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Estimation of life expectancy and the expected years of life lost among heroin users in the era of opioid substitution treatment (OST) in Taiwan

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ABSTRACT

Background: Opioid substitution treatment (OST) has been implemented in Taiwan since 2006. We estimated the life expectancy (LE) and expected years of life lost (EYLL) in a cohort of heroin users stratified by OST for comparison.
Methods: A total of 1283 heroin users recruited from 2006 to 2008 were linked to the National Mortality Registry until the end of 2011. Among them, 983 received OST, while 300 did not. Kaplan–Meier estimation for survival was performed, and it was extrapolated to 50 years to obtain the LE using a semi-parametric method. We further estimated the EYLL for both cohorts by subtracting their life expectancies from the age- and sex-matched referents of the general population. Cause-specific standardized mortality ratios (SMRs) were calculated and compared with the national cohort to validate the representativeness of this sample.
Results: After extrapolation to 50 years of survival, the estimated average LE and EYLL were 27.4 and 10.6 for OST subjects, respectively, while those of the non-OST were 20.2 and 18.4 years. The all-cause mortality rates (per 1000 person-years) in the observational period for the OST and non-OST group were 15.5 and 23.9, respectively, representing a 7.5- and 10.2-fold SMR compared to the general population, indicating a high representativeness for our sample. But SMR of suicide mortality elevated 16.2 and 3.1 folds in OST and non-OST group, respectively.
Conclusions: OST saves 7.8 EYLL more than non-OST after accounting for lead time bias. Effective suicide prevention programs could enhance its life-saving effect, especially among those co-morbid with depressive disorders.

1. Introduction

Illicit opioid use contributes to a heavy burden of disease globally (Degenhardt et al., 2013), and mortality rates have been reported to be as high as six to thirty times that of the general population (Darke et al., 2007). This excess mortality is concentrated across several causes of death: drug overdose, trauma, including suicide and homicide, and somatic causes, including blood-borne infection (Clausen et al., 2009). It should be noted that geographic differences have been evident, and mortality rates appear to be the highest in Asia (Degenhardt et al., 2011). Despite the fact that life expectancy (LE) and/or years of potential life lost (YPLL) for heroin cohorts have been reported (Smyth et al., 2006; Degenhardt et al., 2014), a follow-up study regarding this important issue in Asia seems to be lacking.

The opioid substitution treatment (OST), a long-term pharmacological maintenance on methadone and buprenorphine for opioid dependence, has received wide attention because of its effect to

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reduce excess mortality risks (Degenhardt et al., 2009; Cornish et al., 2010; Kimber et al., 2010). However, the life-saving effect of OST is salient only while heroin users remained under treatment, and many OST participants are exposed to an elevated overdose risk after treatment cessation and during the induction to methadone treatment (Brugal et al., 2005; Degenhardt et al., 2009; Cornish et al., 2010; Degenhardt et al., 2011). Although Bell et al. (2009) have shown that heroin users entering buprenorphine treatment have lower mortality risk during induction, the long-term survival for these two agents did not appear to be quite different (Degenhardt et al., 2009; Gibson et al., 2008). In addition, few existing examinations have had sufficient power to examine mortality between heroin users seeking OST and those who do not.

Taiwan adopted an OST (commonly oral methadone) program in response to the HIV epidemic in 2006 (Chen and Kuo, 2007). Thereafter, mortality studies on heroin cohorts have reported findings between 2006 and 2008 (Huang et al., 2011; Huang and Lee, 2013; Lee et al., 2013; Liao et al., 2013). Huang et al. (2011) have shown that continued participation in OST is associated with substantial lower mortality among ex-prisoners. One hospital-based study has reported that older age, HIV infection, psychiatric treatment history and alcohol use disorders are risk factors for mortality (Huang and Lee, 2013). Studies employed nationwide registry data showed no significantly increased overdose mortality during the induction or rapid titration of methadone treatment (Huang et al., 2011; Liao et al., 2013). Moreover, Lee et al. (2013) detected a high risk of premature death through suicide. However, the expected years of life lost (EYLL) for a heroin cohort has not yet been investigated.

Because many heroin cohorts may not have been followed for a sufficient amount of time, we used a semiparametric method for lifetime extrapolation (Hwang and Wang, 1999). By recruiting a heroin cohort stratified by OST for comparison, we attempted to determine the LE and EYLL of both OST and untreated subjects. In addition, we also examined the standardized mortality ratio (SMR) to evaluate the representativeness of our cohort.

2. Methods

This study commenced after the approval of the Institutional Review Board of the Jianan Psychiatric Center, MOHW (JMH08033 and JMH12050)

2.1. Data sources

In the beginning of 2006, the Taiwan Center for Disease Control (CDC) proposed a pilot methadone maintenance treatment (MMT) program in four of Taiwan's 23 administrative regions (three in northern Taiwan and in the Jianan Psychiatric Center in the south). In addition to existing detoxification and drug-free psychosocial programs, as well as the new MMT program, the Taiwan CDC also permitted buprenorphine (Suboxone) to be used as a substitution treatment as a pilot study beginning in 2006. Among different hospitals, the Jianan Psychiatric Center was the only pilot OST program institution providing both oral methadone and sublingual buprenorphine. We conducted an observational cohort study by recruiting heroin users into the study and OST first, which were linked to the National Mortality Registry to determine if the subject was deceased and the cause of mortality. The SMRs (standardized mortality ratios) were then calculated and compared with those of linkage between the National OST system and National Mortality Registry to assure the representativeness of our cohort.

All subjects included in this study were diagnosed with opioid dependence by qualified psychiatrists from the Jianan Psychiatric Center research team from March, 2006 to July, 2008. The inclusion criteria were: (1) being more than 20 years old; (2) meeting the DSM-IV (Fourth edition of Diagnostic and Statistical Manual of Mental Disorders) criteria for opioid dependence; (3) no other OST contraindication, such as severe liver cirrhosis. The cohort was comprised of 1609 participants, of whom 983 voluntarily joined our OST programs during the recruitment period. Of the total of 983 subjects registered in the OST program, about one-tenth (94/983) received buprenorphine treatment, while all the others received methadone. To minimize financial burden, Taiwan CDC stipulates that any subject originally randomized to receive buprenorphine in a pilot study be shifted into methadone treatment if he/she cannot adhere to the medication schedule. At the end of the 2011, 92 subjects shifted to methadone maintenance treatment.

The National OST system was managed and maintained by the Taiwan CDC. It was established after OST programs began in 2006. All clinics and hospitals are required to provide information on every methadone or publically funded buprenorphine patient, including the date of prescription, dose, quantity, and record of daily attendance. Of the remaining 626 participants, we defined 300 subjects as the untreated (non-OST) group after verification with the national registry of the OST system during the 70 months of follow-up after the first evaluation. The other 326 were excluded because they were later enrolled into OST programs sometime in our studying period. In fact, these subjects shifted back and forth frequently between the two groups and we have decided to exclude them to avoid confounding in the end.

Almost all OST participants received blood tests for HIV, HCV, HBV and syphilis, while 287 out of 300 non-OST heroin users received blood test for HIV. Only about 170 non-OST heroin users completed blood tests for HCV, HBV and syphilis and there was no significant difference with regard to demographic and clinical characteristics stratified by those received blood test or not.

2.2. Cause of death

Deaths in our study cohort were identified by the patient's chart or by record linkage with the National Death Certification Registry system, which is regularly managed by the Taiwan's Ministry of Health and Welfare and contains all information reported in the death certificates, including name, identification number (ID), date of birth, sex, date of death and the cause of death. Deaths were coded using the International Classification of Disease, Ninth Revision (ICD-9) (2006–2008) or International Classification of Disease, Tenth Revision (ICD-10) (2009–2011). In addition, we conducted telephone interviews with a key person related to the deceased to explore relevant information on the cause of death, opioid or other substance use behaviors, and related physical condition.

2.3. Statistical analysis

We were able to follow this cohort and applied the Kaplan–Meier method to estimate survival function based on the follow-up data from 2006 to 2011. Person years of follow-up were calculated from baseline interview date until date of death or censored on December 31, 2011. 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 of deaths, with age-, sex-, year-, and cause-specific mortality rates in the Taiwan population used to calculate the expected number of deaths.

2.4. Extrapolation of long-term survival for the OST and non-OST cohort

Heroin users usually would die of mortality causes that are directly related to this illness, such as suicide and trauma, in addition to the common causes experienced by age- and sex-matched general population. Assuming that such additional mortality would become stable, or, that constant excess hazard exists after several years of follow-up, we can apply an extrapolation method to quantify their lifetime survival function by borrowing information from general population or life tables of national vital statistics (Hwang and Wang, 1999; Fang et al., 2007).

The method was composed of three processes (Hwang and Wang, 1999), briefly summarized as follows: for every individual in the OST or non-OST cohort, we first created an age- and sex-matched referent from the life tables of the general population using the Monte Carlo method. The life tables for the general population were obtained directly from the national vital statistics published by the Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan. The survival curve for the cohort of age- and sex-matched referents was obtained by applying the Kaplan–Meier method. Second, we fitted a simple linear regression line to the logit of the ratio of survival functions between the OST (or non-OST) and referent cohorts to the end of the follow-up. Finally, the regression line and survival curve for the cohort of referents were used to predict a long-term survival curve beyond the follow-up for this cohort. We extrapolate the unfinished survival curves up to 50 years to account for the usual life expectancy of general population with a similar age.

The standard errors of the means were also calculated by the bootstrap method for 100 repeated samples in these parameters, as stratified by OST or not. To facilitate the computation, we used the ISQoL (integration of survival and quality of life) software program, which can be freely downloaded from http://www.stat.sinica.edu.tw/isqol/. Detailed methods and mathematical proofs are described in the previous studies (Chu et al., 2008; Fang et al., 2007; Hung et al., 2014; Hwang and Wang, 1999; Liu et al., 2013). We provide technical material as a supplement.

2.5. Estimation of EYLL

Subsequently, the LE and EYLL in both the OST and non-OST group were estimated and potential LY saved by the effect of OST were calculated. The average EYLL of the OST (or non-OST) cohort was estimated as the difference in the area between the mean survival curves of the OST (or non-OST) cohort and the reference population. This calculation provides a measure of the burden of opioid dependence on an individual and yields an estimation of how much an individual's life is likely to be shortened by opioid dependence. It could also represent the amount of an individual's life that is likely to be saved by treatment.