of all men. Among both women and men, overdose and other harms related to alcohol and drug use was a principal cause of death (47.1%, 42.5%) (Table 3), however among men the leading cause of death was disease-related (47.2%) whereas among women although disease accounted for a significant proportion of deaths (43.6%), the leading cause of death was alcohol and drug-related. Trauma and suicide accounted for 5.4% and 3.5% of deaths among women, and 4.3% and 3.9% of deaths among men. Homicide accounted for more deaths among men than among women (2.2% vs. 0.4%), but this difference was not statistically significant. Age at

death was not different by gender; 43.5 (11.6) years among women and 44.1 (13.5) among men (data not shown).

The crude mortality rate (CMR) among women was 9.5 (95% CI: 8.4, 10.7) deaths per 1,000 person-years, and among men it was 15.7 (95% CI: 14.6, 16.8). Women had a higher risk of mortality compared to the general population (SMR 5.1 95% CI: 4.5, 5.7) than men (SMR 4.3 95% CI: 4.0, 4.6). The relative risk of death for women compared with men was 1.18 (95% CI: 1.02, 1.36).

Factors associated with all-cause mortality risk were examined in multiple Cox proportional hazards regression with time-varying covariates. In the overall model, women had a lower instantaneous hazard of all-cause mortality than men (HR 0.58, 95% CI 0.50, 0.68), controlling for all of the factors listed in Table 4 (data not shown). To compare the differences in the factors associated with mortality by gender, hereafter we present results based on models stratified by gender (Table 4).

For both women and men, the risk of mortality risk was similarly attenuated by both detoxification (HR among women 0.28, 95% CI 0.11, 0.68; HR among men 0.20, 95% CI 0.11, 0.37) and methadone maintenance treatment (HR among women 0.24, 95% CI 0.17, 0.33; HR among men 0.29, 95%CI 0.23, 0.35). For both genders, mortality risk was also increased by older age and the presence of a disability.

As for gender-specific factors, among men but not among women, a significant increase in the hazard of mortality was associated with non-daily heroin use (compared with daily heroin use) (HR 1.22, 95%CI, 1.02, 1.47), having a hepatitis C diagnosis (HR 1.25, 95%CI 1.04, 1.49), reporting medical problems in the past 30 days (HR 2.04, 95%CI 1.56, 2.65), being tested for HIV (HR 1.22, 95%CI 1.03, 1.44), and being a Medi-Cal beneficiary (HR 1.31, 95%CI 1.11, 1.56). Also among men, but not among women, a significant reduction in the hazard of mortality was associated with being Hispanic (HR 0.75, 95%CI 0.63, 0.90), African American (HR 0.61, 95%CI 0.47, 0.80), or another race/ethnicity (HR 0.70, 95%CI 0.51, 0.96), relative to being white, being employed full-time (HR 0.60, 95%CI 0.48, 0.75), and using prescription opioids on a non-daily basis (compared with daily heroin use) (HR 0.74, 95%CI 0.55, 0.99). Otherwise, among women a significant increase in the hazard of mortality was associated with concurrent use of methamphetamine or cocaine (HR 1.43, 95% CI 1.05, 1.94), whereas among men, secondary use of methamphetamine or cocaine decreased the hazard of death (HR 0.80, 95%CI, 0.65, 0.98).

Each interaction term was tested individually (data not shown) and then simultaneously included in a multiplicative model (Table 4). Statistically significant results indicated that among men, but not among women, being employed full-time decreased the risk of death whereas non-daily heroin use (relative to daily heroin use) and having medical problems increased the risk of death. The interaction term for gender X concurrent use of methamphetamine/cocaine confirmed the findings from the gender-stratified models, indicating that the secondary use of methamphetamine or cocaine increased the hazard of death for women, and decreased it for men. While gender-stratified models indicated race/ethnicity had a significant effect on mortality risk among men but no effect among women,

the race/ethnicity X gender interaction term was not statistically significant when tested in the multiplicative model. This result suggests that the ways in which race/ethnicity impacts the risk for mortality is not different by gender.

4.0 Discussion

4.1 Summary of findings

A key finding from this study is that compared with men, women had a lower risk of death as well as a lower crude mortality rate but a higher standardized mortality ratio; the relative risk of death for women compared with men was 1.18 (95% CI: 1.02, 1.36). These findings are consistent with prior research that has documented that women treated for heroin dependence tend to die at a younger age compared with women in the general population and that this gap is greater among women than it is among men (Degenhardt et al., 2009, 2010). Opioid dependence appears to elevate the risk of death for women such that it narrows the larger gender differences in mortality that are observed in the general population. Therefore, although death occurred at a similar age for both women and men in this study, i.e. in their early 40s, death at this age generally represented more years of potential life lost for women than it did for men. It is in this sense that even though opioid dependent women are generally at a lower risk for mortality than men, women's opioid dependence nevertheless represents a significant burden on population health.

We also found that opioid dependent women initiated use of their primary drug at an older age than men, and women first entered treatment for opioid dependence after fewer years of use. The former finding is consistent with other studies of treatment samples that have reported women first use heroin at an older age than men (Hartel et al., 2006). Other studies, however, report there are no gender differences in age at first heroin use (Hernandez-Avila et al., 2004; Lynskey et al., 1998). Our findings contribute to current knowledge and also point to the need for further research on gender differences in heroin use onset. The finding that women entered treatment after fewer years of use may be related to a well-established but poorly understood phenomenon in which women progress more rapidly than men from substance use to a disorder (Hernandez-Avila et al., 2004; Lewis et al., 2014), a "telescoping" process which may also be accompanied by women's suffering of more serious medical and social consequences despite use for shorter durations than men, and ultimately may compel opioid-dependent women to seek treatment sooner than men (Brady & Randall, 1999; Hernandez-Avila et al., 2004; Piazza et al., 1989).

Consistent with extant knowledge, receipt of treatment, compared with no treatment, was associated with a lower mortality risk for both genders. It is well-established that treatment for opioid dependence reduces the risk for mortality (Evans et al., 2015; Hser et al., 2015). However, also evident in the present study were gender differences in the duration and type of treatment received for opioid dependence. Women spent more time than men in treatment overall, and particularly in maintenance treatment, and women spent less time in detoxification settings. Continued participation in treatment is a factor that is strongly associated with transitioning from active substance abuse to sustained recovery, particularly for women (Grella et al., 2008; Timko et al., 2002; Weaver et al., 2000). It has been suggested that the social stigma for substance use that places women at risk for addiction

initially may function among women in recovery as a major motivating factor to remain engaged with treatment (Cloud & Granfield, 2008). Views by treatment providers and the general public of women as victims may also encourage or coerce women to enter treatment, thereby leading to women's earlier treatment initiation or longer treatment career. Continued engagement with maintenance treatment over time may be a primary reason why opioid dependent women demonstrate a lower mortality risk than men despite exhibiting more co-morbid risk factors for opioid dependence and even though both genders are often initially treated in the same setting.

We also found that among men, but not among women, being employed full-time decreased the risk of death whereas non-daily heroin use (relative to daily heroin use) and having medical problems increased men's risk of death. Men with chronic illnesses tend to seek health care later in the course of the disease than women (Matheson et al., 2014). It may be that in our sample, men more than women suffered from untreated physical problems that ultimately contributed to their death. This idea is further supported by our findings that among men the leading cause of death was disease-related; among women, although disease accounted for a significant proportion of deaths, the leading cause of death was alcohol and drug-related.

Regarding the association between non-daily heroin use and men's mortality risk, it is well-established that periods of heroin abstinence or infrequent use generally result in reduced opioid tolerance, which in turn increases the risk of fatal overdose (Warner-Smith et al., 2001). It may be that after a period of infrequent heroin use, men are more likely than women to use more frequently, in larger amounts, or in combination with alcohol or other substances that increase men's risk of death. As for the findings regarding employment, being employed may reduce the risk of mortality among opioid dependent men because it provides a means to access needed health care but also because employment is particularly critical to men's identity formation (Leufstadius et al., 2009; Luyckx et al., 2008), and it also influences physical and mental well-being and overall quality of life (Falba et al., 2009; Mossakowski, 2008; Zabkiewicz, 2010). While being employed can create these benefits for women too, women more than men access health care through their spouse's employment situation and women's social roles as mother and homemaker provide important and alternative sources for women's identify formation and sense of well-being (Fryers, 2006). We speculate that it is for these reasons that the lack of employment may have a greater impact on mortality risk among men with opioid dependence than it does among women.

Finally, concurrent opioid and methamphetamine/cocaine use increased mortality risk among women but decreased it among men. Reasons for this gender difference were not explored. In other research, women reportedly use stimulants more than men to lose weight and to improve daily functioning (e.g., to gain energy or to focus their attention) (Brecht et al., 2004). Furthermore, sex-specific physiological effects of some types of stimulants have been documented, suggesting that the euphoric effects of cocaine and amphetamines may also be influenced by women's hormone levels (see review, Terner & de Wit, 2006). It is believed that progesterone is a clear mechanism specific to women that plays a significant role in influencing women's physical reaction to stimulants (Evans et al., 2007). When considered together, these findings indicate that although women may initially use

stimulants to control weight, to improve daily functioning, or for other reasons, women's repeated use can produce effects that are highly induced by hormonal influences. More research is needed to understand whether these mechanisms explain why stimulant use impacts mortality risk differentially among opioid dependent women and men.

4.2 Limitations

Our analysis had several limitations. First, some misclassification occurs when administrative databases are used for research (Evans et al., 2010; Hser & Evans, 2008). To address this issue, we implemented several rules and used previously-implemented algorithms to minimize linkage and data management errors (Nosyk et al., 2014). Second, we only captured individuals treated at publicly-funded facilities in California and we focused on all-cause mortality. Therefore, we did not examine gender differences among patients treated in other settings (e.g., office-based buprenorphine treatment, Veterans Health Administration-based opioid treatment programs) or in the predictors of cause-specific mortality. Finally, data restrictions meant that we were not able to examine the effect of certain types of substances (e.g., benzodiazepine) and our decision to collapse alcohol and marijuana into a single secondary drug problem type masked any differential effects that these substances may have had on mortality risk. Study strengths include the large and ethnically diverse sample of women and men, inclusion of all public opioid treatment programs statewide, a comprehensive set of patient- and treatment-related risk and protective factors, measurement of several variables as time-dynamic, thereby permitting more precise measurement, and examination of mortality among women and men over several years of the life course.

4.3 Conclusion

The long-held assumption that substance use disorders mostly affect men and rarely occur among women (Brady et al., 1993, 2009; Brady & Randall, 1999; Greenfield et al., 2007; Tuchman, 2010) has likely contributed to the fact that women are underrepresented in studies on mortality among opioid-dependent populations. In the 1990s federal guidelines called for expanded research on women, gender differences, and health (FDA, 1994; Mathias, 1995). Our study helps to address this gap in knowledge. In particular, an important implication of our findings for clinical practice is that treatment for opioid dependence is likely to reduce mortality risk among opioid-dependent men by addressing employment and medical problems, and via interventions to reduce overdose risk after a period of heroin abstinence, and among women by attending to the concurrent use of methamphetamine/cocaine and opioids. Ultimately, understanding and addressing the risks of opioid use disorders in ways that are specific to each gender may improve the treatment process and also reduce the risk of premature mortality for both women and men.

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- Opioid-dependent women have a greater risk of death compared to the general population than men.
- Women have a lower mortality risk than men, controlling for treatment engagement and other factors.
- Employment, heroin use, and health problems uniquely impact men's mortality risk.
- Stimulant use increases mortality risk among women and decreases it among men.

Table 1

Characteristics of women and men at entry into first treatment for opioid dependence

	Women (n=11,564)	Men (n=20,758)
Age in years at admission	35.2 (11.9)	35.3 (12.7)
Race/ethnicity***		
White	68.6	66.2
Hispanic	15.7	19.7
African American	9.4	7.0
Other	6.4	7.1
Education**		
< High School	29.1	30.4
≥ High School	70.9	69.6
Labor force participation***	23.7	34.0
Legal status***	11.2	16.5
Age at first use***		
<16	15.0	16.1
16–21	35.2	43.4
21–30	28.1	25.4
>30	21.7	15.2
Primary drug type***		
Heroin	55.9	67.5
Other drugs	44.2	32.5
Primary drug use frequency***		
< Daily	24.1	20.9
Daily	75.9	79.1
Secondary drug type***		
Heroin	1.8	2.1
Prescription opioids	16.3	13.9
Methamphetamine/cocaine	17.2	14.2
Marijuana	4.6	7.7
Alcohol	3.9	5.1
Other	16.3	13.9
None	56.2	57.1
Injection drug user***	49.0	58.6
Years from 1st primary drug use to 1st treatment episode***		
<5 years	35.3	32.4
>= 5 and <10 years	21.5	20.3
>=10 years	43.1	47.3
Mental illness***	32.1	18.0
Medical problems, past 30 days***	24.1	16.2

	Women (n=11,564)	Men (n=20,758)
Has a physical disability***	18.6	14.2
Diagnosed with hepatitis C	12.3	12.7
Diagnosed with tuberculosis***	1.6	2.4
Tested for HIV***	70.4	62.6
Medi-Cal beneficiary***	37.7	21.1

* p<0.05,

** p<0.01,

*** p<0.001

Table 2

Opioid treatment utilization among women and men over the 5-year follow-up period

	Women (n=11,564 women; 31,150 episodes)		Men (n=20,758 men; 59,359 episodes)	
	Mean / %	**SD**	**Mean / %**	**SD**
Proportion of episodes that were***				
Detoxification	25.5		28.1	
Maintenance treatment	34.4		29.4	
Out of treatment	40.2		42.5	
Total proportion of time out of treatment***	0.52	0.41	0.60	0.39
Total proportion of time in treatment***	0.48	0.41	0.40	0.39
Proportion of time in detoxification***	0.06	0.16	0.07	0.17
Proportion of time in maintenance***	0.42	0.41	0.33	0.39
Total number of episodes***	2.69	2.04	2.85	2.20
Total number of out of treatment episodes***	1.08	1.08	1.22	1.14
Total number of in treatment episodes**	1.61	1.07	1.64	1.15
Detoxification***	0.68	0.89	0.80	0.98
Maintenance***	0.92	0.75	0.84	0.79
Total number of days out of treatment***	497.28	522.71	569.70	533.90
Total number of days in treatment***	366.0	435.3	298.2	396.2
Days in detoxification***	32.6	99.6	39.2	108.3
Days in maintenance***	333.4	432.7	259.0	390.1

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$

Table 3

Cause of death among women and men treated for opioid dependence

	Women (n=259)			Men (n=772)		
	n	**%**	**CMR (95% CI)**	**n**	**%**	**CMR (95% CI)**
Drug-related[1]	122	47.1	4.5 (3.7–5.3)	328	42.5	6.6 (6.0–7.4)
Disease[2]	113	43.6	4.1 (3.4–5.0)	364	47.2	7.4 (6.7–8.2)
Trauma[3]	14	5.4	0.5 (0.3–0.9)	33	4.3	0.7 (0.5–0.9)
Suicide[4]	9	3.5	0.3 (0.2–0.6)	30	3.9	0.6 (0.4–0.9)
Homicide	1	0.4	0.04 (0.0–0.3)	17	2.2	0.3 (0.2–0.6)
Total	259	2.2	9.5 (8.4–10.7)	772	3.7	15.7 (14.6–16.8)

CMR = crude mortality ratio; 95% CI = 95% confidence interval

Differences by gender in the proportion of deaths attributable to each cause of death were not statistically significant.

[1] Overdose (i.e., accidental poisoning by alcohol or other drugs) (110 deaths among women; 284 among men) and other drug-related causes (i.e., harmful alcohol or drug use or dependence) (12; 44).

[2] Cardiovascular disease (30 deaths among women; 117 among men), cancer (20; 60), respiratory disease (11; 43), liver disease (11; 38), hepatitis C (9; 34), diabetes (4; 9), HIV-related (3; 11), infections/parasites (3; 9), endometriosis (2; 8), digestive disease (2; 5), renal disease (5; 2), central nervous system (1; 6), other (12; 16), and unknown (0; 6).

[3] Accidental injury, traffic accidents.

[4] Intentional self-harm or self-poisoning.

Table 4

Factors associated with mortality among women and men accessing pharmacological treatment for opioid dependence in California, 2006–2010

	Gender-stratified models		Multiplicative model
	Women (n=31141 episodes)	**Men (n=59344 episodes)**	**Total (n=90485 episodes)**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Women (ref: men)	--	--	0.54 (0.45, 0.66)***
Age at first treatment admission in years	1.04 (1.03, 1.06)***	1.04 (1.03, 1.05)***	1.04 (1.03, 1.05)***
Race/ethnicity (ref: White)			
Hispanic	1.01 (0.73, 1.38)	0.75 (0.63, 0.90)**	0.80 (0.69, 0.94)**
African American	0.82 (0.54, 1.24)	0.61 (0.47, 0.80)***	0.66 (0.53, 0.83)***
Other	1.03 (0.63, 1.66)	0.70 (0.51, 0.96)*	0.77 (0.60, 1.01)
Attained high school degree (ref: <high school degree)	1.01 (0.77, 1.33)	1.09 (0.93, 1.28)	1.07 (0.93, 1.23)
Labor force status (ref: not in the labor force)^			
Employed full-time	1.01 (0.68, 1.51)	0.60 (0.48, 0.75)***	0.61 (0.49, 0.76)***
Employed part-time	0.81 (0.48, 1.36)	0.88 (0.68, 1.13)	0.86 (0.68, 1.08)
Frequency/type of primary drug use (ref: daily heroin)^			
Daily prescription opioids	1.12 (0.81, 1.55)	0.97 (0.79, 1.20)	1.02 (0.86, 1.22)
Non-daily prescription opioids	0.90 (0.59, 1.37)	0.74 (0.55, 0.99)*	0.78 (0.62, 1.00)*
Non-daily heroin	0.87 (0.61, 1.24)	1.22 (1.02, 1.47)*	1.24 (1.04, 1.49)*
Secondary drug type (ref: none)^			
Heroin/prescription opioids	0.97 (0.67, 1.40)	1.10 (0.88, 1.37)	1.08 (0.89, 1.30)
Methamphetamine/cocaine	1.43 (1.05, 1.94)*	0.80 (0.65, 0.98)*	0.79 (0.65, 0.97)*
Alcohol/marijuana	0.79 (0.47, 1.34)	1.02 (0.82, 1.27)	0.97 (0.80, 1.19)
Years from 1st primary drug use to 1st treatment episode (ref: <5 years)^			
>= 5 and <10 years	1.28 (0.85, 1.92)	1.00 (0.78, 1.27)	1.07 (0.86, 1.32)
>= 10 years	1.25 (0.87, 1.78)	0.94 (0.76, 1.16)	1.02 (0.85, 1.22)
Involved with criminal justice system^	0.84 (0.56, 1.26)	0.97 (0.80, 1.18)	0.94 (0.79, 1.12)

	Gender-stratified models		Multiplicative model
	Women (n=31141 episodes)	**Men (n=59344 episodes)**	**Total (n=90485 episodes)**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Mental illness^	1.14 (0.87, 1.49)	1.15 (0.97, 1.37)	1.14 (0.99, 1.32)
Has a disability^	1.62 (1.21, 2.17)**	1.42 (1.19, 1.71)***	1.49 (1.28, 1.74)***
Diagnosed with tuberculosis^	1.59 (0.81, 3.13)	1.22 (0.87, 1.72)	1.27 (0.93, 1.72)
Diagnosed with hepatitis C^	1.31 (0.96, 1.79)	1.25 (1.04,1.49)*	1.27 (1.09, 1.48)**
Medical problems, past 30 days^	1.02 (0.60, 1.74)	2.04 (1.56, 2.65)***	2.00 (1.54, 2.60)***
Tested for HIV^	1.25 (0.93, 1.69)	1.22 (1.03, 1.44)*	1.23 (1.06, 1.42)**
Medi-Cal beneficiary^	1.29 (0.99, 1.69)	1.31 (1.11, 1.56)**	1.30 (1.13, 1.20)***
Treatment episode type (ref: out of treatment) ^			
Detoxification	0.28 (0.11, 0.68)**	0.20 (0.11, 0.37)***	0.22 (0.14, 0.36)***
Maintenance treatment	0.24 (0.17, 0.33)***	0.29 (0.23, 0.35)***	0.27 (0.23, 0.32)***
Interaction terms			
Women (ref: men) X Full-time employment (ref: not employed)	--	--	1.57 (1.02, 2.43)*
Women (ref: men) X Non-daily heroin use (ref: daily heroin use)	--	--	0.68 (0.47, 0.98)*
Women (ref: men) X Has medical problems (ref: no medical problems)	--	--	0.54 (0.30, 0.97)*
Women (ref: men) X Secondary drug is methamphetamine/cocaine (ref: none)	--	--	1.87 (1.33, 2.62)***

^time-varying variable. HR= Hazard Ratio; 95% CI = 95% confidence interval. 24 observations were omitted due to missing data. Secondary drug problem type was categorized to group together substances with similar physiological effects (e.g., heroin/prescription opioids, methamphetamine/cocaine) or similar social stigma and adverse social consequences (alcohol/marijuana).

*p<0.05,

**p<0.01,

***p<0.001