Opium Dependence, the Potential Impact of Changes in Treatment Coverage Level: A Dynamic Modeling Study

Supplementary file 1. Estimation of model parameter’s values

In this section, the calculations and how to estimate each of the parameters are explained in detail.

- Opium dependent population in Iran and the of each treatment group’s entry to percentage

The annual entry to detoxification treatment based on secondary analysis of TEDS\(^1\) data and RSA report\(^2\) was 11.1% and 8.9%, respectively. So, the share of detoxification and relapse prevention treatment (except NA treatment) was considered 5% of the total treatment, based on the experts’ consensus about the population of opium dependence throughout the country. We also considered NA group within this group and according to RSA, 37.1 percent of opioid substance dependence had experienced some types of treatment and 12 steps (NA) groups accounted for 14% of treatment experienced people. In other words, 5 percent of all opium substance dependence. According to a study conducted in Mashhad, Iran, about 50% of patients in the NA group were opium dependence,\(^3\) while this amount for whole country is 70% of all addictions (RSA study), so with regard to this ratio and consensus of experts, NA entry percentage after detoxification was considered equal to 3.5% of all opium dependence in Iran. So, coverage of detoxification and relapse prevention treatment was considered 8.5% of the total treatment and this amount will be 2.42% for the whole population.

The ratio of MMT to BMT maintenance treatment entrance for opium dependence was 79.42 vs. 20.58 based on new cases data of IDATIS for 2019,\(^4\) and this amount was also agreed upon by experts and was considered in the model.

The evidence-based medicine treatment coverage was 27.5% based on the results of TEDS. Also, in the National Mental Health Survey,\(^5\) 25% of opioid dependence had the experience of referring to outpatient treatment centers. In the RSA study, about 55% of all opioid dependence experienced treatment in one of the maintenance or drug detoxification groups. Which according to expert's opinion, this percentage for those “opioid dependents that were not recruited from any service settings” is at least half of all addicts, so in this case we will reach 27.5% of treatment coverage.

Based-on RSA study, the experience all types of treatment (evidence-based and non-evidence-based medicine) was 37% for the participants, while for outpatients and medium-term residential drug treatment centers it was 100% and for those not recruited from any service settings, it was 15.8%.

- Prevalence of opium dependence in Iran

In the IranMHS study\(^5\) (which was a household survey), the prevalence of 12-month opioid substances use disorder was 2.23% based-on DSM-5. Considering that 84% of these cases were related to opium dependence and its derivatives, the prevalence of opium dependence for the population aged 15-64 years was 1.87%. On the other hand, according to experts and considering 30% underestimation which arises due to the social stigma of addiction and the nature of household survey studies, and 20% overestimation due to considering the mild cases in DSM-5, the final prevalence of Opium dependence was estimated 2.06% for the population of 15 -64 years old in Iran.
- **Heroin dependence following Opium dependence**

The results of a longitudinal study, on changes in the consumption pattern of 70 patients with soft opioid substances dependence (including opium, SHIREH and prescription opioids) showed that 5.7% of patients (95% CI: 2.1 to 14.6) were changed to hard opioid users (including heroin or crack heroin) after 6 years. On the other hand, in the secondary analysis of TEDS data, heroin use prevalence in opioid dependence who had referred to treatments was 2.68% per year. Based on these results and the consensus of experts, the annual percentage of heroin dependence following opium dependence was considered equal to 1.5%.

- **Annual mortality from opium dependence**

According to the results of INCAS systematic review and meta-analysis study of mortality of Iranian drug dependence, the crude death rate in opioid dependence is reported to be 1.52% per year. (Table S1 and Figure S1). Excluding the study of Nazer, 2008 and Rahimi-Movaghar A., 2011 (due to the study of more high-risk addicts) the crude death rate was 1.15% per year (95% CI: 0.27 to 2.03) based on the meta-analysis of the remaining three studies. (Figure S1). Based on the consensus of experts, this death rate was considered as the total death in the opium dependence in Iran.

In the meta-analysis of international studies, the all causes mortality rate for the non-heroin non-injection opioid dependence group was 1.19% per year. Based on meta-analysis, treatment group’s annual mortality rate for the methadone and buprenorphine maintenance treatment was 0.80 and 0.40, respectively (Figure S2). In this group of addicts (non-heroin, non-injection group), the mortality ratio of MMT and BMT groups to total mortality rate was 0.67 and 0.34, respectively. Considering this ratio for the total annual mortality rate of Iranian opium dependence (1.15% per year), the death rates for MMT and BMT groups of Iran were 0.77 and 0.39, respectively.

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The mortality ratio of the detoxification and relapse prevention treatment group to total was estimated to be 0.46 based on the Evans, E. study. The mortality rate in this treatment group for the Iranian opium dependence was 0.53% per year, based on ratio and total opium dependence mortality rate. The total mortality rate equation was consisted of four parts (3 treatment groups and one untreated or non-evidence-based medicine treatment group) and the only unknown mortality rate was untreated groups, which was calculated using available information and obtained 1.34% (Table S2).

- **Percentage of annual retention in maintenance treatments**

Annual retention in MMT for opioid dependence has been reported to be between 34% and 44% in the majority of reviewed Iranian studies. According to the literature review and discussion in the panel of experts, this amount was estimated 33.3% per year for Iranian opium dependence. Also, according to Mattick (2014) meta-analysis of 11 studies, the ratio of BMT to MMT retention was 0.83, which was agreed to be 0.9 for the Iranian opium dependence treatment. Therefore, the annual retention rate in BMT treatment was considered to be 0.30%.

- **Treatment success in each treatment group**

12-month abstinence rate in maintenance treatment is reported from 4 to 47% in various studies. However, in most of the studies, this rate was reported to be about 15%. Since these studies have been conducted on both opioid and heroin dependence, it can be expected that this amount to be higher when considering opium dependence separately. According to another INCAS study, of the 159 opioid dependence who had been on maintenance treatment for more than a year, three had a
positive urine test, and five reported self-reported recent drug use. In other words, a maximum of 3% of people remain in treatment (failed to abstinence). Since in this study, urine test was performed only once and also a considerable percentage of people were in treatment for more than a year, we expect the failure rate to be higher at the end of first year. Finally, after expert discussion, the percentage of abstinence at the end of one year was estimated at 27% and 26% for MMT and BMT, respectively.

The success of treatment (abstinence) in the detoxification group plus oral naltrexone in three Iranian studies was 32.8% and 43.6% at one year follow-up, and 83.3% for six-month follow-up. In two Iranian 12-month follow-up studies about the success of treatment of NA group, the success rate was reported 28% and 33%, and in another study, this value was equal to 34% for 6 months. Due to the fact that all above mentioned studies were conducted in a controlled condition and limited special medical clinics in Iran, and with regard to the available documents and the result of the FGD, the abstinence rate of detoxification and relapse prevention treatment group (psychological, NA group, oral and extended-release (XR) injection naltrexone) for opium dependence in Iran was estimated at 10%.
### Table S1. Characteristics of the included studies on mortality among drug users in Iran

| Study ID (First author, year of publication, and language); Reference | Study design | Province | Target Population                                                                 | Opioid use                                                                 | Sampling sites | Sampling method                                                                 | Sample size (Male, Female) |
|----------------------------------------------------------|---------------|---------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------|---------------------------------------------------------------------------------|----------------------------|
| Rahimi-Movaghar, unpublished data of youth cohort, 2019 (personal contact) | Cohort study  | Fars    | 15-34 years old residents who has positive history of any opioid use in last 12 months at baseline | Opium 99.2%; Heroin 4%; Tramadol 14.8%; Illicit Buprenorphine or methadone 31.18% | General population of Fasa and Ravansar | Cluster random sampling of households | 263 (235,28) |
| Khademi 2012, English; | Prospective cohort | Golestan | Opium users aged 40-75                                                                 | 100% Opium                                                                 | Household | Urban: random systematic clustering Rural: census | 8487 (6132, 2355) |
| Rahimi-Movaghar, 2011, Persian; | Follow-up study | Tehran | Street addicts who were arrested for mandatory treatment of addiction (Nejat program) | Opium 86.3%; Heroin 54.1%; Tramadol 20.5%; Buprenorphine 5.6% | Valiasr garrison | Census | 497 (495,2) |
| Nazer, 2008, English (Congress Abstract) | Retrospective cohort | Lorestan | Subjects enrolled in the drug treatment program (HIV positive, negative or untested) | UK | Treatment facilities | Census | 2996 (UK) (814 HIV positive, 10635 HIV negative, 1119 untested) |
| Jafari, 2010, English | Follow-up study | Fars | Drug users referred for treatment of opium, heroin or buprenorphine dependence | Opium 99%; Heroin 9%; buprenorphine 24% | Treatment facility | UK | 273 (UK) |
**Figure S1.** Crude death rate (per 100-person year) for opioid dependence in Iran, based on the INCAS systematic review by high-risk and non-high-risk (representative of opium dependence)

| Author, Year | Province | ES (95% CI) | Weight |
|--------------|----------|-------------|--------|
| No high risk |          |             |        |
| Jafari S., 2010 | Fars     | 0.0105 (0.0061, 0.0178) | 20.11  |
| Rahimi-Movaghar A., 2019 | National | 0.0038 (0.0007, 0.0213) | 15.43  |
| Khademi 2012 | Golestan | 0.0185 (0.0172, 0.0199) | 32.48  |
| Subtotal (I² = %, p = .) | | 0.0115 (0.0027, 0.0203) | 68.02  |
| High risk | | | |
| Rahimi-Movaghar A., 2011 | Tehran | 0.0470 (0.0161, 0.1294) | 0.58   |
| Nazer M.R., 2008 | Lorestan | 0.0157 (0.0179, 0.0216) | 31.40  |
| Subtotal (I² = %, p = .) | | 0.0197 (0.0179, 0.0216) | 31.98  |
| Heterogeneity between groups: p = 0.074 | | | |
| Overall (I² = 84.0964%, p = 0.0000) | | 0.0152 (0.0112, 0.0191) | 100.00 |

**Figure S2.** Crude death rate (per 100-person year) for the non-heroin non-injection opioid dependence by treatment group

| Study, year | Country | ES (95% CI) | Weight |
|-------------|---------|-------------|--------|
| ^MHT | | | |
| Cousins, 2016 | Ireland | 0.0051 (0.0043, 0.0061) | 14.69  |
| Degenhardt, 2015 | Australia | 0.0038 (0.0024, 0.0050) | 14.13  |
| Evins, 2015 | USA | 0.0069 (0.0050, 0.0079) | 14.62  |
| Kimmer, 2015 | Australia | 0.0063 (0.0043, 0.0122) | 8.89   |
| Fellows-Smith, 2011 | Australia | 0.0058 (0.0041, 0.0085) | 12.48  |
| Cornish, 2010 | UK | 0.0152 (0.0124, 0.0186) | 4.59   |
| Peles, 2010 | Israel | 0.0151 (0.0103, 0.0222) | 5.41   |
| Apel, 2000 | USA | 0.0080 (0.0063, 0.0097) | 100.00 |
| Cushman, 1977 | USA | 0.0040 (0.0033, 0.0049) | 67.66  |
| Subtotal (I² = 91.38%, p = 0.000) | | 0.0027 (0.0009, 0.0075) | 28.72  |
| ^BMT | | | |
| Kimmer, 2015 | Australia | 0.0040 (0.0022, 0.0059) | 100.00 |
| Cornish, 2010 | UK | 0.0053 (0.0023, 0.0087) | 19.76  |
| Reece, 2010 | Australia | 0.0051 (0.0023, 0.0087) | 100.00 |
| Subtotal (I² = %, p = .) | | 0.0023 (0.0019, 0.0298) | 80.24  |
| ^Untreated | | | |
| Clausen, 2008 | Norway | 0.0553 (0.0455, 0.0670) | 19.76  |
| Riesser, 2001 | Australia | 0.0051 (0.0023, 0.0087) | 100.00 |
| Subtotal (I² = %, p = .) | | 0.0239 (0.0191, 0.0298) | 80.24  |
| ^Total | | | |
| Abrahamsson, 2017 | Sweden | 0.0167 (0.0150, 0.0185) | 7.77   |
| Cousins, 2016 | Ireland | 0.0074 (0.0065, 0.0085) | 8.26   |
| Degenhardt, 2015 | Australia | 0.0078 (0.0064, 0.0088) | 8.12   |
| Evins, 2015 | USA | 0.0137 (0.0129, 0.0146) | 8.33   |
| Kimmer, 2015 | Australia | 0.0094 (0.0080, 0.0098) | 8.48   |
| Fellows-Smith, 2011 | Australia | 0.0088 (0.0068, 0.0114) | 7.28   |
| Cornish, 2010 | UK | 0.0138 (0.0130, 0.0146) | 7.98   |
| Peles, 2010 | Israel | 0.0195 (0.0195, 0.0235) | 5.83   |
| Reece, 2010 | Australia | 0.0029 (0.0038, 0.0066) | 7.99   |
| Degenhardt, 2009 | Australia | 0.0089 (0.0064, 0.0086) | 8.50   |
| Clausen, 2008 | Norway | 0.0195 (0.0171, 0.0222) | 6.98   |
| Riesser, 2001 | Australia | 0.0270 (0.0222, 0.0311) | 4.77   |
| Apel, 2000 | USA | 0.0207 (0.0179, 0.0240) | 6.54   |
| Gudeman, 1977 | USA | 0.0230 (0.0146, 0.0272) | 3.76   |
| Subtotal (I² = 97.19%, p = 0.000) | | 0.0119 (0.0105, 0.0135) | 100.00 |
Table S2. Estimation of mortality rate of different groups of opium dependence

| In treatment group of non-heroin, non-injecting opioid dependent | Meta-analysis result | Death rate ratio of treatment group to total dependence | Estimation of annual mortality rate for subgroups of opium dependence in Iran (%) |
|---|---|---|---|
| | Number of articles | Crude death rate | References |  |
| In MMT | 9 | 0.80 (0.63 to 0.97) | 13, 36-43 | 0.67 | 0.77<sup>a</sup> |
| In BMT | 3 | 0.40 (0.22 to 0.59) | 37, 42, 44 | 0.34 | 0.39<sup>a</sup> |
| In untreated | 2 | 3.01 (2.53 to 3.48) | 45, 46 | 2.53 | 1.34<sup>b</sup> |
| Total dependence | 14 | 1.19 (1.05 to 1.33) | 13, 36-48 | 1.0 | 1.15 |

<sup>a</sup> Based-on the ratio of death rate in subgroups to death rate in total addicts obtained from meta-analysis of international studies

<sup>b</sup> Calculation based-on the total death rate in Iran and taking into account the death rate for other treatment groups

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