Drug and Alcohol Dependence 201 (2019) 197–204

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Opioid agonist treatment reduces losses in quality of life and quality-adjusted life expectancy in heroin users: Evidence from real world data

Kun-Chia Chang[a,b], Kuan-Ying Lee[a], Tsung-Hsueh Lu[b], Jing-Shiang Hwang[c], Chia-Ni Lin[b], Shuo-Yen Ting[d], Chih-Cheng Chang[e,f], Jung-Der Wang[b,g,*]

[a] Jianan Psychiatric Center, Ministry of Health and Welfare, 539 Yuzhong Rd., Rende Dist., Tainan 71742, Taiwan
[b] Department of Public Health College of Medicine, National Cheng Kung University, 1 University Rd., East Dist., Tainan 701, Taiwan
[c] Institute of Statistical Science, Academia Sinica, 128 Academia Road, Section 2, Taipei 11529, Taiwan
[d] Tsaotun Psychiatric Center, Ministry of Health and Welfare, 161 YuPin Rd., Caotun Township, Nantou 542, Taiwan
[e] Department of Psychiatry, Chi Mei Medical Center, 901 Zhonghua Rd., Yongkang Dist., Tainan 71004, Taiwan
[f] Department of Health Psychology, Chang Jung Christian University, No.1, Changda Rd., Gueiren District, Tainan 71101, Taiwan
[g] Departments of Internal Medicine and Occupational and Environmental Medicine, National Cheng Kung University Hospital, 138 ShengLi Rd., North Dist., Tainan 704, Taiwan

ARTICLE INFO

Keywords:
Heroin
Opioid agonist treatment
Quality-adjusted life expectancy
Quality-adjusted life year
Quality-of-life
Utility

ABSTRACT

Background: This study estimated the long-term changes of opioid agonist treatment (OAT) in quality of life (QOL) and quantified the quality-adjusted life years (QALY) from the loss of quality-adjusted life expectancy (QALE) in heroin users.

Methods: A total of 1283 heroin users stratified by OAT were linked to the National Mortality Registry for 8 years (2006–2014) to obtain survival functions, which were extrapolated to lifetime by applying a rolling extrapolation algorithm to survival ratio between the sub-cohorts and age- and sex-matched referents simulated from vital statistics of Taiwan. We performed cross-sectional measurement of EQ-5D on 349 participants, including those with a valid state of OAT or non-OAT plus newly recruited consecutive patients, during 2015–2017 for utility values, while the QOL of referents were abstracted from the 2009 National Health Interview Survey. The QALE was calculated by summing the products of the mean QOL and survival rate throughout life. The QALE difference between the cohort and corresponding referents was the loss-of-QALE.

Results: QOL of the OAT group was significantly better than that of the non-OAT group in every domain of the EQ-5D, which was quantified to be 0.23 for utility after controlling for other variables. After extrapolation to 70 years, the estimated QALE and loss-of-QALE were 17.8 and 18.2 QALY for OAT subjects, respectively, while those of the non-OAT group were 9.2 and 27.9 QALY.

Conclusions: Receiving OAT could reduce QALE lost by 9.7 QALYs compared with non-OAT after accounting for QOL differences along time and different age and sex distributions.

1. Introduction

Over the past two decades, mortality attributed to opioid dependence has increased (Degenhardt et al., 2013; Peacock et al., 2018) and the opioid epidemic is now a priority for public health globally (Imtiaz et al., 2018; Rehm and Probst, 2018). Although opioid agonist treatment (OAT) with either methadone (MET) or buprenorphine (BUP) has received wide attention because of its effect on reducing mortality, decreasing drug addiction, and improving short-term wellbeing (Hser et al., 2016; Kimber et al., 2015; Krebs et al., 2016; Nosyk et al., 2015; Sordo et al., 2017; Tran et al., 2012), the long-term impact on quality of life (QOL) remains equivocal and seems to be lower than healthy individuals in studies of Western countries (Krebs et al., 2016; Nosyk et al., 2011, 2015). An Asian cross-sectional study (Tran and Nguyen, 2013) compared health utility measured with EQ-5D between OAT and non-OAT HIV/AIDS drug users and the difference between these two groups was similar to the estimated improvement in health utility within OAT groups over 9-months of follow-up (Tran et al., 2012).

* Corresponding author at: Department of Public Health College of Medicine, National Cheng Kung University, 1 University Rd., East Dist., Tainan 701, Taiwan.
E-mail addresses: kunchiachang0517@gmail.com (K.-C. Chang), ky67122@hotmail.com (K.-Y. Lee), robertlu@mail.ncku.edu.tw (T.-H. Lu), jshwang@stat.sinica.edu.tw (J.-S. Hwang), near1980@gmail.com (C.-N. Lin), kamating@yahoo.com.tw (S.-Y. Ting), rabiata@mail.chimei.org.tw (C.-C. Chang), jdwang121@gmail.com (J.-D. Wang).

https://doi.org/10.1016/j.drugalcdep.2019.05.003
Received 12 November 2018; Received in revised form 2 May 2019; Accepted 3 May 2019
Available online 20 June 2019

However, none of the above studies seemed to successfully quantify the long-term effect of OAT on QOL because of difficulty in keeping such cohorts for a long time. Thus, this study hypothesizes that OAT has a positive long-term effect on QOL and tries to tackle the above challenge through an alternative design of combining the limited number of patients with persistent adherence to OAT (and non-OAT) after 8 years of follow-up with newly recruited participants for measurement of QOL. Although the QOL of participants were measured cross-sectionally, we applied the kernel-smoothing method in data analysis to show the dynamic changes of OAT over time after beginning OAT by assuming that our sample was quasi-random.

In clinical cost-effectiveness analysis, one of the most common measures of health benefit is the quality-adjusted life year (QALY), which takes both survival and quality of life (QOL) into consideration (Kind et al., 2009; Weinstein et al., 2009). Also, given the chronic and relapsing nature of opioid dependence, it would be more comprehensive for researchers to consider the health effects of OAT from a lifetime horizon. The quality-adjusted life expectancy (QALE) for heroin users can be quantified via adjusting the survival function with the mean QOL at each time point t, through the following equation (Hwang et al., 1996; Hwang and Wang, 2004):

$$\mathrm{QALE} = \int_0^\infty \mathrm{QoL}(t) \times \mathrm{S}(t)\mathrm{d}t$$

In which, $\mathrm{QOL}(t)$ denotes the mean QOL function for opioid dependent individuals at time t and $\mathrm{S}(t)$ denotes the survival function of the cohort at time t. The QALE estimate can be obtained by summing up the product of the estimates of lifetime survival and mean QOL functions throughout lifetime. This study was conducted to quantify the number of QALY that could be reduced through OAT by comparing QALE lost in age- and sex-matched referents based on an 8-year follow-up cohort. In other words, we attempted to estimate the QOL utility difference, the QALE and loss-of-QALE for heroin users stratified by OAT for comparison, which could provide basic evidence for the allocation of health resources for people with opioid use disorder.

2. Methods

This study commenced after approval from the Institutional Review Boards of the Jianan Psychiatric Center (JMH08033, JPC14-022 and JMH12050) and the Chi Mei Medical Center, Tainan, Taiwan (10403-004). Every interviewed heroin user provided written, informed consent. The establishment of OAT and non-OAT cohorts and the recruitment of subsamples of participants for QOL measurements are summarized in Fig. 1.

2.1. Establishment of the 8-year follow-up cohort for estimation of survival

The Taiwan/OAT study (survival cohort) (see Chang et al., 2015, 2017 for details) was a pilot OAT program started in 2006 by the Taiwan Center for Disease Control (CDC), and Jianan Psychiatric Center was the only hospital with both methadone and buprenorphine treatments during this time frame. Also, the National OAT registry was first established in 2006 by the Taiwan CDC and has been under careful management ever since. The inclusion criteria for this study were aged 20 or older and meeting the DSM-IV (Fourth edition of Diagnostic and Statistical Manual of Mental Disorders) criteria for opioid dependence. Participants in this study were recruited according to the following procedures: We contacted amnestied prisoners who were imprisoned for crimes related to illegal drug use before the enactment of the “2007 Sentence Commutation Bill” (Huang et al., 2011) after they were released and provided face-to-face interviews; we also encouraged all patients who were once treated in our hospital to refer more subjects to join through snowball sampling. From March 2006 to July 2008, there were 983 patients who received OAT (OAT group) and 626 subjects in the untreated (non-OAT) group, of which 326 subjects later received OAT and were excluded after verification with the national OAT registry during 2006–2014. We also documented that the OAT group had a substantial period of OAT treatment during follow-up (see Chen et al., 2017 for details). Linkages with the Taiwan National Mortality Registry (2006–2014) were performed to ascertain if a person was deceased. Subjects who were incarcerated were still recorded and not censored.

2.2. Rolling extrapolation of survival function to lifetime

Life expectancy (LE) and expected years of life lost (EYLL) were estimated using a rolling extrapolation algorithm to extrapolate survival for up to 70 years to derive the lifetime survival function after diagnosis for each individual with opioid dependence in these two cohorts (namely, OAT and non-OAT groups). Details of the method are summarized in the Supplementary Material.

For every subject in the index cohort, we simulated age-, sex-, and calendar year-matched referents from the vital statistics of Taiwan and estimated their lifetime survival function by the Kaplan-Meier method. The area between the lifetime survival curve of the index cohort and the age- and sex-matched referents is the estimate of EYLL, or, loss of life expectancy (loss-of-LE). The standard errors of these estimates were obtained using bootstrap methods, which we performed 100 times for each estimate. The extrapolation method applied in this study for opioid dependence was validated in a similar way using the same dataset in a previous study (Chang et al., 2017), that is, extrapolating the first 4 years of data to 8 years and comparing it with actual Kaplan-Meier’s estimate, to obtain the relative bias, which was only −0.5%. Detailed methods and data have been described in previous studies (Chang et al., 2015; Fang et al., 2007; Hwang et al., 2017) and the R package, iSQoL2, was used to compute these estimates (Hu, 2018).

2.3. Estimation of mean QOL functions for OAT and non-OAT groups

Longitudinal studies have characterized heroin users as following a recurrent pattern of frequent use, treatment, abstinence and relapse that are of varying durations and acuity (Boeri et al., 2011; Hser et al., 2015). We recruited subjects who met the criteria for QOL measurement, as summarized in Fig. 1. We excluded all non-OAT subjects who later shifted to OAT (N = 326) in our cohort of non-OAT by cross-checking each of the 626 subjects originally recruited in 2006-8 with the National OAT registry. After excluding 51 patients who became deceased during the follow-up period and 10 patients who did not use heroin daily at the time of interview, we successfully measured the QOL of 47 heroin users from our original non-OAT cohort (response rate 20%). Eleven cases refused to be interviewed, while most other non-respondents were those that could not be reached after 3 phone calls. To enrich our sample, we recruited additional non-OAT heroin users who relapsed to opioid dependence without any addiction treatment for at least 6 months from the Jianan Psychiatric Center, Chi Mei Medical Center and Changhua Hospital. Thus, all participants of the non-OAT group for QOL measurements fulfilled the criteria. One hundred and thirty-eight subjects from the original OAT cohort recruited in 2006-8 who maintained regular treatment as validated by the National OAT registry, received QOL measurements. Then, we applied the same criteria to recruit new OAT cases from Chi Mei Medical Center and Changhua Hospital (Fig. 1).

We measured the QOL of heroin users by using the Taiwanese version of the Euroqol questionnaire (EQ-5D), which has been validated in previous works (Chang et al., 2007; Cheng et al., 2017; Lee et al., 2013). The EQ-5D is a self-reporting questionnaire measuring five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each of which has three levels of severity (no problems, some/moderate problems, and severe/extreme problems). The measurements were transformed into a utility value according to the population norm in Taiwan (Lee et al., 2013) that ranges from 0 to 1 based on the five-dimensional health-state classification, with 0

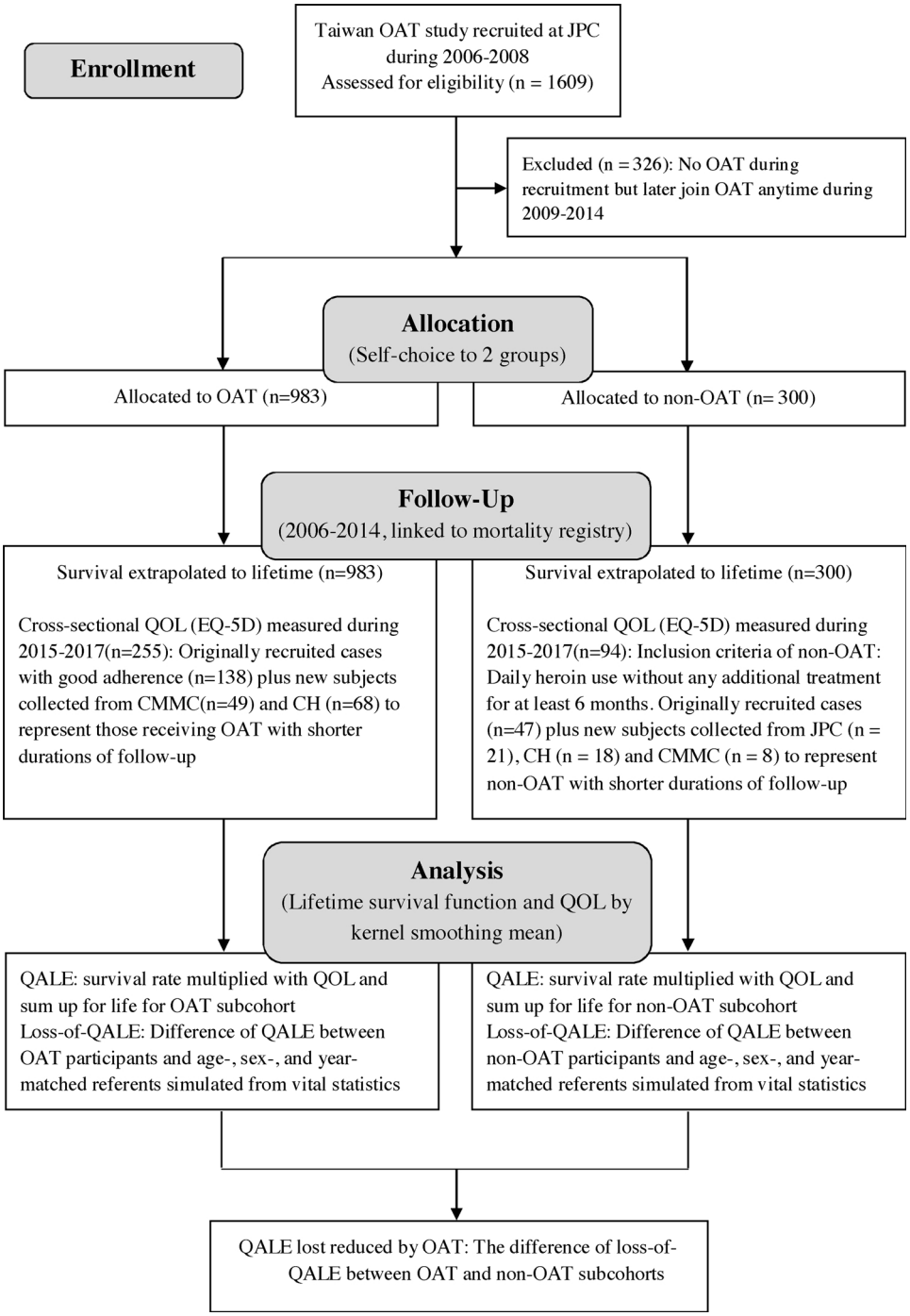

Fig. 1. Flow diagram of the inclusion of study participants for estimations of QOL (quality of life), lifetime survival function, QALE (quality-adjusted life expectancy) and loss-of-QALE. (Abbreviations: OAT = opioid agonist treatment; JPC = Jianan Psychiatric Center; CMMC = Chi Mei Medical Center; CH = Changhua Hospital; EQ-5D = Euroqol 5-dimension questionnaire; QALE = quality-adjusted life expectancy).

representing the worst health status and 1 indicating perfect health. In general, each heroin user was measured once using the EQ-5D. For each interview, we recorded the utility value of the subject and the duration-to-date for the measurement which was the period between the date of opioid dependence diagnosis (or OAT) and the date of interview.

We applied a simple kernel smoothing method with a bandwidth of 0.1 to the survey data to estimate the mean QOL function (Hwang and Wang, 1999, 2004). Specifically, for each time point, we first identified 10% of the duration-to-dates nearest to the time point from the interview data. We then estimated the mean QOL at the time point by averaging the utility values measured in those identified duration-to-dates. It has been suggested that a random sample size of 50 is the minimal requirement to estimate the mean QOL function (Hwang et al., 1996). The mean QOL values beyond the follow-up period were assumed constant and deemed by the average of utility values measured at the longest 10% near the end of follow-up. We also constructed a multiple linear regression model to determine the important demographic and clinical variables of QOL utility and tested several associated interaction terms.

2.4. Estimation of QALE and Loss-of-QALE

The product of lifetime survival function and mean QOL function of an index cohort (OAT or non-OAT group) is called the quality-adjusted survival curve and the area under this curve is the QALE of the cohort (Hwang et al., 1996). The loss-of-QALE of the index cohort can be estimated by the difference between the QALEs of the age-, and sex-matched referents and the cohort. We generated the lifetime survival function of the reference population from the rolling survival extrapolation of the index cohort. The mean QOL function of the referents were estimated using QOL measurements of a representative sample from the general population according to the following steps. First, we used the QOL measurements sampled from the general population to calculate the mean QOL for each age group and sex, denoted as Q(age, sex). Second, for the ith generated referent with survival time T_i, age a_i, and sex s_i, we calculated the referent's QOL utility function by $q_i(ta_i, s_i) = Q(a_i + t, s_i)$ where $t = 0,1, ..., T_i$. Finally, the mean QOL function value at time t was obtained by averaging the utility values at time t of those referents whose survival times were beyond that time point. We abstracted the EQ-5D utility values of the age- and sex-matched general population from the 2009 National Health Interview Survey in Taiwan for this analysis (Yu et al., 2015). The computation of loss-of-QALE was also conducted using the R package iSQoL2.

The loss-of-QALE was the expected lifetime utility lost due to opioid dependence because the referents were age- and sex-matched with every heroin user. The difference-in-differences between the OAT and non-OAT subjects (namely, the difference in loss-of-QALE between the two groups), was the expected lifetime utility saved by OAT, which had already been adjusted for different age distributions between the two cohorts. Detailed methods and mathematical proofs have been described in previous studies (Chang et al., 2016; Hung et al., 2015; Lee et al., 2016; Yang et al., 2017).

3. Results

3.1. Characteristics of the original (Survival) cohorts and QOL subsamples

The Taiwan OAT cohort for estimation of survival consisted of 983 patients who were registered for OAT (the OAT group), and 300 who were not (the non-OAT group, had never registered for OAT during the 8 years of follow-ups). Simultaneously, we cross-sectionally collected subsamples for measuring QOL: 255 from the OAT group and 94 from the non-OAT group (Fig. 1). Table 1 compares the demographic and clinical characteristics of the OAT and non-OAT groups. Most of the participants in our cohorts and subsamples were in their mid-thirty's; most were males and about half of them were employed except for 73% of the OAT subsample for QOL measurements who were employed. About 70% of our cohort and subsample were also amphetamine users and one-fifth reported amphetamine use in the previous 30 days. Only 5% of our subsample received psychiatric medication for mood disorders in the previous 30 days. The OAT group had significantly higher proportions of HIV and HCV infections.

3.2. Mortality of the 8-year follow-up cohort

The total sum of follow-up was 8128 person-years. Overall, the results of mortality of our OAT versus non-OAT cohorts were similar to the findings of our previous 6-year study (Chang et al., 2015). The crude mortality rate among OAT patients was lower than that of the non-OAT group (17.3 versus 24.2 per 1000 person-year). Among the 107 (10.9%) OAT subjects who died during the observation period, 48.6% (N = 52) were unnatural deaths and nearly half of the deaths were due to suicide (N = 27). In the non-OAT cohort, there were 47 deceased cases (15.7%), and 44.5% (N = 21) of them died due to unnatural deaths; 16 of these 21 were due to overdose. The cause-specific mortality among both groups were similar to the results of our previous six-year follow-up study (Chang et al., 2015).

Table 1
Clinical characteristics of opioid dependent participants with agonist therapy (OAT) and non-OAT (untreated) heroin users for outcome research.

	OAT		Non-OAT	
	Cohort for survival (n = 983) %	Subsample for QOL (n = 255) %	Cohort for survival (n = 300) %	Subsample for QOL (n = 94) %
Demographics				
Age at diagnosis, mean(SD) year	37.8(7.7)	38.4(5.9)	36.6(11.7)	36.6(8.5)
Sex				
Male	88.3	88.2	86.3	84.0
Female	11.7	11.8	13.7	16.0
Education				
7–9 years[a]	54.3	48.6	28.0	27.7
≧10 years	33.6	38.0	47.3	45.7
Marital status				
Single	48.2	47.1	53.6	48.9
Married	28.0	22.7	27.6	26.6
Living with family[a]	66.7	75.7	90.8	78.7
Employed[b,c]	54.8	73.3	60.5	48.9
Drug use				
Heroin use				
Age of first use, Mean(SD)	25.9(6.5)	25.5(6.9)	26.2(6.8)	26.0(5.9)
Amphetamine use history	70.3	67.8	67.3	66.0
Amphetamine use (past 30 days)	19.5	18.8	20.3	21.3
Medical co-morbidity				
HIV positive[a]	18.1	15.3	6.3	8.5
HCV positive	91.4	87.8	86.4	84.0
Medication for mood problems (past 30 days)	NA	5.5	NA	5.3

QOL, quality-of-life; NA: not available.
[a] Had significant difference between the OAT and non-OAT group (survival cohort) ($p < .01$).
[b] Had significant difference within OAT group ($p < .01$).
[c] Had significant difference between OAT and non-OAT group (QOL Subsample) ($p < .01$).

3.3. Estimation of mean QOL functions, QALE and loss-Of-QALE for OAT and non-OAT groups

The characteristics of QOL measurements and dynamic changes are illustrated in Fig. 2. Overall, the chi-square tests for the trends of all five dimensions were significant ($p < 0.001$) and the biggest difference was in the dimension of "pain/discomfort". Moreover, more than half of the patients in both groups reported some problems for anxiety/depression. The utility values of QOL for OAT participants were significantly higher than non-OAT heroin users (0.83 vs. 0.63, $p < 0.05$). Table 2 summarizes the estimated regression coefficients (β) for significant variables after controlling potential confounders. In addition to OAT, the QOL utility values of participants were affected by current psychiatric medications, age, amphetamine use in the previous 30 days and being infected with HIV. Interestingly, the interaction term of OAT and current psychiatric prescriptions was also significantly associated with poor QOL ($p = .015$) (Table 2). After multiplying the survival probability by the mean QOL at each time (duration-to-date), we obtained the quality-adjusted survival curve, as shown in Fig. 3 (upper panels). Based on the utility function of the age- and sex-matched referents from the 2009 National Health Interview Survey in Taiwan, the

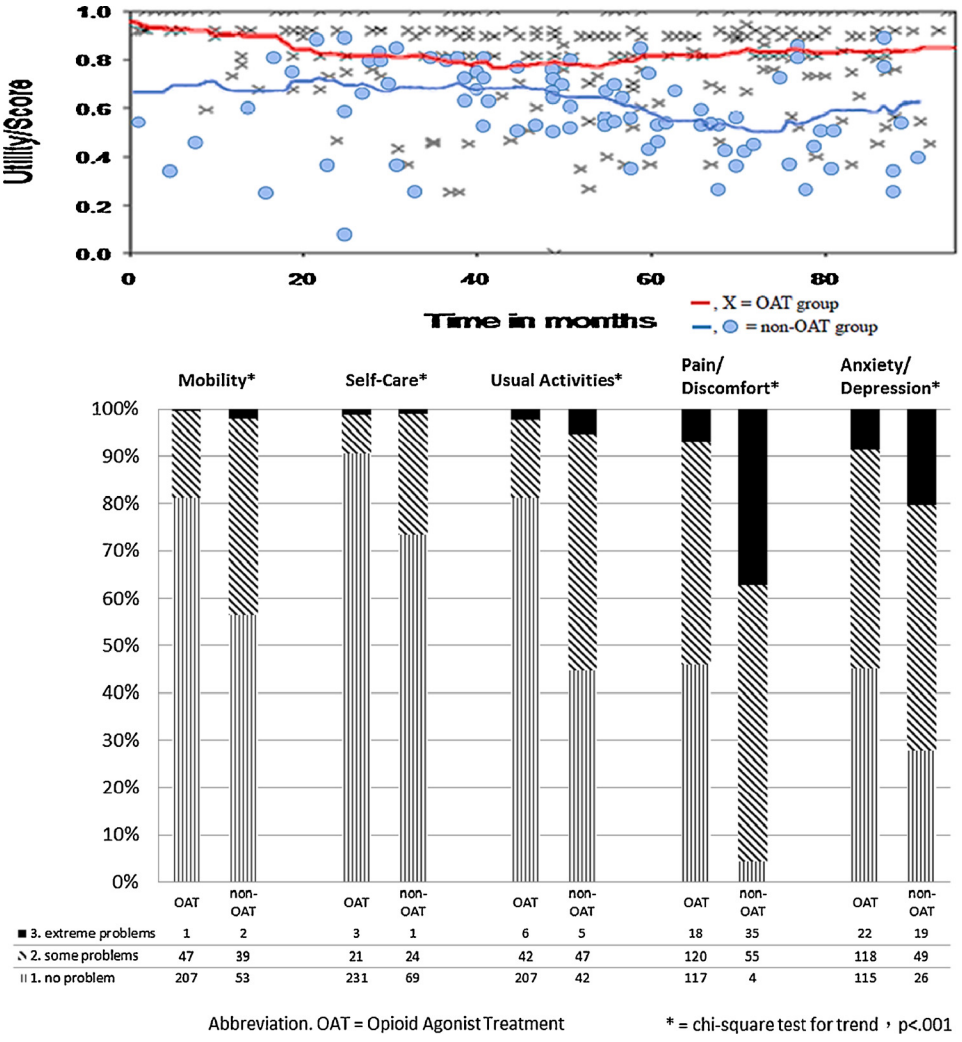

Fig. 2. The upper panel shows the dynamic changes of utility values after diagnosis or beginning treatment along follow-up time. The reddish line represents the kernel smoothing mean of patients receiving OAT (opioid agonist treatment)(x, n = 255), while the blue line represents that of non-OAT participants (o, n = 94). The lower panel indicates score distributions of EQ-5D of heroin users receiving OAT vs. non-OAT (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 2
Regression coefficients with 95% CI (confidence interval) of demographic and clinical variables in fitted multiple linear regression models for utility value measured with EQ-5D in heroin users (n = 349).

	EQ-5D Utility Adjusted R^2 = .443	
	β (95% Cl)	*p*
Constant	0.96(0.84˜1.06)	< .001
OAT (yes)	0.23(0.19˜0.27)	< .001
Age	−0.01(-0.01˜-0.01)	< .001
Amphetamine (the past 30 days)	−0.10(-0.14˜-0.07)	< .001
HIV positive	−0.09(-0.13˜-0.06)	< .001
Medication for mood disorders (the past 30 days)	−0.15(-0.29˜-0.01)	.039
Interactions*		
OAT x Medication for mood disorders (the past 30 days)	−0.21(-0.37˜-0.04)	.015

OAT: opioid agonist treatment; EQ-5D: EuroQol 5-dimension questionnaire.
* Interaction terms between several variables were considered, but only the significant term is reported here to save space.

difference between the areas under the quality-adjusted survival curve of the OAT cohort (or non-OAT cohort) and that of the referents was the loss-of-QALE (lower panels of Fig. 3). The QALE for OAT participants differed significantly from the QALE for non-OAT heroin users (17.8 vs. 9.2 QALY, $p < 0.01$), as did the loss-of-QALE for the two groups (18.2 vs. 27.9 QALY, $p < 0.01$).

4. Discussion

Because our participants may have cycled in and out of OAT during the follow-up period, we must first justify the representativeness of both subsamples before making any further inference. We propose the following arguments to support the above assumption: First, all our OAT participants who received QOL measurements from 2015 to 2017 were those who regularly received OAT. The cross-sectional subsample of OAT participants is composed of those who were originally recruited during 2006–8 and have been under regular treatment for a long period of time (n = 138) plus those who were consecutively recruited from the two hospitals (n = 117), representing subjects who were followed for a shorter period of time. Second, we assured a valid subsample of non-OAT participants by excluding 326 who received OAT at least once and 51 who became deceased during the follow-up period. We successfully measured 47 of those with a longer period of follow-up. Then, we consecutively recruited new participants for the non-OAT group from all 3 hospitals (N = 47) with shorter periods of follow-up. Table 1 provides evidence to show that our final subsamples for QOL

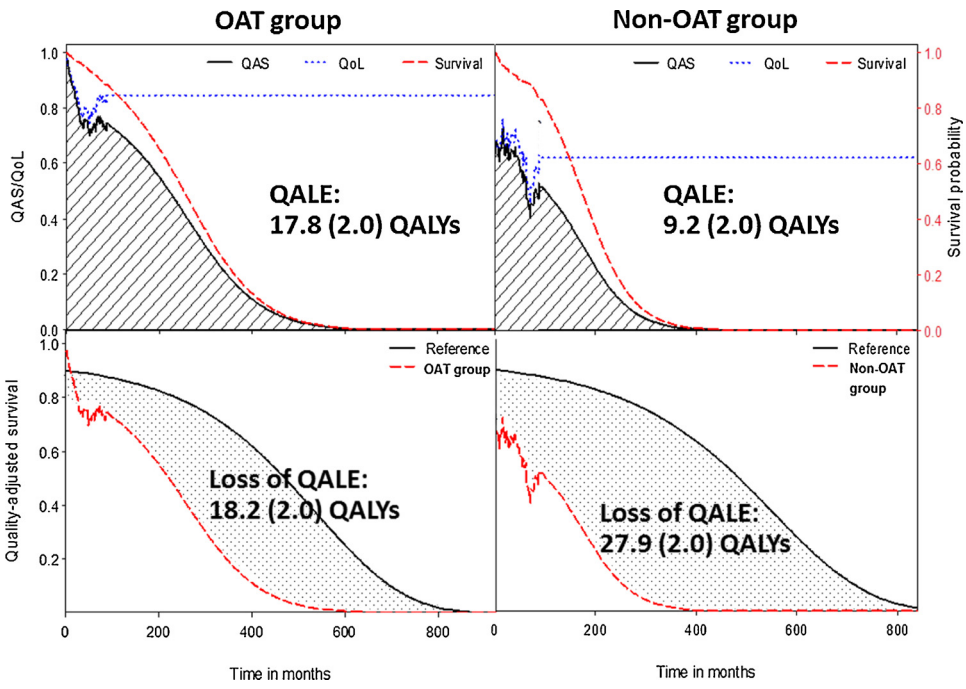

Fig. 3. Quality-adjusted life expectancy (QALYs, mean (SE)) and loss-of-QALE (QALYs, mean (SE)) of sub-cohorts receiving opioid agonist treatment (OAT) (left) and non-OAT heroin users (right). In the upper panels, the survival curves (dashed lines), mean utility functions (dotted lines), and quality-adjusted survival curves (solid lines) of both groups are shown, and the shaded area represents the QALE. In the lower panels, solid lines depict the quality-adjusted survival curves of the corresponding age-, and sex-matched referents of each sub-cohort, of which the area under the curve is the QALE of referents. The shaded area between the QAS curve of each sub-cohort and that of the corresponding referents is the loss-of-QALE (quality-adjusted life expectancy), which has been adjusted for different age and sex distributions. (SE: standard error).

measurements seemed to be similar to the original cohort both clinically and demographically, and relatively homogeneously distributed along the 8 year follow-up period. Namely, they could be considered as quasi-random samples from those who were willing to be measured on QOL. The results from the kernel-smoothing mean were close to long term follow-up observations (Hwang et al., 1996; Hwang and Wang, 2004). The fact that more than half of the non-OAT subjects recruited during 2006–2008 shifted to receiving OAT at least once before the end of 2014 implies that a poorer QOL may have lead them to try new solutions.

To the best of our knowledge, we are the first to estimate the difference in lifetime utility loss between OAT participants and non-OAT heroin users through integration of survival and mean QOL functions measured from actual cohorts and controlled for different age and sex distributions. The contributions of this research were as follows: First, although the survival functions of the two groups after the 8-year follow-up appeared similar to our previous 6-year study (Chang et al., 2015), extending the follow-up by two more years would be more comprehensive for lifetime extrapolation. Second, the revised rolling extrapolation method has the advantage of loosening the assumption of constant excess hazard by repeatedly constructing a restricted cubic splines model after extrapolating the survival function for each month (Hwang et al., 2017 and Supplementary Material). Namely, we applied a new algorithm each time, which corroborates the assumption of constant excess hazard and accuracy of the estimated lifetime survival function. Third, since our subsamples for QOL utility measurements were quasi-random, as mentioned in the previous paragraph, the kernel smoothing mean would be able to estimate the dynamic changes of longitudinal follow-up (upper panel of Fig. 2). Fourth, we multiplied the survival functions of our cohorts with the QOL mean at each time t and summed them up throughout life, which estimated the QALE for the two sub-cohorts. Then, they were subtracted from the corresponding age-, sex-, and calendar year-matched referents to obtain the loss-of-QALE; the difference-in-differences of them would indicate the adjustment for different distributions of age, sex, and calendar year between the OAT and non-OAT groups. Finally, the basic health unit of this study is QALY, which would facilitate direct comparison across different health technologies (e.g., extended-release naltrexone) (Lee et al., 2018; Solli et al., 2018) and incorporate opioid use disorder into routine decisions on health policies. Thus, we tentatively conclude that providing OAT for heroin users would reduce losses in both QOL and survival with a lifetime total of 9.7 QALYs.

Given the higher prevalence rates of chronic medical comorbidities (e.g., HIV or HCV infection) of the OAT group, the non-OAT group showed significantly lower utility values (0.63) along the 8 years of follow-up, and the OAT effect on QOL was even larger after adjustment for confounders. Our findings of QOL corroborate the results of other studies (Larson et al., 2007; Rosenblum et al., 2003; van der Zanden et al., 2006; Volkow and McLellan, 2016). Moreover, we found the difference between the loss-of-LE and loss-of-QALE from improving QOL was 1.9 [= 9.7-(26.6-18.8)] QALY, which could be directly compared with other clinical conditions, in contrast to estimations using disability-adjusted life year (DALY) (Degenhardt et al., 2013; Peacock et al., 2018). However, the significant negative interaction term of OAT with current psychiatric medications implies that OAT participants with psychiatric prescriptions are more likely to have poor QOL. Because there is only about 5% of OAT subjects receiving psychiatric medication in Taiwan in contrast to 27% in the U.S., together with a higher suicide mortality rate in the former subjects (Chang et al., 2017), we suspect that over-conservative psychiatric treatments for patients receiving OAT in Taiwan probably delay the timely help for mental health problems in such patients.

This study has the following limitations: First, since we applied the age- and sex-matched reference populations for both cohorts without taking other chronic conditions (e.g., HIV or HCV infection) and mental disorders into account, the QOL and survival of both cohorts might be affected. For example, approximately more than two-thirds of our subjects were also amphetamine users and one-fifth of them actually used it in the last 30 days, while current use of amphetamine was associated with lower QOL utility. More than 15% of our OAT participants were co-infected with HIV and 87% were co-infected with HCV, which were higher than those of non-OAT heroin users. Reasons for this phenomenon might be that our OAT program was initiated to control the HIV epidemic among IDUs, and treatment was free for patients with HIV infection (Lin et al., 2016). Therefore, our results cannot be directly generalizable to other populations with opioid use disorder in Western countries, for which the effects of OAT on reducing the loss-of-QALE might be higher. Second, because all subjects received QOL measurements when they were out of prison, our estimates of QOL utility would generally be higher or over-estimated than those who were

incarcerated. Moreover, while extrapolating the QOL function to lifetime, it was assumed that heroin users remained at the same level of QOL near the end of the follow-up period. Although Krebs et al. (2016) found the longitudinal trajectories of EQ-5D remained stable regardless of OAT, our assumption could result in overestimated or higher QOL because the actual utility value might gradually decline with age (Fryback et al., 2007). Hence, the QALE would be overestimated while the loss-of-QALE would be underestimated. Third, the estimation of QOL would have been more accurate if we had actually measured every subject repeatedly in our original (survival) cohort during the follow-up period. Unfortunately, conducting such a study was not possible because heroin users may shift in and out of OAT and the duration of OAT in an individual participant was variable. We recruited OAT and non-OAT participants from our original cohort plus an additional consecutive, cross-sectional subsample of heroin users from two more hospitals (Table 1 indicates the relative representativeness). The dynamic changes of QOL in the upper panel of Fig. 2 would be more informative than simply providing overall means and variances. However, unmeasured differences could still exist between our original non-OAT cohort and new subsample collected later on and the QOL status of untreated heroin users should be interpreted with caution, as we have not performed repeated measurements of QOL for every participant during longitudinal follow-up. Lastly, since the sample size of the EQ-5D survey in the current study was relatively limited, future studies with larger sample sizes and longer periods of follow-up would allow for stratification to further identify high risk groups to improve decision-making for related policies.

5. Conclusions

This study successfully estimated the QOL, QALE and loss-of-QALE of heroin users stratified by OAT for comparison. The lifetime utility lost reduced by OAT would be 9.7 QALY after adjustment for age, sex and QOL. Future research on cost-effectiveness (Byford et al., 2013; Dijkgraaf et al., 2005; Krebs et al., 2018; Nosyk et al., 2012; Stephen et al., 2012; Tran and Nguyen, 2013) is warranted to estimate the incremental cost-effectiveness ratios and potential social impacts for the implementation of OAT.

Role of funding sources

This project is was supported by grants from the Ministry of Health and Welfare, Executive Yuen, Taiwan (MOHW-10646, MOHW-10243, MOHW-10740, MOHW-10444 and MOHW-10445) and partially supported by the following grants funded by the Ministry of Science and Technology, Executive Yuen, Taiwan (MOST 106-2627-M-006-015 and MOST 107-2627-M-006-007). The funder has no role in the study design, data analysis, or preparation of this manuscript.

Informed consent

All participants provided informed consent before joining the study.

Contributors

Authors KCC, THL and JDW conceived and designed the study and wrote the protocol. Authors KYL, SYT and CCC contributed materials and performed the study. KYL and CNL analyzed the data. KCC and JDW wrote the first draft of the manuscript, revised, and finalized the manuscript. JSH interpreted the data and validated the statistical analysis. All authors contributed to and

have approved the final manuscript. (KCC: Kun-Chia Chang; KYL: Kuan-Ying Lee; THL: Tsung-Hsueh Lu; JSH: Jing-Shiang Hwang; CNL: Chia-Ni Lin; SYT: Shuo-Yen Ting; CCC: Chih-Cheng Chang; JDW: Jung-Der Wang).

Ethical approval

The copies of two approval documents from the two Institutional Review Boards of two hospitals have been attached at the end of this statement, as follows: Ethics Committees of the Jianan Psychiatric Center and the Chi Mei Medical Center where these works were undertaken and they conform to the provisions of the Declaration of Helsinki in 1995.

Compliance with ethical standards

The material contained in the manuscript represents the original work, has not been published elsewhere, and is not under consideration for publication elsewhere. The study has been approved by the constituted Ethics Committees of the Jianan Psychiatric Center (JMH08033, JPC14-022 and JMH12050) and the Chi Mei Medical Center (IRB number: 10403-004) where these works were undertaken and they conform to the provisions of the Declaration of Helsinki in 1995. Every patient has provided an informed consent. The patient anonymity has been preserved throughout all processes of data analysis, making inference, and preparation of manuscript. Authorship has been granted only to those individuals who have contributed substantially to the manuscript, and is agreed on by all authors.

Acknowledgments

We extend our sincere appreciation to our participating networks: Department of Psychiatry, Chi Mei Medical Center, Tainan, Taiwan; Jianan Psychiatric Center, Ministry of Health and Welfare, Tainan, Taiwan; Department of Public Health College of Medicine, National Cheng Kung University, Tainan, Taiwan; Chang-Hua Hospital, Ministry of Health and Welfare, Puxin Township, Changhua County, Taiwan.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.05.003.

References

Boeri, M., Whalen, T., Tyndall, B., Ballard, E., 2011. Drug use trajectory patterns among older drug users. Subst. Abuse Rehabil. 2, 89–102.
Byford, S., Barrett, B., Metrebian, N., Groshkova, T., Cary, M., Charles, V., Lintzeris, N., Strang, J., 2013. Cost-effectiveness of injectable opioid treatment v. Oral methadone for chronic heroin addiction. Br. J. Psychiatry 203, 341–349.
Chang, K.C., Lu, T.H., Lee, K.Y., Hwang, J.S., Cheng, C.M., Wang, J.D., 2015. Estimation of life expectancy and the expected years of life lost among heroin users in the era of opioid substitution treatment (OST) in Taiwan. Drug Alcohol Depend. 153, 152–158.
Chang, K.C., Wang, J.D., Saxon, A., Matthews, A.G., Woody, G., Hser, Y.I., 2017. Causes of death and expected years of life lost among treated opioid-dependent individuals in the United States and Taiwan. Int. J. Drug Policy 43, 1–6.
Chang, T.J., Tarn, Y.H., Hsieh, C.L., Liou, W.S., Shaw, J.W., Chiou, X.G., 2007. Taiwanese version of the EQ-5D: validation in a representative sample of the Taiwanese population. J. Formos. Med. Assoc. 106, 1023–1031.
Chang, Y.T., Hwang, J.S., Hung, S.Y., Tsai, M.S., Wu, J.L., Sung, J.M., Wang, J.D., 2016. Cost-effectiveness of hemodialysis and peritoneal dialysis: a national cohort study with 14 years follow-up and matched for comorbidities and propensity score. Sci. Rep. 6, 30266.
Chen, H.M., Lu, T.H., Chang, K.C., Lee, K.Y., Cheng, C.M., 2017. Opioid users with comorbid hepatitis C spent more time in agonist therapy: a 6-year observational study in Taiwan. Addict. Behav. 72, 133–137.
Cheng, C.M., Lin, Y.C., Chang, K.C., 2017. Psychological distress is correlated with erectile dysfunction among patients receiving methadone maintenance in Taiwan. J. Dual Diagn. 13, 312–316.
Degenhardt, L., Whiteford, H.A., Ferrari, A.J., Baxter, A.J., Charlson, F.J., Hall, W.D., Freedman, G., Burstein, R., Johns, N., Engell, R.E., Flaxman, A., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. Lancet 382, 1564–1574.
Dijkgraaf, M.G.W., van der Zanden, B.P., de Borgie, C.A.J.M., Blanken, P., van Ree, J.M., van den Brink, W., 2005. Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. BMJ 330, 1297.

Fang, C.T., Chang, Y.Y., Hsu, H.M., Twu, S.J., Chen, K.T., Lin, C.C., Huang, L.Y., Chen, M.Y., Hwang, J.S., Wang, J.D., Chuang, C.Y., 2007. Life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy. QJM 100, 97–105.

Fryback, D.G., Dunham, N.C., Palta, M., Hanmer, J., Buechner, J., Cherepanov, D., Herrington, S.A., Hays, R.D., Kaplan, R.M., Ganiats, T.G., Feeny, D., Kind, P., 2007. US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. Med. Care 45, 1162–1170.

Hser, Y.I., Evans, E., Grella, C., Ling, W., Anglin, D., 2015. Long-term course of opioid addiction. Harv. Rev. Psychiatry 23, 76–89.

Hser, Y.I., Evans, E., Huang, D., Weiss, R., Saxon, A., Carroll, K.M., Woody, G., Liu, D., Wakim, P., Matthews, A.G., Hatch-Maillette, M., Jelstrom, E., Wiest, K., McLaughlin, P., Ling, W., 2016. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. Addiction 111, 695–705.

Hu, T.H., 2018. iSQoL 2 Package for Windows [webpage on the Internet]. Accessed 07/11/18. http://sites.stat.sinica.edu.tw/isqol/.

Huang, Y.F., Kuo, H.S., Lew-Ting, C.Y., Tian, F., Yang, C.H., Tsai, T.I., Nelson, K.E., 2011. Mortality among a cohort of drug users after their release from prison: an evaluation of the effectiveness of a harm reduction program in Taiwan. Addiction 106, 1437–1445.

Hung, M.C., Lai, W.W., Chen, H.H., Su, W.C., Wang, J.D., 2015. Comparison of expected health impacts for major cancers: integration of incidence rate and loss of quality-adjusted life expectancy. Cancer Epidemiol. 39, 126–132.

Hwang, J.S., Hu, T.H., Lee, L.J., Wang, J.D., 2017. Estimating lifetime medical costs from censored claims data. Health Econ. 26, e332–e344.

Hwang, J.S., Tsauo, J.Y., Wang, J.D., 1996. Estimation of expected quality adjusted survival by cross-sectional survey. Stat. Med. 15, 93–102.

Hwang, J.S., Wang, J.D., 1999. Monte Carlo estimation of extrapolation of quality-adjusted survival for follow-up studies. Stat. Med. 18, 1627–1640.

Hwang, J.S., Wang, J.D., 2004. Integrating health profile with survival for quality of life assessment. Qual. Life Res. 13, 1–10.

Imtiaz, S., Probst, C., Rehm, J., 2018. Substance use and population life expectancy in the USA: interactions with health inequalities and implications for policy. Drug Alcohol Rev. 37, S263–S267.

Kimber, J., Larney, S., Hickman, M., Randall, D., Degenhardt, L., 2015. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry 2, 901–908.

Kind, P., Lafata, J.E., Matuszewski, K., Raisch, D., 2009. The use of QALYs in clinical and patient decision-making: issues and prospects. Value Health 12, S27–S30.

Krebs, E., Enns, B., Evans, E., Urada, D., Anglin, M.D., Rawson, R.A., Hser, Y.I., Nosyk, B., 2018. Cost-effectiveness of publicly funded treatment of opioid use disorder in California. Ann. Intern. Med. 168, 10–19.

Krebs, E., Kerr, T., Wood, E., Nosyk, B., 2016. Characterizing long-term health related quality of life trajectories of individuals with opioid use disorder. J. Subst. Abuse Treat. 67, 30–37.

Larson, M.J., Paasche-Orlow, M., Cheng, D.M., Lloyd-Travaglini, C., Saitz, R., Samet, J.H., 2007. Persistent pain is associated with substance use after detoxification: a. Prospective cohort analysis. Addiction 102, 752–760.

Lee, H.Y., Hung, M.C., Hu, F.C., Chang, Y.Y., Hsieh, C.L., Wang, J.D., 2013. Estimating quality weights for EQ-5D (EuroQol-5 dimensions) health states with the time trade-off method in Taiwan. J. Formos. Med. Assoc. 112, 699–706.

Lee, J.D., Nunes, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., Rotrosen, J., 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391, 309–318.

Lee, L.J., Lin, C.K., Hung, M.C., Wang, J.D., 2016. Impact of work-related cancers in Taiwan-Estimation with QALY (quality-adjusted life year) and healthcare costs. Prev. Med. Rep. 4, 87–93.

Lin, T., Chen, C.H., Chou, P., 2016. Effects of combination approach on harm reduction programs: the Taiwan experience. Harm Reduct. J. 13, 1.

Nosyk, B., Bray, J.W., Wittenberg, E., Aden, B., Eggman, A.A., Weiss, R.D., Potter, J., Ang, A., Hser, Y.I., Ling, W., Schackman, B.R., 2015. Short term health-related quality of life improvement during opioid agonist treatment. Drug Alcohol Depend. 157, 121–128.

Nosyk, B., Guh, D.P., Sun, H., Oviedo-Joekes, E., Brissette, S., Marsh, D.C., Schechter, M.T., Anis, A.H., 2011. Health related quality of life trajectories of patients in opioid substitution treatment. Drug Alcohol Depend. 118, 259–264.

Nosyk, B., Guh, D.P., Bansback, N.J., Oviedo-Joekes, E., Brissette, S., Marsh, D.C., Meikleham, E., Schechter, M.T., Anis, A.H., 2012. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. CMAJ 184, E317–E328.

Peacock, A., Leung, J., Larney, S., Colledge, S., Hickman, M., Rehm, J., Giovino, G.A., West, R., Hall, W., Griffiths, P., Ali, R., Gowing, L., Marsden, J., Ferrari, A.J., Grebely, J., Farrell, M., Degenhardt, L., 2018. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 113, 1905–1926.

Rehm, J., Probst, C., 2018. Decreases of life expectancy despite decreases in non-communicable disease mortality: the role of substance use and socioeconomic status. Eur. Addict. Res. 24, 53–59.

Rosenblum, A., Joseph, H., Fong, C., Kipnis, S., Cleland, C., Portenoy, R.K., 2003. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA 289, 2370–2378.

Solli, K.K., Latif, Z.H., Opheim, A., Krajci, P., Sharma-Haase, K., Benth, J.Š., Tanum, L., Kunoe, N., 2018. Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial. Addiction 113, 1840–1849.

Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Ferri, M., Pastor-Barriuso, R., 2017. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ 357, j1550.

Stephen, J.H., Halpern, C.H., Barrios, C.J., Balmuri, U., Pisapia, J.M., Wolf, J.A., Kampman, K.M., Baltuch, G.H., Caplan, A.L., Stein, S.C., 2012. Deep brain stimulation compared with methadone maintenance for the treatment of heroin dependence: a threshold and cost-effectiveness analysis. Addiction 107, 624–634.

Tran, B.X., Nguyen, L.T., 2013. Impact of methadone maintenance on health utility, health care utilization and expenditure in drug users with HIV/AIDS. Int. J. Drug Policy 24, e105–10.

Tran, B.X., Ohinmaa, A., Duong, A.T., Do, N.T., Nguyen, L.T., Mills, S., Houston, S., Jacobs, P., 2012. Cost-effectiveness of methadone maintenance treatment for HIV-positive drug users in Vietnam. AIDS Care 24, 283–290.

van der Zanden, B.P., Dijkgraaf, M.G., Blanken, P., de Borgie, C.A., van Ree, J.M., van den Brink, W., 2006. Validity of the EQ-5D as a generic health outcome instrument in a heroin-dependent population. Drug Alcohol Depend. 82, 111–118.

Volkow, N.D., McLellan, A.T., 2016. Opioid abuse in chronic pain–misconceptions and mitigation strategies. N. Engl. J. Med. 374, 1253–1263.

Weinstein, M.C., Torrance, G., McGuire, A., 2009. QALYs: the basics. Value Health 12, S5–S9.

Yang, S.C., Lai, W.W., Lin, C.C., Su, W.C., Ku, L.J., Hwang, J.S., Wang, J.D., 2017. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. Lung Cancer 108, 183–191.

Yu, S.T., Chang, H.Y., Yao, K.P., Lin, Y.H., Hurng, B.S., 2015. Validity of EQ-5D in general population of Taiwan: results of the 2009 national health interview and drug abuse survey of Taiwan. Qual. Life Res. 24, 2541–2548.