Research Paper

Evaluation of the treatment failure ratio in individuals receiving methadone maintenance therapy via the network scale up method

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ABSTRACT

Background: The network scale up (NSU) method is an indirect size estimation method that has received remarkable attention in estimating the sensitive behaviors. Using methadone maintenance therapy (MMT), which is a treatment for opioid use disorder, is a sensitive topic in many societies. The aim of this manuscript was to estimate the number of MMT users and its failure ratio using the NSU method in the city of Kerman, Iran, in 2016.

Methods: In this cross-sectional study, 1275 men and 1275 women which were aged > 18 years and who had lived in the city of Kerman for at least 5 years were recruited via multistage sampling. Data was collected via face-to-face interviews using a questionnaire that was included questions for estimating the network size of the residents of Kerman as well as the number of MMT users and the existing failure among them.

Results: In total, the average network size of the citizens of Kerman was 235; among them, 97 were men and 138 were women. Overall, the numbers of MMT users and failures were estimated at about 5289 and 2731, respectively, leading to a failure ratio about 52%. The treatment failure ratio in the women and men was equal to 55% and 51%, respectively. Among the men, the failure ratio in all age groups was equal to ˜50%. Among the women, the failure ratio in those who were aged < 18 years was equal to 76%.

Conclusion: The considerable failure ratio indicates the need for conducting studies on MMT services in order to understand the reasons which exist regarding this failure. This is of particular importance in specific groups, such as in young women. Further, the comparable results with other direct methods indicate that the NSU method could be used in the size estimation of MMT failure ratios.

Introduction

The network scale up (NSU) method, which is an indirect method of size estimation, has received a growing attention in estimating the sensitive and hidden behaviors such as usage of drugs (Bernard et al., 2010), Prostitution (Salganik et al., 2011) and abortions (Rastegari et al., 2014). These behaviors are hidden due to religious, cultural, or law restrictions against them (Ezoe, Morooka, Noda, Sabin, & Koike, 2012). Drug usage in many societies is highly stigmatized; therefore, any action indicating usage of drugs, including services for drug treatment, is concealed (Semple, Amaro, Strathdee, Zians, & Patterson, 2009).

Among different methods of drug treatment, methadone maintenance therapy (MMT) has been widely used in many countries for the treatment of drug use and harm reduction (WHO, 2017). In order to evaluate an MMT program, correct data is needed.

However, many individuals who use drugs are reluctant to disclose their addiction or usage of services related to the treatment of drug addiction (Castle, 2004). Therefore, data which are gained from formal registration systems and direct methods of data collection are more

likely to be inaccurate (Johnston et al., 2013). Among different indices, treatment failure ratio is an important index for evaluating MMT (Afsar, Poorolaja, Hazavehei, Vatan Nawaz, & Zinat Motlagh, 2014). Treatment failure ratio shows the ratio of relapse among methadone users. Regarding this, there are two distinct definitions: lapse and relapse. A lapse represents a temporary return to usage of drugs while being under MMT (usually a one-time occurrence). Whereas a relapse shows a more permanent return occurring over 3 months after starting MMT (Marlatt & Donovan, 2005).

Iran, as a Middle Eastern country, has faced significant drug-related problems, including drug use. This has been mainly due to the geostrategic condition of the country and locating close to Afghanistan borders. According to the national authorities, there are over 1325000 opiate addicted individuals in the country (2.26% of the adult population) (UNODC, 2016). Among all provinces in Iran, Kerman, which is the largest province and is close to Afghanistan borders, has been greatly involved with drug problems including drug trafficking, drug seizure, and drug usage (Veicy, 2017). According to statistics, the most frequent drug seizure has been occurred in Kerman province which following by Sistan-Baloochestan province as second place (Shah bahrami, 2010).

The war against drugs has a long history in Iran, and the policy has changed remarkably overtime, and it happened from criminalization to the treatment of addiction (Ghorbani, Mohamadi, & Hosseini, 2017). Accordingly, the Ministry of Health has initiated programs for preventing and treating drug usage t into the primary health care system; thus, public facilities have been expanded around the country such as diagnosis, treatment, and rehabilitation centers, including MMT centers (Kheiltash, M. R., & Ehterami, 2009).

Despite the considerable growth in the number of MMT centers in Iran, the stigma regarding using drugs and subsequently using MMT services is still high (karimi Talabri & Rafie, 2013). Therefore, many MMT service users might refuse to provide accurate personal information to MMT centers and might even change the centers that they use or use different centers over time. This, in turns, can lead to incomplete data which is recorded at the MMT centers.

To the best of our knowledge, there are sparse studies on the estimation of the treatment failure ratio, which are mainly based on MMT centers̀ data (Brands et al., 2008; Banazadeh & Kheradmand, 2009; Shahrbabaki et al., 2011; Mullen et al., 2012). However, due to the limitation regarding using a direct method and data of MMT centers, it is useful to apply an indirect method to estimate the failure ratio (Shokoohi, Baneshi, & Haghdoost, 2010).

The aim of this manuscript was to estimate the number of MMT users and its failure ratio in the city of Kerman, Iran, in 2016 indirectly. Practicality of the NSU, as well as its strengths and drawbacks were discussed.

Material and methods

A) Sampling

In two separate cross-sectional studies following a multistage sampling, we recruited 1275 men and 1275 women which were aged > 18 years and who had lived in the city of Kerman for at least 5 years. Our previous experience suggests that, in the case of stigmatized behaviors, street-based interviews provide more accurate responses and increase the response rate (Maghsoudi, Baneshi, Neydavoodi, & Haghdoost, 2014; Mohebbi, Baneshi, Haji-Maghsoodi, & Haghdoost, 2014). In order to obtain a representative sample, in the first stage, the city was divided into three zones regarding socioeconomic status: high, medium, and low and according to the governor's expert opinion. This was happened, due to the fact that there was no available formal information on distribution of socioeconomic status across the city to our best knowledge, the governmental bodies that we approached for obtaining such information are the best sources for our setting. In each zone, five streets

were selected randomly. Thereafter, 85 men and 85 women, were selected from pedestrians in each of the selected places proportionate to the age distribution of the latest census of the general population. Data was collected via face-to-face gender-match interviews. Only pedestrians who consented verbally were interviewed. The first part of the questionnaire included demographic characteristics (age, education, marital status and occupation).

B) NSU philosophy

In the NSU, data is collected from members of the general population and, participants respond on behalf of their network rather than themselves (Russell Bernard, Johnsen, Killworth, & Robinson, 1991). The NSU assumes that the prevalence of a behavior in the network of a randomly selected sample (m∕ C) can be generalized to the whole population (e∕ t). Here, 'm' is the number of individuals in the hidden group which are known as the respondent, 'C' is the respondent's network size, 'e' is the real size of the hidden group and 't' is the size of the total population (Guo et al., 2013; Johnsen, Bernard, Killworth, Shelley, & McCarty, 1995). Therefore, the calculating the network size is regarded as a prime in the NSU studies.

B.1) Estimation of network size (C)

The second part of the questionnaire involved 25 reference groups with known sizes for the estimation of the network size. It has been suggested that the prevalence of reference groups in the general population should be in the range of 0.1% to 4%. We selected 25 reference groups (13 female and 12 male first names) with known sizes (shown by "ej"); real size of these reference groups was obtained from the national civil registration office.

We asked the participants to count the number of residents from Kerman which they knew in each of 25 reference groups. Residents from Kerman were defined as those who used to live in Kerman at least in the past five years. 'Know' was defined as "people whom you know and who know you, in appearance or by name actually, with whom you can interact if needed, and with whom you have contacted over the last two years personally, or by telephone or e-mail" (Rastegari et al., 2013; Shokoohi et al., 2010).

In order to avoid confusion, names which were used for both genders were not selected. We asked the respondents to stratify their reply based on age group (< 18, 18–30, 30–50, > 50).

The definition for each participant, Eq. (1) was applied in order to combine information of all the 25 reference groups and calculate the network size. The mean of these values was used as the average network size of residents from Kerman. Here, "mij" shows the number of people which are known by the respondent "i" in the reference group "j."

$$C_i = (t * \Sigma m_{ij}) / \Sigma e_j \qquad (1)$$

B.2) Refinement of network size

There is some evidence that respondents do not recall size of all reference groups accurately. It has been shown that respondents usually overestimate size of large and underestimate size of small reference groups (Rastegari et al., 2013). In order to exclude ineligible reference groups, we back-calculated the size of all the reference groups applying Eq. (2). The ratio of the back-calculated size to the real size for all the reference groups was calculated. Thereafter, the absolute logarithm based on two of all ratios was calculated. The reference group with the worst ratio was eliminated. This is due to the worst ratio which is corresponded to the highest degree of bias. Then, the "C" was re-estimated using the remaining reference groups. This process was repeated until all the absolute logarithms based on two of all ratios remained less

than 1.

B.3) Determination of age-gender distribution of network

We determined the age-gender distribution to be able to provide the number of MMT users and its failure rate in each age-gender category. In order to determine the number of males which are known by residents from Kerman, only replies which were related to 12 male names were analyzed. The analysis was stratified by age category. The same methodology was applied to determine the female part of the network.

B.4) Assessment of internal validity of network size

In order to assess the internal validity, the intra-class correlation (ICC) between the back-calculated and real sizes of the eligible reference groups as well as root mean square of error (RMSE) were calculated. The RMSE was the root of the mean of the square differences between the real and back-calculated sizes of the eligible reference groups. We also fitted a regression line so that the back-calculated and real sizes of the dependent and independent variables of the reference groups were obtained, respectively. An intercept of zero and slope of 1 were considered as the evidence of agreement between the back-calculated and real sizes.

C) Estimating the size of MMT service users and its failure ratio

In the third part of the questionnaire, we asked the respondents "how many residents do you know from Kerman, using the standard definition of "know", who has received service from MMT centers in the past 3 years?" This was followed by asking "how many of them failed to maintain on methadone program and returned to their previous drugs". In this study, the respondents were not aware of the exact time of the failure; therefore, our estimates included both lapse and relapse. We also were not able to distinguish whether they returned to using their previous drugs as well as to using methadone as a top-up. Hence, they might have used other drugs with or without methadone.

Eq. (2) was applied to estimate the crude size of the hidden groups.

$$e_{crude} = (t * \Sigma m_i) / \Sigma C_i \qquad (2)$$

Results

The mean (SD) age of the male and female participants was equal to 36.58 (14.22) years and 36.46 (13.96) years, respectively. Nearly one-third of the male participants and˜28% of the female participants were single. Moreover, half of the respondents had academic degrees (Tables 1and 2). We did not collect any information regarding income and ethnicity.

A response rate of 87% was obtained in this study. In total, the average network size of the residents of Kerman was equal to 235; among them, 97 were men and 138 were women (Table 3). This indicates that nearly 40% of the network of residents from Kerman was male. Moreover, the respondents were more likely to know women in outer age ranges (< 18 or > 80) than men. On average, the respondents knew 49 women and only 13 men in these age groups.

The low RMSE and high ICC between the back-calculated and real sizes of the reference groups indicated a high agreement between such sizes. All the ICC values were above 70%. Moreover, most of the slopes of the regression lines were above 0.70, and their intercepts were close to zero reasonably. The lowest C was calculated in the men who were aged < 18 years. Here, the slope of the regression line was equal to 0.53 (Table 3).

As shown in Table 4, the lowest number of MMT users were in women who were aged < 18 (30 95% CI: 23, 38). This was significantly different with other categories, as no overlap was seen between CIs.

Table 1
Demographic characteristics of participants men.

Variable	Category	n (%)
Age	18–24	302 (23.7)
	25–34	385 (30.2)
	35–49	333 (26.1)
	≥ 50	255 (20.0)
Marital status	Single	424 (33.3)
	Married	819 (64.2)
	Divorced/widowed	31 (2.4)
Job	Employee	168 (13.2)
	Student	196 (15.4)
	Self-employed	746 (53.5)
	Retired	159 (12.5)
	Unemployed	6 (0.5)
Education	≤ 9 years	251 (19.8)
	12 years	413 (32.4)
	12–16 years	510 (40)
	≥ 18	100 (7.8)
Spouse's job	Employee	137 (10.7)
	housewife	559 (43.8)
	Self-employed	111 (8.7)
	Retired	29 (2.3)
	Student	9 (0.7)
Spouse's education	≤ 9 years	240 (18.8)
	12 years	295 (23.1)
	12–16 years	268 (21)
	≥ 18	40 (3.1)

Table 2
Demographic characteristics of participants women.

Variable	Category	n (%)
Age	18–24	301 (23.6)
	25–34	391 (30.7)
	35–49	328 (25.7)
	≥ 50	255 (20.0)
Marital status	Single	358 (28.1)
	Married	829 (65.0)
	Divorced/widowed	88 (6.9)
Job	Employee	181 (14.1)
	Student	195 (15.3)
	Self-employed	172 (13.5)
	Retired	59 (4.6)
	Unemployed	36 (2.8)
	Housewife	632 (49.6)
Education	≤ 9 years	267 (20.9)
	12 years	457 (35.8)
	12–16 years	455 (35.7)
	≥ 18	95 (7.5)
Spouse's job	Employee	215 (25.93)
	worker	61 (7.36)
	Self-employed	425 (51.27)
	Retired	114 (13.75)
	student	14 (1.6)
Spouse's education	≤ 9 years	238 (28.71)
	12 years	320 (38.60)
	12–16 years	202 (24.37)
	≥ 18	69 (8.32)

The crude number of those which were treated with methadone was equal to 4124, whereas the number of the men was nearly nine times higher than that of the women (3741 versus 383). We observed that the male to female ratio was as low as 4.5 in those who were aged < 18 (135 versus 30). The corresponding ratio as high as 33 in those who were aged > 50 was (1078 versus 32). The ratio was about 8 in the other two age groups.

The total number of individuals who returned to use opioid was equal to 2130 (1921 in the men and 209 in the women). The treatment failure ratio in the women and men was equal to 55% and 51%, respectively.

As noted above, we fitted the regression model for back-calculated

Table 3

Age-gender distribution of network size of residents of Kerman and assessment of its internal validity.

Gender	Age group	C	Number of eligible groups	ICC[**]	Correlation	Slope[#]	Intercept[##]	RMSE[*]
Male	< 18	7	7	0.74	0.85	0.53	202.08	433.97
	18-29	47	10	0.88	0.82	0.61	186.99	529.45
	30-49	37	8	0.94	0.87	0.93	32.61	352.89
	> 50	6	4	0.89	0.77	0.80	11.31	256.19
Female	< 18	18	5	0.98	0.77	0.76	73.02	263.12
	18-29	49	8	0.85	0.84	0.45	377.15	405.51
	30-49	40	9	0.90	0.81	0.76	139.46	403.98
	> 50	31	4	0.85	0.73	0.80	50.68	258.6

[*] RMSE (Root Mean Square of Error): The root of the mean of square differences between real and back-calculated size of the eligible reference group.

[**] ICC (Intraclass correlation coefficient) between back-calculated and real size of reference groups.

[#] Slope of regression line of back-calculated versus real sizes.

[##] Intercept of regression line of back-calculated versus real sizes.

size = a + b* (real size) using the reference groups. We used the estimated slopes, which are provided in Table 3, in order to adjust our statistics. We assumed that a slope of 0.50 indicated 50% underestimation in size. Therefore, we divided the crude estimates by the slope of the regression lines in each age-sex group in order to obtain the adjusted estimates. The adjusted results suggested that the total number of those which have used of MMT service was equal to 5289; among them, 2731 people have returned to use opioid.

Based on the national statistics, the number of males and females living in Kerman was equal to 308,614 and 302,787, respectively. This means that, out of 1000 men, 15.27 are under MMT. The corresponding figure among women was equal to 1.90 (Province, 2017)

Among the men, no remarkable difference was observed between the failure ratios among the age groups. The failure ratio was equal to ˜50% in all the age groups. Among the women, the failure ratio was as high as 76% in those who were aged < 18 years, while in the other age groups, the corresponding figure was about 50%. However, the difference, was not statistically significant, as the failure ratio of CIs had overlap.

Discussion

In order to estimate the failure ratio using the NSU method, first we estimated the age-sex distribution of the network in Kerman. We observed that 60% of the network of the residents of Kerman were women. We also found that 15.27 and 190 per 1000 men and women,

respectively, were under methadone treatment in the study setting.

In the current study, the treatment failure ratio in MMT was estimated at 52% using the NSU method over the past 3 years (55% among the women and 51% among the men). This rate was approximately close to 48.2% and 59%, respectively as were estimated by Afsar and Taraghi, (Taraghi, Poorafkari, & Seydi, 2005; Afsar et al., 2014).Their studies were conducted on outpatients which were treated with methadone in addiction treatment centers. In these studies, there was no specification on the time span for the failure, which was similar to our study.

Other studies yielded different results. For example, the result of the review which was conducted in the Center of National Studies on Addiction in Iran showed that the relapse rate was equal to 24% at the end of the third month and 31% at the end of the sixth month (Fakhraie & Babayance, 2007). In another study, the relapse rate was equal to 32% at the end of the first year of treatment and 42% over a year (Taraghi et al., 2005). Lion found a failure rate of about 32.2% 12 months after MMT (Lions et al., 2014). In US, in the clinics setting among outpatients, the effect of doses of methadone in failure of MMT was examined using a double-blind trial. They defined the outcome as having a positive opioid results in urine test and found that the rate of positive test was higher in lower dose of methadone, but was over 50% in both high and moderate doses (53.0%; 95% CI 46.9%–59.2% in high dose of methadone and 61.9%CI, 55.9%–68.0% in moderate dose of methadone) (Strain, Bigelow, Liebson, & Stitzer, 1999). Moreover, another study was conducted in three methadone clinics in Australia

Table 4

Calculation of the crude and adjusted number of methadone users and failures based on age -gender network.

Gender	Age group	C	Crude estimates		Adjusted estimates		Failure treatment (%)
			Methadone therapy	Reuse opioid	Methadone Therapy	Reuse opioid	
Male	< 18	7	135 (110, 160)	69 (52, 86)	255 (208, 302)	130 (98, 162)	51 (47, 53)
	18-29	47	699 (677, 721)	347 (331, 362)	1146 (1110, 1182)	569 (543, 593)	50 (49, 51)
	30-49	37	1829 (1790, 1868)	959 (930, 987)	1966 (1925, 2009)	1031 (1000, 1061)	52 (51, 53)
	> 50	6	1078 (1022, 1134)	546 (506, 586)	1347 (1278, 1418)	682 (633, 733)	51 (49, 52)
	Sum		3741	1921	4714	2412	51
Female	< 18	18	30 (23, 38)	23 (10, 36)	39 (30, 50)	30 (13, 47)	76 (43, 94)
	18-29	49	82 (75, 89)	43 (33, 53)	182 (167, 198)	95 (73, 118)	52 (44, 59)
	30-49	40	239 (225, 253)	126 (116, 136)	314 (296, 333)	166 (153, 179)	53 (51, 54)
	> 50	31	32 (28, 36)	17 (14, 20)	40 (35, 45)	28 (18, 25)	53 (51, 56)
	Sum		383	209	575	319	55

comparing the retention on buprenorphine and methadone based on urinalysis. They found that retention was higher among methadone users, which was equal to 59% compared to 50% among buprenorphine users. Hence, the failure to retention could be calculated as 41% for methadone therapy (Mattick et al., 2003).

The difference between these statistics can be due to the differences in the definitions of treatment failure, time span of the study, target group, and methodology of research. Some of the studies (Liu et al., 2009; Mino, Page, Dumont, & Broers, 1998; Hosseini et al., 2010) defined treatment failure as a completely discontinued treatment, while others (Li, Lin, Wan, Zhang, & Lai, 2012; Lin, Wu, & Detels, 2011; Lions et al., 2014) defined it as a simultaneous usage of drugs and methadone during the treatment process. For example, in Lion's study the main outcome was not to prescribing opioid for 12 months after starting MMT. In this study, we did not specify the time of returning to the usage of drugs.

Regarding differences between the methodologies of researches, most of the studies (Lin et al., 2011; Liu et al., 2009; Moeeni, Mahmoudi, & Pashaei, 2013) that used direct methods recruited outpatients under methadone treatment in MMT centers. However, we recruited participants from the general population and used an indirect method.

In our study, we found that the failure rate was slightly higher among the women (55%) than the men (51%). There is a controversy in the literature regarding this issue; some studies reported that the failure rate was higher among men rather than women (Chatham, Hiller, Rowan-Szal, Joe, & Simpson, 1999; Schottenfeld, Pakes, & Kosten, 1998; Xie, McHugo, Fox, & Drake, 2005). Other studies found results that are similar to those of our study, that is, MMT is more likely to fail in women (McCaul, Svikis, & Moore, 2001; Sansone, 1980; Wechsberg, Craddock, & Hubbard, 1998). A possible explanation for this difference could be due to this fact that many healthcare services inappropriate regarding the needs of women (Rahimi, 2004; Naghizadeh, Rezaei, Zarei, Firoozi, & Ahmadi, 2014), therefore creating a higher failure rate among them.

In this study, we found that the treatment failure ratio in the women who were aged < 18 years was higher than those in the other age groups. Although the difference was not statistically significant, 76% failure rate in this subgroup was remarkable. Low number of MMT users in this category led to a wide CI. Therefore, in this subgroup, our power was underestimated. However, adolescent girls usually have a weak self-esteem. Therefore, they can be one of the most vulnerable groups in the field of addiction (Alimardani & Ehteshami, 2011, 2011). Inappropriate family's reactions towards teenagers which are involved in addiction and peer pressures could play a role in such a higher treatment failure rate (Ashrafi Hafez & Shayan Sh, 2014).

High response rate is regarded as one of the strengths of this study. While most of survey-based studies lack low response rate, we could obtain a response rate of about 87%. This might be justified partially as we adopted an indirect method.

Limitations

While this study may provide new opportunities for the evaluation of MMT in specific populations, we acknowledge that there are limitations in this study. First, we failed to address the time of failure in the process of data collection; therefore, we were unable to distinguish between lapses and relapse. Moreover, we were not able to calculate the number of those who received methadone on top of other drugs (i.e., those who used methadone and drug simultaneously). Furthermore, the visibility rate of the behaviors should be available in order to adjust the estimates for obtaining accurate estimations of the behavior using the NSU method. However, that was not the case in our study; and in order to estimate the visibility rate, we needed a separate sample. However, due to budget and time limitations, we failed to estimate it separately. Instead, we adopted a novel approach in which the slope of the

regression models was used as a post correction factor. However, the correction factor for being under MMT and its failure was not the same necessarily. We hypothesized that the visibility of failure might be lower. Therefore, our failure ratio estimates are likely underestimated.

Conclusion

Despite the mentioned limitations, to the best of our knowledge, this study was the first which attempted to use the NSU method for the evaluation of the failure ratio among patients under MMT. Indirect methods, including the NSU method, are efficient methods for the estimation of hidden behaviors and also could be very useful for sensitive behaviors and in many settings that there are not available accurate registration systems. Furthermore, this study suggests that direct methods should be adopted to confirm the results. In addition, re-examination of MMT could be useful to determine the possible reasons causing the high ratio of failure. While the number of women who were aged < 18 and who were under MMT was low, the failure rate was very high among them. Therefore, the identification of women's needs and adapting appropriate health services regarding their conditions should be helpful in order to gain better results in women's treatment.

Declaration of Competing Interest

There is no conflict of interest statement.

Acknowledgements

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