



Research paper

Causes of death and expected years of life lost among treated opioid-dependent individuals in the United States and Taiwan

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ABSTRACT

Aims: This study compared the cause-specific standardized mortality ratios (SMRs) and expected years of life lost (EYLL) among opioid-dependent individuals in the United States and Taiwan.**Methods:** Survival data came from two cohorts followed until 2014: The U.S. data were based on a randomized trial of 1267 opioid-dependent participants enrolled between 2006 and 2009; the Taiwan data were from a study of 983 individuals that began in 2006, when opioid agonist treatment (OAT) was implemented in Taiwan. SMRs were calculated for each national cohort and compared. Kaplan–Meier estimation was performed on the survival data, then lifespans were extrapolated to 70 years (840 months) to estimate life expectancy using a semi-parametric method. EYLLs for both cohorts were estimated by subtracting their life expectancies from the age- and gender-matched referents within the general population of their respective country.**Results:** Compared with age- and gender-matched referents, the SMRs were 3.2 for the U.S. sample and 7.8 for the Taiwan sample; the EYLLs were 7.7 and 16.4 years, respectively. Half of decedents died of unnatural causes in both cohorts; overdose deaths predominated in the U.S. and suicide in Taiwan.**Conclusions:** Our study identified differences by country in EYLL and causes of deaths. These findings suggest that intervention strategies to reduce mortality risk by overdose (particularly in the U.S.) and suicide (particularly in Taiwan) are urgently needed in these countries.

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Introduction

Opioid dependence contributes to a heavy burden of disease globally, including excessive early mortality (Degenhardt et al., 2013). According to a meta-analysis based on 58 studies, the estimated crude mortality rate (CMR) was 21 per 1000-person years (PY), and a standardized mortality ratio (SMR) of 15 was found among opioid-dependent individuals across the world, with the highest mortality rates in Asia (Degenhardt et al., 2011). Moreover, variations in years of potential life lost (YPLL) among Western countries were substantial (Darke et al., 2016; Degenhardt, Larney, Randall, Burns, & Hall, 2014; Smyth, Hoffman, Fan, &

Hser, 2007). Geographic differences in opioid-involved mortality raise questions about causes, but epidemiological studies comparing related phenomena across regions are lacking.

Unnatural causes of death, such as accidental overdose, suicide and homicide, predominate as the reasons for the excess mortality of opioid-dependent individuals (Clausen, Waal, Thoresen, & Gossop, 2009; Degenhardt et al., 2014; Evans, Li et al., 2015). Previous studies have found regional variations not only in death rates but also in causes of death. For example, overdose mortality accounted for more than half of deaths in one Australian cohort (the ATOS study, Darke et al., 2016) which was followed for 15 years, but for less than 15% of deaths in a national sample in Taiwan followed for one year (Lee et al., 2013). In addition, one systematic review (Darke & Ross, 2002) reported suicide proportions ranging from 3% to 35% among opioid cohorts. However, there has been little research comparing relative causes of death and

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expected years of life lost (EYLL) for opioid users in distinct nations during similar periods of time.

Opioid agonist treatment (OAT) with either methadone (MET) or buprenorphine (BUP) can reduce mortality, especially during medication-adherent treatment (Evans, Li et al., 2015; Kimber et al., 2010). MET has been available in the United States since the 1960s. In contrast, Taiwan started MET programs in 2006, primarily in response to the HIV/AIDS epidemic among drug users (Chen & Kuo, 2007). The treatment programs in both nations are highly regulated (e.g., they both have restrictive admission criteria and patient compliance requirements). In the United States, methadone programs require a special program license and are often stand-alone programs separated from the mainstream healthcare system. Most methadone programs in Taiwan have been established in the psychiatric department of hospitals, but program regimens are usually restricted to methadone dispensing without psychiatric services, mainly because addiction treatment is not covered by the national universal health insurance (Fan, Tan, Chien, & Chou, 2013). Additionally, methadone is a Schedule II drug in Taiwan, and there is no take-home allowed in methadone programs. BUP, which was approved by the FDA in 2002 in the United States, can be prescribed by qualified practitioners in the general healthcare settings and does not have the program requirements that methadone has. BUP was not widely available in Taiwan until around 2010, but it is still listed as a Schedule III controlled drug.

Comparing treatment outcomes associated with the distinctive treatment systems and policies in different regions or countries may shed light on strategies needed to improve care and outcomes. Taking advantage of the availability of the opioid cohorts in the United States and Taiwan, this present study aimed to compare the cause-specific SMRs and EYLL among opioid users in the two countries. The similarities or differences between the countries should provide insight as to optimal strategies needed to address the disease burden of opioid use overall, and to each country specifically.

Methods

Data sources

The U.S. START study (see Saxon et al., 2013; for details) was a multisite prospective study at eight federally licensed opioid treatment programs across the United States that examined the effects of BUP and MET on indices of liver health in opioid-dependent patients seeking OAT. Eligibility criteria included being age 18 or older and currently opioid dependent. Patients who had medical and psychiatric conditions such as cardiopathy, liver disease, and acute psychosis were excluded from the study. START recruited 1267 individuals from May 2006 to October 2009.

The Taiwan OAT study (see Chang et al., 2015; for details) was a pilot methadone maintenance treatment (MMT) program started in 2006 by the Taiwan Center for Disease Control (CDC) in four of Taiwan's 23 administrative regions (3 in northern Taiwan and one in the Jianan Psychiatric Center in the south). The Taiwan CDC also permitted buprenorphine-naloxone (Suboxone[®]) to be used in a second pilot study, beginning, as well, in 2006. Among the various hospitals involved in the study, the Jianan Psychiatric Center was the only institution providing both methadone and buprenorphine-naloxone. Inclusion criteria for both pilot studies were: (1) age 20 or older, (2) meeting the DSM-IV (fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*) criteria for opioid dependence, and (3) no other OST contraindication, such as severe liver disease or acute psychosis. For the comparisons presented in this paper, we used data from the 983 patients who participated in OAT between March 2006 and July 2008.

Participants

Clinical profiles at baseline for the 1267 participants in the U.S. START study and the 983 cases in the Taiwan OAT study are provided in Table 1 and have been presented in previous articles (Chang et al., 2015; Hser et al., 2014, 2016). The mean age at baseline was 37.4 for the U.S. START participants and 37.8 for the Taiwan OAT participants. Most U.S. START participants were white (71.5%) and two-thirds were male, whereas almost all Taiwan OAT participants were male (88.3%; all were Asian). The proportion of injection drug use in the past 30 days was 67.8% for the U.S. START participants and 91.0% for the Taiwan OAT participants. The majority of both cohorts were cigarette smokers, with the proportion of smokers being extremely high (99.5%) among the Taiwan OAT participants. Regarding infectious diseases, the proportion of U.S. START patients with hepatitis C (HCV) was significantly lower than that among the Taiwan OAT patients (43.5% versus 91.4%, $p < 0.001$), as was the proportion with HIV (1.1% among U.S. START participants versus 18.1% among Taiwan OAT participants).

Also presented in Table 1 are measures of receipt of psychiatric medications collected at follow-ups. The majority (60.1%) of the U.S. START participants reported receiving medications for mood problems in their lifetime, and 27.8% had received prescribed medication in the past 30 days. In contrast, fewer than 5.4% of the Taiwan OAT participants ever received psychiatric medication treatment and only 2.2% currently took medication for mood problems.

Mortality and cause of death

The date and cause of deaths between the baseline assessment date and 2014 were determined for all the U.S. START participants using the National Death Index (Hser et al., 2016). Deaths among Taiwan OAT participants were identified by record linkage with the Taiwan National Death Certification Registry system, which is regularly managed by the Ministry of Health and Welfare and contains all information reported in death certificates, including name, identification number (ID), date of birth, sex, date of death, and cause of death. In addition, within the Taiwan system, the cause of all deaths from unnatural causes (suicide, overdose, and homicide) was decided upon by a death verdict jointly determined by a prosecutor and a coroner, whose main concern is the possibility of homicide. In a previous study in Taiwan, only 2 out of 117 suicides were judged to have been classified as accidental rather than deliberate (Cheng, 1995). Because the cause of death entry in these national registries is often delayed, there were 6 missing causes of deaths among U.S. START participants at the time we conducted these analyses, and we excluded the 2014 death records from the Taiwan OAT sample due to the potential misclassification of cause of death.

Statistical analysis

We applied the Kaplan–Meier method to estimate survival functions of these two cohorts based on follow-up data from 2006 to 2014. Person-years of follow-up were calculated from the baseline date to the date of death, or were censored on Dec. 31, 2014, and crude mortality rates per 1000 person-years (PY), with 95% confidence intervals (CIs), were calculated. Standardized mortality ratios (SMRs) were calculated as the observed number of deaths divided by the expected number, with age-, sex-, year-, and cause-specific mortality rates in the U.S. or Taiwan populations used to calculate the expected versus the actual number of deaths (Breslow & Da, 1993). A semi-parametric method for EYLL

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